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# Total Synthesis of the Prenylated Indole Alkaloid (±)-Notoamide N via an Electrochemically Mediated Vilsmeier–Haack Formylation of a Chlorinated Indole

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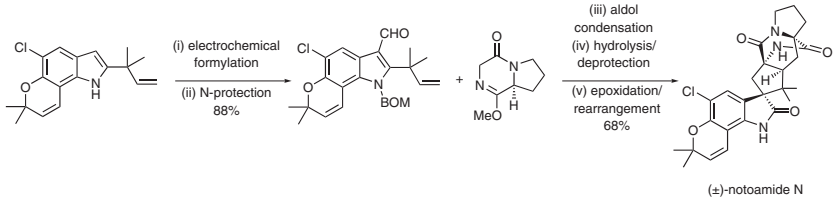



Received: 07.10.2024
Accepted after revision: 21.10.2024
Published online: 02.01.2025 (Version of Record)
DOI: 10.1055/s-0043-1773504; Art ID: SO-2024-10-0040-OP



**Abstract** A total synthesis of the racemic modification of the prenylated indole alkaloid notoamide N has been realised. A crucial step involved the electrochemically mediated Vilsmeier–Haack formylation of a chlorinated 1,7-dihydropyrano[2,3-*g*]indole. The product aldehyde was engaged in biomimetic and tandem aldol condensation/intramolecular Diels–Alder reactions with a diketopiperazine derivative to give a diazabicyclo[2.2.2]octane-containing adduct. Epoxidation of this adduct led, via an in situ semi-pinacolic rearrangement of the initially formed oxirane, to the targeted spiro-oxindole notoamide N.

**Keywords** aldol reaction, cycloaddition, electrochemistry, epoxidation, rearrangement, total synthesis

The prenylated indole alkaloids or PIAs are a class of microbially derived natural product that have attracted considerable attention,[1] perhaps most particularly since 2002 when a research group at Bristol-Myers Squibb reported the isolation of stephacidin A (**1**, Figure 1) and a related heterodimer, both of which display notable cytotoxic effects.[2] The distinctive diazabicyclo[2.2.2]octane substructure associated with such compounds is encountered in many other more recently discovered PIAs including 6-*epi*-stephacidin A (**2**)[3] and taichunamide A (**3**)[1e,4] (Figure 1). Biosynthetically, the bicyclo[2.2.2]diazaoctane motif most likely arises through an intramolecular Diels–Alder reaction involving pendant diketopiperazine and prenyl residues in precursors such as notoamide E (**4**), a likely progenitor to congeners **1** and **2**.[5] Compounds such as stephacidin A (**1**) are, in turn, converted in vivo and presumably via oxidation and semi-pinacolic rearrangement steps,[6,7] into naturally occurring spiro-fused PIAs such as notoamide B (**5**). A nuclear chlorination of compound **5** or a precursor to it would lead to notoamide N (**6**),[8] both these compounds being diastereoisomerically related to the versicolamide class of PIAs of which congener B (**7**)[1] is a representative member. These biosynthetic cascades have inspired the development of various total syntheses of such compounds[1] including ones that we have reported recently.[9] A key step in our approaches has been the electrochemically mediated Vilsmeier–Haack formylation of highly substituted indoles, processes that have proven superior (in terms of yield) to their traditional and strictly chemical equivalents of these processes.[9] To expand upon these discoveries, we sought to establish whether or not halogenated indoles could be similarly engaged. Herein we report that this is indeed the case and allows us to complete a total synthesis of the racemic modification of the title PIA by a route distinct from that which we reported earlier.[9]

The opening stages of the total synthesis of notoamide N (**6**) detailed herein are shown in Scheme 1 and started with the commercially available chloroaniline **8** which upon reaction with methanesulfonyl chloride in the presence of triethylamine afforded the sulfonamide **9**[10] (98%) that was itself *N*-alkylated using 2,2-diethoxyethyl trifluo-

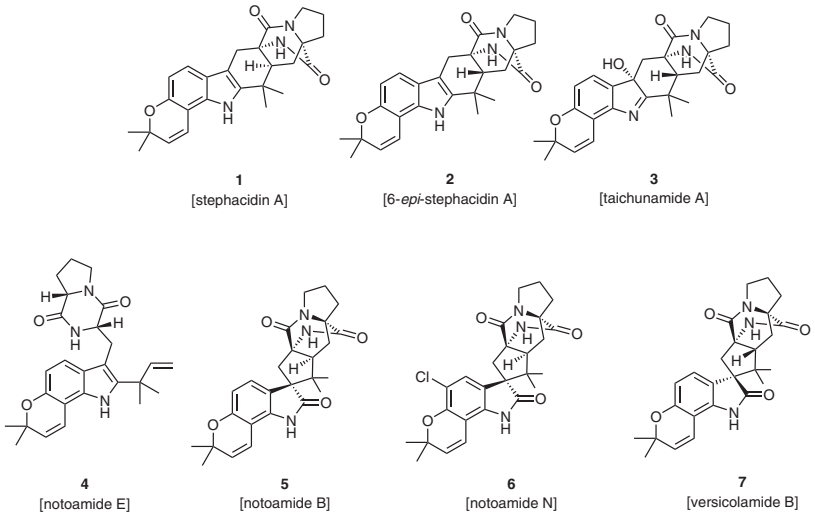
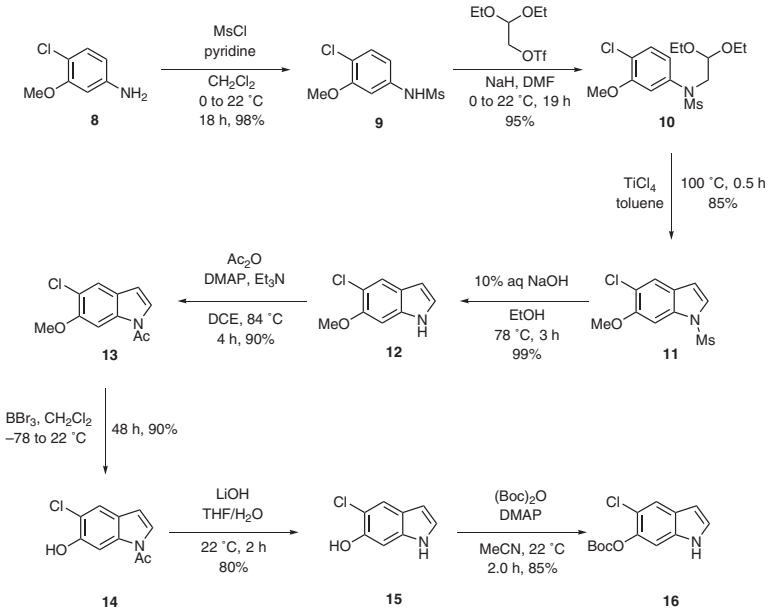



**Figure 1** The structures of the representative PIAs **1–7**

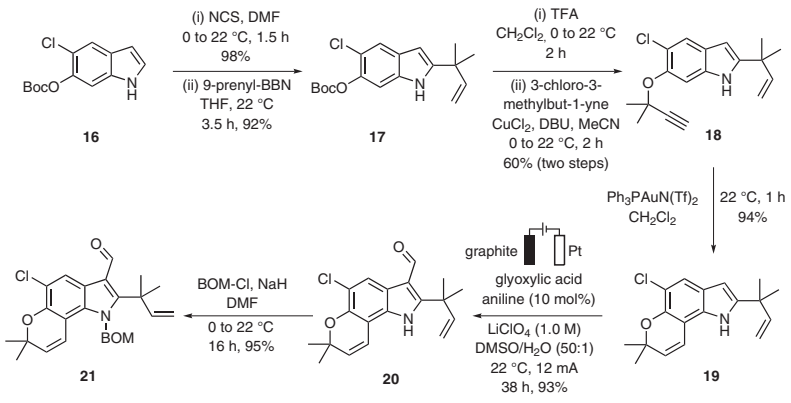
romethanesulfonate[11] in the presence of sodium hydride. On treating product **10** (95%) with titanium tetrachloride a Friedel–Crafts-type cyclisation/aromatisation reaction sequence took place to afford the indole derivative **11** (85%) that was itself treated with aqueous sodium hydroxide in ethanol to afford 5-chloro-6-methoxy-1*H*-indole (**12**)[12] in 99% yield. *N*-Acylation of compound **12** under standard conditions afforded acetamide **13** (90%) and so setting the stage for a demethylation reaction that was effected with boron tribromide and delivered compound **14** in 90% yield. Cleavage of the acetamide residue associated with indole derivative **14** was achieved under standard conditions and the free phenolic residue of product **15** (80%) was then selectively protected using di-*tert*-butyl dicarbonate in the presence of DMAP to give the mixed carbonate **16** in 85%. All the spectral data acquired on the compounds shown in Scheme 1 were in accord with the assigned structure and that of indole **11** by confirmed by single-crystal X-ray analysis (see experimental section and Supporting Information for details).



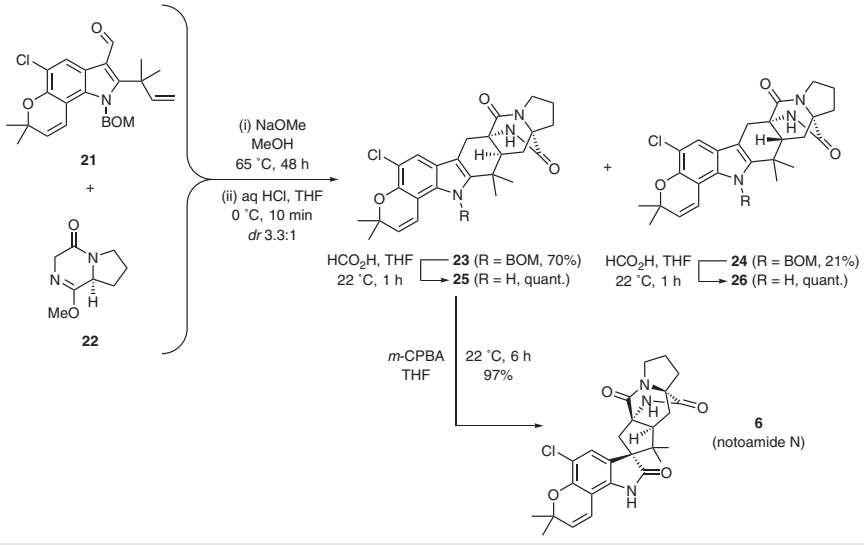

**Scheme 1** The conversion of the chlorinated aniline **8** into indole **16**

The disubstituted indole **16** could be converted, as shown in Scheme 2, into the reverse prenylated derivative **17** under conditions reported by Danishefsky.[13] Specifically, substrate **16** was treated with *N*-chlorosuccinimide (NCS) and the resulting α-chloroimine reacted with 9-prenyl-BBN to afford, after work-up, the anticipated product **17** (90% yield over two steps). Cleavage of the Boc-protecting group in this last compound was readily achieved using trifluoroacetic acid (TFA) and the product phenol then converted into the reverse-prenylated derivative **18** (60% over two steps) on treatment with 3-chloro-3-methylbut-1-yne in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The Au(I)-catalysed intramolecular hydroarylation of compound **18** proceeded with excellent levels of regioselectivity to give the 1,7-dihydropyrano[2,3-*g*]indole **19** in 94% yield. Compound **19** proved to be an entirely competent substrate for the foreshadowed electrochemically mediated formylation reaction where, as in our earlier studies, glyoxylic acid was used as the source of the formyl group. Under these conditions (see the Supporting Information for details of the experimental set up) the chlorine residue remained unaffected and the required product **20** was obtained in 93% yield. This was itself readily converted, under standard conditions, into the *N*-BOM protected derivative **21** (95%). This protection was necessary to ensure outcomes for the subsequent (tandem) aldol and intramolecular Diels–Alder (IMDA) reactions (as detailed immediately below) centred on the newly introduced formyl group proceeded efficiently.

The means for converting compound **21** into the racemic modification of the final target **6** [*viz.* (±)-notoamide N] is shown in Scheme 3. In the opening stages of the reaction sequence involved, a sodium methoxide mediated condensation of aldehyde **21** with the readily prepared diketopiperazine derivative **22** led, via an initial aldol-type condensa-




**Scheme 2** Conversion of indole **16**, via an electrochemically mediated Vilsmeier–Haack formylation reaction, into the pivotal 1,7-dihydropyrano[2,3-*g*]indole **21**




**Scheme 3** Completion of the synthesis of (±)-notoamide N (**6**)

tion reaction followed by protropic shift and intramolecular Diels–Alder reactions (with the pendant prenyl reside acting as dienophile in the last of these steps), to an epimeric pair of diazabicyclo[2.2.2]octane-containing cycloadducts which each incorporate an imidate residue. Acid-catalysed hydrolysis of this residue within these adducts then gave the chromatographically separable compounds **23** (70%) and **24** (21%). The former product arises through an *exo*-IMDA process while its counterpart **24** arises through the corresponding *endo*-one.[1] Reaction of adduct **23** with formic acid in THF at ambient temperatures resulted in smooth cleavage of the associated BOM group to afford the *N*-deprotected indole **25** in quantitative yield. Similarly, adduct **24** was converted into indole **26** (quant.). On treating compound **25** with *m*-chloroperbenzoic acid (*m*-CPBA) in THF at ambient temperatures an oxidative rearrangement took place that involved initial epoxidation of the indole 2,3-double bond followed by a semi-pinacolic rearrangement of the resulting oxirane, to give (±)-notoamide N [(±)-**6**] in 97% yield. All the spectral data acquired on this material were in complete accord with the assigned structure and matched those derived from the material produced by the route we reported earlier (see the Supporting Information for a tabulated comparison of the relevant $^{13}C\{^1H\}$ NMR spectral data sets).

The studies detailed above, when considered in conjunction with our earlier reports,[9] suggest that the electrochemical formylation of indoles is a useful protocol that can accommodate a significant range of functionalities attached to this heterocyclic framework. Indeed, this can be more efficient than the traditional and strictly chemical Vilsmeier–Haack process. As such the conversion reported here adds to the remarkable repertoire of chemical transformations that can now be accomplished electrochemically.[14]

The NMR spectra associated with this work are provided in the Supporting Information accompanying this paper while the corresponding X-ray data sets (cifs) have been deposited with the Cambridge Crystallographic Data Centre (CCDC) and can be accessed as detailed under the section 'Structure Determinations'.

### *N*-(4-Chloro-3-methoxyphenyl)methanesulfonamide (9)

A magnetically stirred and chilled (ice-water bath) solution of aniline **8** (15.76 g, 100 mmol) and pyridine (8.1 mL, 100 mmol) in $CH_2Cl_2$ (200 mL) maintained under a $N_2$ atmosphere was treated, dropwise, with MsCl (8.10 mL, 104 mmol). The ensuing mixture was then warmed to r.t. and stirring continued for 18 h. After this time $CH_2Cl_2$ (400 mL) was added to the mixture and the resulting solution washed with distilled water (2 × 100 mL). The separated organic phase was then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give the title compound **9**[10] (27.4 g, 98%) as a brown, crystalline solid; mp 112–113 °C; $R_f$ = 0.5 (1:2 petroleum ether/EtOAc).

IR: 3256, 3015, 2933, 1594, 1491, 1382, 1316, 1196, 1141, 1067, 972, 873, 844, 763, 696, 618, 539, 515, 440 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.44 (s, 1 H), 7.30 (d, *J* = 8.5 Hz, 1 H), 6.92 (d, *J* = 2.4 Hz, 1 H), 6.79 (dd, *J* = 8.5, 2.4 Hz, 1 H), 3.89 (s, 3 H), 3.04 (s, 3 H).

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 155.7, 136.5, 130.7, 119.2, 113.1, 105.3, 56.3, 39.1.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_8H_{10}{}^{35}ClNNaO_3S$: 257.9962; found: 257.9957.

### *N*-(4-Chloro-3-methoxyphenyl)-*N*-(2,2-diethoxyethyl)methanesulfonamide (10)

A magnetically stirred and chilled (ice-water bath) suspension of NaH (60% dispersion in mineral oil, 3.74 g, 94 mmol) in DMF (35 mL) maintained under a $N_2$ atmosphere was treated, over 0.5 h, with a solution of compound **9** (17.0 g, 72 mmol) in DMF (100 mL). After the evolution of $H_2$ gas had ceased, freshly prepared 2,2-diethoxyethyl trifluoromethanesulfonate[11] (23.0 g, 86.4 mmol) was added, in one portion, to the mixture and the resulting solution was warmed to r.t. and stirring continued for 6 h. Thereafter, additional quantities of NaH (60% dispersion in oil, 0.86 g, 21.6 mmol, 0.3 equiv.) and 2,2-diethoxyethyl trifluoromethanesulfonate (3.84 g, 17.3 mmol, 0.2 equiv.) were added and stirring was continued for a further 13 h. The mixture was then quenched with water (200 mL) (***CAUTION***: possibility of $H_2$ gas evolution) and extracted with EtOAc (3 × 200 mL). The combined organic phases were then washed with distilled water (1 × 200 mL) before being dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 8:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.35), compound **10** (24.1 g, 95%) as a grey solid; mp 67–68 °C.

IR: 3486, 2975, 2932, 2361, 1588, 1487, 1450, 1405, 1338, 1272, 1206, 1152, 1101, 1063, 1028, 966, 861, 757, 709, 625, 545, 513 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 2.4 Hz, 1 H), 6.89 (dd, *J* = 8.4, 2.4 Hz, 1 H), 4.61 (t, *J* = 5.5 Hz, 1 H), 3.91 (s, 3 H), 3.75 (d, *J* = 5.5 Hz, 2 H), 3.67 (m, 2 H), 3.52 (m, 2 H), 2.96 (s, 3 H), 1.17 (t, *J* = 7.0 Hz, 6 H).

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 155.4, 139.9, 130.3, 122.3, 120.3, 113.5, 100.9, 62.6, 56.3, 53.4, 38.2, 15.3.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{22}{}^{35}ClNNaO_5S$: 374.0799; found: 374.0788.

### 5-Chloro-6-methoxy-1-(methylsulfonyl)-1*H*-indole (11)

A magnetically stirred and chilled (ice-water bath) solution of compound **10** (5.28 g, 15.0 mmol) in toluene (250 mL) maintained under a $N_2$ atmosphere was treated, dropwise, with a solution of $TiCl_4$ (2.14 mL, 19.5 mmol) in toluene (100 mL). The mixture was then heated to 100 °C, stirred at this temperature for 0.5 h before being cooled to r.t. and then quenched with sat. aq. $NaHCO_3$ solution (100 mL). The separated organic phase was washed with 1.0 M aq HCl solution (1 × 100 mL) and distilled water (1 × 100 mL) before being dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give a crystalline solid. Recrystallisation ($Et_2O$) of this material afforded compound **11** (3.31 g, 85%) as a grey, crystalline solid; mp 127–128 °C; $R_f$ = 0.35 (silica gel, 5:1 petroleum ether/EtOAc).

IR: 3115, 2921, 1613, 1473, 1438, 1361, 1334, 1317, 1246, 1215, 1164, 1124, 1048, 1011, 969, 952, 879, 833, 765, 700, 553, 509 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.63 (s, 1 H), 7.52 (s, 1 H), 7.37 (d, *J* = 3.7 Hz, 1 H), 6.63 (d, *J* = 3.7 Hz, 1 H), 4.00 (s, 3 H), 3.10 (s, 3 H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 153.2, 134.2, 125.6, 124.3, 122.4, 119.9, 108.4, 96.9, 56.6, 40.6.

HRMS (ESI, +ve): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}{}^{35}ClNO_3S$: 260.0143; found: 260.0143.

### 5-Chloro-6-methoxy-1*H*-indole (12)

A magnetically stirred solution of compound **11** (3.31 g, 12.7 mmol) in EtOH (120 mL) was treated with NaOH (60.0 mL of 10% w/v aq solution). The ensuing mixture was heated under reflux for 2 h before being cooled to r.t. then diluted with water (120 mL) and EtOAc (60 mL). The separated aqueous layer was extracted with EtOAc (3 × 80 mL) and the combined organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 5:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **12**[12] (2.29 g, 99%) as a white, crystalline solid; mp 114–115 °C.

IR: 3360, 3105, 2919, 1622, 1504, 1481, 1457, 1308, 1235, 1201, 1168, 1043, 877, 822, 759, 721, 684, 522 cm$^{-1}$.

$^1$H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.07 (s, 1 H), 7.58 (s, 1 H), 7.27 (t, *J* = 2.8 Hz, 1 H), 7.09 (s, 1 H), 6.35 (br s, 1 H), 3.86 (s, 3 H).

$^{13}$C{$^1$H} NMR [126 MHz, $(CD_3)_2SO$]: δ = 150.0, 135.0, 125.1, 121.8, 120.4, 114.2, 100.6, 95.2, 56.0.

HRMS (ESI, +ve): *m*/*z* [M + H]$^+$ calcd for $C_9H_9{}^{35}ClNO$: 182.0367; found: 182.0367.

### 1-(5-Chloro-6-methoxy-1*H*-indol-1-yl)ethan-1-one (13)

A magnetically stirred solution of compound **12** (2.29 g, 12.6 mmol) in $Et_2O$ (120 mL) maintained at r.t. was treated with DMAP (308 mg, 2.52 mmol), $Et_3N$ (3.50 mL, 25.2 mmol), and acetic anhydride (2.36 mL, 25.2 mmol.). The ensuing mixture was stirred for 4 h then quenched with sat. aq $NaHCO_3$ solution (20 mL) before being diluted with EtOAc (70 mL). The separated aqueous phase was extracted with EtOAc (3 × 40 mL) and the combined organic phases were then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 8:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **13** (2.14 g, 90%) as a white, crystalline solid; mp 149–150 °C.

IR: 3663, 2919, 2849, 2360, 1704, 1646, 1535, 1472, 1440, 1422, 1378, 1334, 1276, 1242, 1219, 1051, 932, 892, 838, 706, 630 cm$^{-1}$.

$^1$H NMR [300 MHz, $(CD_3)_2SO$]: δ = 8.07 (s, 1 H), 7.79 (d, *J* = 3.8 Hz, 1 H), 7.69 (s, 1 H), 6.65 (d, *J* = 3.8 Hz, 1 H), 3.88 (s, 3 H), 2.65 (s, 3 H).

$^{13}$C{$^1$H} NMR [75 MHz, $(CD_3)_2SO$]: δ = 170.3, 152.6, 134.7, 127.4, 124.5, 121.8, 118.2, 107.8, 100.5, 56.6, 24.2.

HRMS (ESI, +ve): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}{}^{35}ClNO$: 224.0473; found: 224.0471.

### 1-(5-Chloro-6-hydroxy-1*H*-indol-1-yl)ethan-1-one (14)

A magnetically stirred solution of compound **13** (2.54 g, 11.3 mmol, 1.0 equiv.) in dry $CH_2Cl_2$ (45 mL) maintained under $N_2$ was cooled to –78 °C (using EtOH contained in an Eyela PSL-1820 freezing bath) then treated, over 0.33 h, with 1.0 M $BBr_3$ in $CH_2Cl_2$ (22.6 mL, 22.6 mmol). The ensuing mixture was stirred at –78 °C for 0.5 h then warmed to r.t. and after a further 13 h quenched with sat. aq $NaHCO_3$ solution (150 mL) before being diluted with $CH_2Cl_2$ (50 mL). The separated aqueous phase was extracted with $CH_2Cl_2$ (3 × 30 mL) and the combined organic phases were then washed with distilled water (1 × 40 mL) and thereafter dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 5:2 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **14** (2.14 g, 90%) as a white, crystalline solid; mp 121–122 °C.

IR: 3357, 3186, 2919, 2849, 2361, 1632, 1469, 1409, 1054, 694, 463 cm$^{-1}$.

$^1$H NMR [300 MHz, $(CD_3)_2SO$]: δ = 10.18 (br s, 1 H), 8.07 (s, 1 H), 7.70 (d, *J* = 3.8 Hz, 1 H), 7.58 (s, 1 H), 6.59 (d, *J* = 3.8 Hz, 1 H), 2.61 (s, 3 H).

$^{13}$C{$^1$H} NMR [75 MHz, $(CD_3)_2SO$]: δ = 170.0, 151.1, 134.8, 126.8, 123.8, 121.5, 117.2, 108.0, 104.0, 24.1.

HRMS (ESI, +ve): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9{}^{35}ClNO_2$: 210.0316; found: 210.0314.

### 5-Chloro-1*H*-indol-6-ol (15)

A magnetically stirred solution of compound **14** (2.14 g, 10.2 mmol) in THF/water (2:1; 120 mL) maintained at r.t. was treated with LiOH (489 mg, 20.4 mmol). After 2 h the mixture was quenched with 1.0 M aq HCl solution to achieve pH <7 then diluted with EtOAc (50 mL). The separated aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic phases were then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 2:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **15** (1.37 g, 80%) as a grey, crystalline solid; mp 108–109 °C.

IR: 3409, 2922, 2852, 1623, 1453, 1342, 1304, 1243, 1155, 1092, 1009, 869, 819, 753, 714, 686 cm$^{-1}$.

$^1$H NMR [300 MHz, $(CD_3)_2SO$]: δ = 10.83 (br s, 1 H), 9.55 (s, 1 H), 7.47 (s, 1 H), 7.17 (m, 1 H), 6.98 (s, 1 H), 6.25 (m, 1 H).

$^{13}$C{$^1$H} NMR [75 MHz, $(CD_3)_2SO$]: δ = 148.4, 135.9, 125.1, 122.0, 120.5, 114.0, 100.9, 98.3.

HRMS (ESI, +ve): *m*/*z* [M + H]$^+$ calcd for $C_8H_7{}^{35}ClNO$: 168.0211; found: 168.0218.

### *tert*-Butyl (5-Chloro-1*H*-indol-6-yl) Carbonate (16)

A magnetically stirred and chilled (ice-water bath) solution of compound **15** (1.37 g, 8.17 mmol) and DMAP (30 mg, 0.24 mmol) in MeCN (200 mL) was treated, dropwise, with di-*tert*-butyl dicarbonate (1.82 mL, 8.17 mmol). The ensuing mixture was allowed to warm to r.t. and after a further 1 h concentrated under reduced pressure. The residue so-obtained was subjected to flash column chromatography (silica gel, 12:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **16** (1.86 g, 85%) as a white, crystalline solid; mp 168–169 °C.

IR: 3395, 2955, 2921, 2852, 1749, 1455, 1370, 1282, 1149, 1089, 882, 765, 727, 635, 559 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.31 (br s, 1 H), 7.67 (s, 1 H), 7.23 (s, 1 H), 7.18 (m, 1 H), 6.47 (m, 1 H), 1.61 (s, 9 H).

$^{13}$C{$^1$H} NMR [75 MHz, $(CD_3)_2SO$]: δ = 151.9, 142.2, 134.0, 126.7, 126.1, 121.2, 119.1, 105.6, 102.2, 84.0, 27.7.

HRMS (ESI, +ve): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}{}^{35}ClNO_3$: 268.0736; found: 268.0737.

### *tert*-Butyl (3,5-Dichloro-1*H*-indol-6-yl) Carbonate

A magnetically stirred and chilled (ice/water bath) suspension of compound **16** (1.86 g, 6.94 mmol, 1.0 equiv.) in DMF (5 mL) was treated, dropwise, with a solution of NCS (927 mg, 6.94 mmol, 1.0 equiv.) in DMF (2 mL). The ensuing mixture was then warmed to r.t. and after a further 3.0 h quenched with brine (50 mL) before being extracted

with EtOAc (3 × 50 mL). The combined organic phases were washed with distilled water (1 × 50 mL) then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 12:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.27), the title compound (2.05 g, 98%) as a white, crystalline solid; mp 111–112 °C.

IR: 3361, 2924, 1740, 1455, 1371, 1280, 1255, 1146, 1055, 886, 821, 693, 497 $cm^{-1}$.

$^1H$ NMR [600 MHz, $(CD_3)_2SO$]: δ = 7.65 (br s, 1 H), 7.61 (s, 1 H), 7.46 (s, 1 H), 1.51 (s, 9 H) (signal due to NH group proton not observed).

$^{13}C\{^1H\}$ NMR [126 MHz, $(CD_3)_2SO$]: δ = 150.8, 142.0, 133.1, 124.9, 123.3, 118.5, 117.4, 107.2, 102.7, 83.5, 27.2.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{13}{}^{35}Cl_2NNaO_3$: 324.0165; found: 324.0161.

### *tert*-Butyl (5-Chloro-2-(2-methylbut-3-en-2-yl)-1*H*-indol-6-yl) Carbonate (17)

A magnetically stirred solution of *tert*-butyl (3,5-dichloro-1*H*-indol-6-yl) carbonate (2.05 g, 6.8 mmol) in THF (90 mL) maintained at r.t. was treated with $Et_3N$ (3.07 mL, 22.1 mmol) and, after 0.33 h, dropwise with prenyl-9-BBN[9] (40.8 mL of a freshly prepared 0.5 M solution in THF, 20.4 mmol). The ensuing mixture was stirred for 2.5 h before being quenched with sat. aq $K_2CO_3$ solution (30 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic phases were then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 16:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **17** (2.10 g, 92%) as a clear, green-tinted oil.

IR: 3354, 2923, 2857, 1762, 1455, 1411, 1370, 1325, 1273, 1252, 1145, 1036, 887, 750 $cm^{-1}$.

$^1H$ NMR [600 MHz, $(CD_3)_2SO$]: δ = 11.11 (s, 1 H), 7.58 (s, 1 H), 7.22 (s, 1 H), 6.18 (br s, 1 H), 6.09 (dd, *J* = 17.5, 10.5 Hz, 1 H), 5.04 (dd, *J* = 10.5, 1.1 Hz, 1 H), 5.00 (dd, *J* = 17.5, 1.1 Hz, 1 H), 1.50 (s, 9 H), 1.44 (s, 6 H).

$^{13}C\{^1H\}$ NMR [151 MHz, $(CD_3)_2SO$]: δ = 151.6, 149.2, 146.4, 141.0, 135.1, 127.0, 120.0, 117.2, 112.2, 106.0, 97.1, 83.7, 38.4, 27.7, 27.4.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{23}{}^{35}ClNO_3$: 336.1361; found: 336.1357.

### 5-Chloro-2-(2-methylbut-3-en-2-yl)-1*H*-indol-6-ol

A magnetically stirred and chilled (ice-water bath) suspension of compound **17** (2.10 g, 6.3 mmol) in $CH_2Cl_2$ (25 mL) maintained under $N_2$ was treated with TFA (6.27 mL, 81.9 mmol). The ensuing mixture was warmed to r.t. and after for 2.0 h quenched with NaOH (10% w/w aq solution) until the solution was basic and, thereafter extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic phases were then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 6:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.25), 5-chloro-2-(2-methylbut-3-en-2-yl)-1*H*-indol-6-ol (1.34 g, 90%) as a grey, crystalline solid; mp 106–107 °C.

IR: 3365, 2954, 2923, 2852, 1717, 1670, 1540, 1458, 1377, 1275, 1260, 1183, 1018, 764, 750 $cm^{-1}$.

$^1H$ NMR [500 MHz, $(CD_3)_2SO$]: δ = 10.58 (s, 1 H), 9.42 (s, 1 H), 7.34 (s, 1 H), 6.92 (s, 1 H), 6.06 (dd, *J* = 17.3, 10.6 Hz, 1 H), 5.97 (m, 1 H), 5.01 (m, 1 H), 4.98 (dd, *J* = 12.9, 1.3 Hz, 1 H), 1.40 (s, 6 H).

$^{13}C\{^1H\}$ NMR [126 MHz, $(CD_3)_2SO$]: δ = 147.4, 146.2, 145.6, 135.9, 121.6, 119.4, 112.9, 111.2, 97.6, 96.0, 37.7, 27.0.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}{}^{35}ClNO$: 236.0837; found: 236.0837.

### 5-Chloro-2-(2-methylbut-3-en-2-yl)-6-((2-methylbut-3-yn-2-yl)oxy)-1*H*-indole (18)

A magnetically stirred and chilled (ice-water bath) suspension of 5-chloro-2-(2-methylbut-3-en-2-yl)-1*H*-indol-6-ol (1.34 g, 5.68 mmol), $CuCl_2$ (8 mg, 0.057 mmol), DBU (2.57 mL, 17.0 mmol) in MeCN (60 mL) maintained under $N_2$ was treated with 3-chloro-3-methylbut-1-yne (1.43 mL, 11.36 mmol). The ensuing mixture was warmed to r.t. and after a further 2.5 h quenched with sat. aq $NH_4Cl$ solution (85 mL) then extracted with EtOAc (3 × 50 mL). The combined organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 18:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.25), compound **18** (1.15 g, 67%) as a white, crystalline solid; mp 133–134 °C.

IR: 3291, 2957, 2923, 1460, 1379, 1274, 1224, 1135, 1024, 919, 887, 704 $cm^{-1}$.

$^1H$ NMR [300 MHz, $(CD_3)_2SO$]: δ = 10.94 (br s, 1 H), 7.55 (s, 1 H), 7.47 (s, 1 H), 6.14–6.02 (complex m, 2 H), 5.05 (d, *J* = 1.1 Hz, 1 H), 5.00 (dd, *J* = 5.0, 1.1 Hz, 1 H), 3.67 (s, 1 H), 1.61 (s, 6 H), 1.42 (s, 6 H).

$^{13}C\{^1H\}$ NMR [75 MHz, $(CD_3)_2SO$]: δ = 148.1, 146.5, 145.5, 135.4, 124.9, 119.9, 119.0, 111.9, 105.1, 96.7, 86.9, 76.7, 74.3, 38.3, 29.5, 27.4.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}{}^{35}ClNO$: 302.1306; found: 302.1306.

### 5-Chloro-7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indole (19)

A magnetically stirred solution of compound **18** (1.15 g, 3.81 mmol) in $CH_2Cl_2$ (35 mL) maintained under air was treated with commercially derived $Ph_3PAuN(Tf)_2$ (28 mg, 0.038 mmol). The ensuing mixture was stirred at r.t. for 2.0 h then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 18:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **19** (1.08 g, 94%) as a white, crystalline solid; mp 147–148 °C.

IR: 3378, 2966, 1431, 1340, 1205, 1132, 919, 885, 750, 498 $cm^{-1}$.

$^1H$ NMR [300 MHz, $(CD_3)_2SO$]: δ = 10.64 (br s, 1 H), 7.30 (s, 1 H), 7.07 (d, *J* = 9.8 Hz, 1 H), 6.11 (m, 1 H), 6.04 (d, *J* = 2.5 Hz, 1 H), 5.81 (d, *J* = 9.8 Hz, 1 H), 5.04 (d, *J* = 2.5 Hz, 1 H), 4.99 (d, *J* = 10.7 Hz, 1 H), 1.43 (s, 6 H), 1.41 (s, 6 H).

$^{13}C\{^1H\}$ NMR [75 MHz, $(CD_3)_2SO$]: δ = 147.2, 146.6, 142.6, 132.0, 130.2, 123.1, 119.5, 118.5, 113.6, 111.9, 106.6, 97.4, 76.7, 38.3, 27.6, 27.4.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}{}^{35}ClNO$: 302.1306; found: 302.1306.

### 5-Chloro-7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indole-3-carbaldehyde (20)

A mixture of compound **19** (1.51 g, 5.0 mmol, 1.0 equiv.), glyoxylic acid monohydrate (1.38 g, 15.0 mmol, 3.0 equiv.), aniline (46 µL, 0.50 mmol, 0.1 equiv.), and $LiClO_4$ (1.06 g, 10.0 mmol, 2.0 equiv.) in DMSO/water (50:1; 100 mL) were added to an undivided cell (250 mL) equipped with a stirring bar. The cell was then fitted with a graphite sheet (3 cm × 3 cm × 0.6 cm) as the anode and a platinum plate (3 cm × 3 cm × 0.01 cm) as the cathode. The anode and the cathode were connected to an AXIOMET AX-3003P DC regulated power supply (see

Figure S1 in the Supporting Information). With the power switched on the mixture was stirred and electrolyzed at a constant current of 12 mA and at r.t. for 38 h. Thereafter the power supply was switched off and the mixture then diluted with brine (100 mL) and water (200 mL) before being extracted with EtOAc (4 × 80 mL). The combined organic phases were washed with water (1 × 80 mL) then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 4:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **20** (1.55 g, 93%) as a white, crystalline solid; mp 225–226 °C.

IR: 3191, 2974, 2926, 1618, 1579, 1443, 1373, 1269, 1192, 1128, 1068, 921, 861, 737, 720, 692 $cm^{-1}$.

$^1H$ NMR [300 MHz, $(CD_3)_2SO$]: δ = 11.13 (br s, 1 H), 10.27 (s, 1 H), 8.00 (s, 1 H), 7.27 (d, *J* = 9.9 Hz, 1 H), 6.32 (m, 1 H), 5.91 (d, *J* = 9.9 Hz, 1 H), 5.23–5.14 (complex m, 2 H), 1.62 (s, 6 H), 1.43 (s, 6 H).

$^{13}C\{^1H\}$ NMR [75 MHz, $(CD_3)_2SO$]: δ = 186.8, 156.7, 146.8, 144.3, 131.2, 130.2, 121.2, 121.0, 118.0, 116.9, 113.3, 112.7, 107.6, 77.2, 40.4, 29.2, 27.6.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}{}^{35}ClNO_2$: 330.1255; found: 330.1264.

**1-((Benzyloxy)methyl)-5-chloro-7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-g]indole-3-carbaldehyde (21)**

A magnetically stirred and chilled (ice-water bath) suspension of NaH (60% dispersion in mineral oil, 300 mg, 7.5 mmol) in DMF (40.0 mL) maintained under a $N_2$ atmosphere was treated, over 0.4 h, with a solution of compound **20** (495 mg, 1.5 mmol) in DMF (120.0 mL). After the evolution of $H_2$ gas had ceased, benzyl chloromethyl ether (840 µL, 6.0 mmol) was added in one portion and the resulting mixture warmed to r.t. After a further 16 h the mixture was quenched with water (100 mL) (***CAUTION***: possibility of $H_2$ gas evolution) and extracted with EtOAc (3 × 40 mL). The combined organic phases were then washed with distilled water (1 × 40 mL) before being dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 15:1 petroleum ether/EtOAc) to afford, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **21** (641 mg, 95%) as a clear, yellow oil.

IR: 2969, 2925, 1643, 1514, 1430, 1360, 1258, 1193, 1118, 1054, 1015, 912, 883, 857, 801, 733, 697, 661, 581 $cm^{-1}$.

$^1H$ NMR [500 MHz, $(CD_3)_2SO$]: δ = 10.54 (s, 1 H), 8.27 (s, 1 H), 7.41–7.34 (complex m, 5 H), 6.94 (d, *J* = 10.0 Hz, 1 H), 6.35 (m, 1 H), 5.87 (d, *J* = 10.0 Hz, 1 H), 5.57 (br s, 2 H), 5.15 (d, *J* = 10.6 Hz, 1 H), 5.08 (d, *J* = 17.5 Hz, 1 H), 4.58 (s, 2 H), 1.71 (s, 6 H), 1.43 (s, 6 H).

$^{13}C\{^1H\}$ NMR [126 MHz, $(CD_3)_2SO$]: δ = 187.3, 153.5, 145.4, 144.2, 135.3, 130.7, 129.8, 127.3, 127.2, 126.9, 120.3, 119.6, 116.6, 116.3, 114.5, 111.0, 106.9, 74.6, 73.0, 67.7, 40.6, 29.1, 25.3.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{29}{}^{35}ClNO_3$: 450.1830; found: 450.1825.

**(*rel*-7a*S*,12a*S*,13a*R*)-15-((Benzyloxy)methyl)-5-chloro-3,3,14,14-tetramethyl-3,7,11,12,1-3,13a,14,15-octahydro-8*H*,10*H*-7a,12a-(epiminomethano)indolizino[6,7-*h*]pyrano-[3,2-*a*]carbazole-8,16-dione [(±)-23] and (*rel*-7a*S*,12a*S*,13a*R*)-15-((Benzyloxy)methyl)-5-chloro-3,3,14,14-tetramethyl-3,7,11,12,13,13a,14,15-octahydro-8*H*,10*H*-7a,12a-(epiminomethano)indolizino[6,7-*h*]pyrano[3,2-*a*]-carbazole-8,16-dione [(±)-24]**

A magnetically stirred solution of compounds **21** (112 mg, 0.25 mmol) and **22** (126 mg, 0.75 mmol) in MeOH (600 µL) contained in a pressure tube was treated with NaOMe (82 mg, 1.5 mmol). Thereafter the tube was sealed then placed in an oil-bath heated to 70 °C. After 48 h the mixture was cooled to r.t., the tube opened, and the contents quenched with sat. aq $NH_4Cl$ solution (3.0 mL) then diluted with EtOAc (15 mL) and water (10 mL). The separated aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic phases were then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was dissolved in THF (22 mL) and the resulting solution cooled to 0 °C then treated with 0.1 M aq HCl solution (7.5 mL). The resulting mixture was stirred at 0 °C for 10 min. then treated with sat. aq $NaHCO_3$ solution (20 mL) before being extracted with EtOAc (3 × 20 mL). The combined organic phases were then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 35:1 $CH_2Cl_2$/MeOH) to afford two fractions, A and B.

Concentration of fraction A ($R_f$ = 0.3) gave compound (±)-**24** (31 mg, 21%) as a yellow, crystalline solid; mp 189–190 °C.

IR: 3241, 2955, 2923, 2853, 1690, 1441, 1406, 1359, 1257, 1192, 1146, 1052, 1023, 751, 699 $cm^{-1}$.

$^1H$ NMR [600 MHz, $(CD_3)_2SO$]: δ = 8.59 (s, 1 H), 7.40 (s, 1 H), 7.40–7.31 (complex m, 5 H), 6.86 (d, *J* = 9.9 Hz, 1 H), 5.78 (d, *J* = 9.9 Hz, 1 H), 5.55 (d, *J* = 10.7 Hz, 1 H), 5.48 (d, *J* = 10.7 Hz, 1 H), 4.65 (d, *J* = 11.4 Hz, 1 H), 4.60 (d, *J* = 11.4 Hz, 1 H), 3.61 (d, *J* = 17.9 Hz, 1 H), 3.44 (m, 1 H), 3.36 (partially obscured m, 1 H), 2.70 (d, *J* = 17.9 Hz, 1 H), 2.54 (partially obscured m, 2 H), 2.20 (m, 1 H), 2.01–1.91 (complex m, 2 H), 1.88–1.80 (complex m, 2 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.29 (s, 3 H).

$^{13}C\{^1H\}$ NMR [151 MHz, $(CD_3)_2SO$]: δ = 172.9, 169.3, 144.8, 141.5, 137.4, 132.8, 130.8, 128.8, 128.7, 128.3, 122.8, 118.5, 118.5, 115.1, 108.4, 106.6, 75.9, 74.7, 69.1, 66.9, 60.2, 47.6, 44.2, 35.8, 32.6, 29.0, 27.6, 27.6, 26.1, 24.4, 22.9, 22.7.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{37}{}^{35}ClN_3O_4$: 586.2467; found: 586.2469.

Concentration of fraction B ($R_f$ = 0.2) gave compound (±)-**23** (103 mg, 70%) as a yellow, crystalline solid; mp 193–194 °C.

IR: 3233, 2955, 2923, 2853, 1691, 1442, 1400, 1359, 1258, 1192, 1147, 1120, 1052, 1026, 751, 698 $cm^{-1}$.

$^1H$ NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.72 (s, 1 H), 7.42–7.27 (complex m, 6 H), 6.86 (d, *J* = 9.9 Hz, 1 H), 5.79 (d, *J* = 9.9 Hz, 1 H), 5.52 (d, *J* = 10.6 Hz, 1 H), 5.47 (d, *J* = 10.6 Hz, 1 H), 4.64 (m, 2 H), 3.38 (partially obscured m, 1 H), 3.29 (partially obscured m, 2 H), 2.62 (d, *J* = 16.1 Hz, 1 H), 2.55 (partially obscured m, 1 H), 2.48 (partially obscured m, 1 H), 2.06 (s, 1 H), 2.05–1.97 (complex m, 2 H), 1.91–1.81 (complex m, 2 H), 1.47 (s, 3 H), 1.37 (s, 3 H), 1.31 (s, 3 H), 1.09 (s, 3 H).

$^{13}C\{^1H\}$ NMR [126 MHz, $(CD_3)_2SO$]: δ = 171.9, 167.0, 143.3, 139.6, 135.8, 131.0, 129.2, 127.2, 127.1, 126.7, 120.8, 116.9, 116.6, 113.5, 106.8, 105.5, 74.3, 73.0, 67.4, 64.9, 57.7, 49.5, 42.4, 34.4, 29.4, 27.4, 26.0, 26.0, 24.4, 22.9, 22.2, 18.9.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{34}H_{36}{}^{35}ClN_3NaO_4$: 608.2287; found: 608.2287.

**(*rel*-7a*S*,12a*S*,13a*R*)-5-Chloro-3,3,14,14-tetramethyl-3,7,11,12,13,-13a,14,15-octahydro-8-*H*,10*H*-7a,12a-(epiminomethano)indolizino[6,7-*h*]pyrano[3,2-*a*]carbazole-8,16-dione [(±)-25]**

A magnetically stirred solution of compound **23** (103 mg, 0.18 mmol) in THF/water (1:1; 6.0 mL) was treated with $HCO_2H$ (6.0 mL). The ensuing mixture was stirred for 4 h at r.t. then quenched with sat. aq $NaHCO_3$ solution (40 mL) before being diluted with water (25 mL) and EtOAc (20 mL). The separated aqueous layer was extracted with EtOAc (3 × 40 mL) and the combined organic phases were then washed with water (1 × 25 mL) and brine (1 × 25 mL) before being dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give compound (±)-**25** (82 mg, quant.) as a white, crystalline solid; mp 283–284 °C.

IR: 3303, 2947, 2835, 1664, 1449, 1410, 1016, 586 $cm^{-1}$.

$^1H$ NMR [500 MHz, $(CD_3)_2SO$]: δ = 10.61 (s, 1 H), 8.71 (s, 1 H), 7.25 (s, 1 H), 6.97 (d, *J* = 9.8 Hz, 1 H), 5.84 (d, *J* = 9.8 Hz, 1 H), 3.36 (partially obscured m, 1 H), 3.31 (partially obscured m, 1 H), 3.26 (m, 1 H), 2.62 (d, *J* = 15.7 Hz, 1 H), 2.54 (partially obscured m, 1 H), 2.44 (m, 1 H), 2.06 (m, 1 H), 1.99 (m, 2 H), 1.87–1.81 (complex m, 2 H), 1.42(4) (s, 3 H), 1.42(1) (s, 3 H), 1.30 (s, 3 H), 1.01 (s, 3 H).

$^{13}C\{^1H\}$ NMR [126 MHz, $(CD_3)_2SO$]: δ = 173.0, 168.3, 142.4, 141.0, 131.4, 130.0, 121.5, 117.8, 117.2, 112.8, 106.3, 103.6, 76.3, 66.0, 59.5, 49.0, 43.5, 34.6, 30.0, 28.6, 27.9, 27.0, 26.9, 24.0, 23.6, 21.5.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{29}{}^{35}ClN_3O_3$: 466.1892; found: 466.1892.

**(*rel*-7a*S*,12a*S*,13a*R*)-5-Chloro-3,3,14,14-tetramethyl-3,7,11,12,13,-13a,14,15-octahydro-8-*H*,10*H*-7a,12a-(epiminomethano)indolizino[6,7-*h*]pyrano[3,2-*a*]carbazole-8,16-dione [(±)-26]**

A magnetically stirred solution of compound **24** (31 mg, 0.05 mmol, 1.0 equiv.) in THF/water (1:1; 1.8 mL) was treated with $HCO_2H$ (1.8 mL). The ensuing mixture was then stirred for 4 h at r.t. before being quenched with sat. aq $NaHCO_3$ solution (8.0 mL) then diluted with water (8.0 mL) and EtOAc (6.0 mL). The separated aqueous layer was extracted with EtOAc (3 × 7 mL) and the combined organic phases were then washed with water (1 × 7 mL) and brine (1 × 7 mL) before being dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give compound (±)-**26** (24 mg, quant.) as a white, crystalline solid; mp 230–231 °C.

IR: 3251, 2955, 2918, 2850, 1667, 1462, 1406, 1377, 1297, 1263, 1188, 1159, 1124, 1024, 996, 818, 727, 642 $cm^{-1}$.

$^1H$ NMR [500 MHz, $(CD_3)_2SO$]: δ = 10.62 (s, 1 H), 8.55 (s, 1 H), 7.31 (s, 1 H), 7.01 (d, *J* = 9.8 Hz, 1 H), 5.85 (d, *J* = 9.8 Hz, 1 H), 3.58 (d, *J* = 17.6 Hz, 1 H), 3.43 (m, 1 H), 3.38 (partially obscured m, 1 H), 2.72 (d, *J* = 17.6 Hz, 1 H), 2.55 (partially obscured m, 1 H), 2.14 (complex m, 2 H), 2.00 (m, 1 H), 1.93–1.79 (complex m, 3 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.31 (s, 3 H), 1.20 (s, 3 H).

$^{13}C\{^1H\}$ NMR [126 MHz, $(CD_3)_2SO$]: δ = 172.4, 168.9, 142.3, 141.1, 131.4, 130.0, 122.0, 117.9, 117.4, 112.8, 106.3, 102.9, 76.2, 66.4, 60.4, 45.5, 43.6, 34.3, 31.6, 28.5, 27.7, 27.0, 26.9, 23.9, 23.8, 22.4.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{29}{}^{35}ClN_3O_3$: 466.1892; found: 466.1903.

**(*rel*-3*R*,5a′*S*,8a′*S*,9a′*S*)-5-Chloro-7,7,8′,8′-tetramethyl-1,2′,3′,7,8a′,9′-hexahydro-1′*H*,2*H*,5′*H*,6′*H*,8′*H*-spiro[pyrano[2,3-g]indole-3,7′-[5a,9a](epiminomethano)cyclopenta[*f*]indolizine]-2,5′,10′-trione [(±)-Notoamide N, (±)-6]**

A magnetically stirred solution of compound (±)-**25** (9 mg, 0.02 mmol) in anhydrous THF (2.0 mL) maintained at r.t. was treated with *m*-CPBA (12 mg of 85% material, 0.06 mmol). After 6 h the mixture was diluted with brine (15 mL), extracted with EtOAc (3 × 25 mL) and the combined organic phases then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 30:1 $CH_2Cl_2$/MeOH) to afford, after concentration of the appropriate fractions ($R_f$ = 0.2), compound (±)-**6** (9 mg, 97%) as a white, crystalline solid.

IR: 2954, 2918, 2850, 1725, 1459, 1376, 1260, 1089, 1019, 858, 799, 730, 496 $cm^{-1}$.

$^1H$ NMR [500 MHz, $(CD_3)_2CO$]: δ = 9.62 (s, 1 H), 8.06 (s, 1 H), 7.20 (s, 1 H), 6.67 (d, *J* = 10.0 Hz, 1 H), 5.86 (d, *J* = 10.0 Hz, 1 H), 3.54–3.44 (complex m, 2 H), 3.31 (m, 1 H), 3.02 (d, *J* = 14.3 Hz, 1 H), 2.67 (m, 1 H), 2.27 (d, *J* = 14.3 Hz, 1 H), 2.08 (partially obscured m, 1 H), 2.03 (partially obscured m, 1 H), 1.93 (m, 1 H), 1.88–1.83 (complex m, 2 H), 1.47 (s, 3 H), 1.46 (s, 3 H), 0.85 (s, 3 H), 0.84 (s, 3 H).

$^{13}C\{^1H\}$ NMR [126 MHz, $(CD_3)_2CO$]: δ = 182.4, 172.9, 169.3, 148.0, 137.0, 130.8, 126.5, 123.4, 116.2, 113.0, 105.9, 77.0, 68.2, 66.0, 61.4, 55.7, 45.4, 43.2, 33.9, 29.8, 29.3, 27.0, 26.9, 24.3, 22.9, 19.3.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{29}ClN_3O_4$: 482.1841; found: 482.1840.

### Crystallographic Data

Compound **11**. $C_{10}H_{10}ClNO_3S$, *M* = 259.70, *T* = 293 K, monoclinic space group $P2_1/c$, *Z* = 4, *a* = 11.1035(6), *b* = 9.8882(4), *c* = 11.6417(6) Å; β = 117.215(7)°; *V* = 1136.69(12) $Å^3$, $D_x$ = 1.518 g $cm^{-3}$, 2229 unique data ($2\Theta_{max}$ = 147.492°), *R* = 0.0665 [for 2006 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.1763 (all data), *S* = 1.036.

Compound **13**. $C_{11}H_{10}ClNO_2$, *M* = 223.65, *T* = 170 K, monoclinic space group *C*2/*c*, *Z* = 8, *a* = 28.4840(19), *b* = 4.8275(3), *c* = 14.9420(11) Å; β = 102.946(7)°; *V* = 2002.4(2) $Å^3$, $D_x$ = 1.484 g $cm^{-3}$, 1937 unique data ($2\Theta_{max}$ = 146.2°), *R* = 0.064 [for 1453 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.175 (all data), *S* = 1.03.

Compound **18**. $C_{18}H_{20}ClNO$ (+ solvent), *M* = 301.80, *T* = 170 K, monoclinic space group *I*2/*a*, *Z* = 8, *a* = 12.3419(2), *b* = 12.3388(3), *c* = 25.1214(5) Å; β = 95.716(2)°; *V* = 3806.57(14) $Å^3$, $D_x$ = 1.053 g $cm^{-3}$, 3715 unique data ($2\Theta_{max}$ = 147.6°), *R* = 0.0594 [for 3369 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.1620 (all data), *S* = 1.088.

### Structure Determinations

Images for compounds **11**, **13**, and **18** were measured on a Rigaku Super Nova X-ray diffractometer (CuKα, graphite monochromator, λ = 1.54184 Å). Using OLEX2,[15] the structures were solved by intrinsic phasing with the ShelXT[16] program and refined, using least squares minimization, with the ShelXL[17] package.[18]

## Conflict of Interest

The authors declare no conflict of interest.

## Funding Information

This work was funded by the National Natural Science Foundation of China (Grant Nos. 22250410259, 22250410258, and 22301104), the Guangdong Science and Technology Plan-International Cooperation Topic Program (Grant No. 2023A0505050093) and the Ministry of Science and Technology of the People's Republic of China.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0043-1773504. Included are an outline of the general synthetic protocols employed in this study, plots arising from the single-crystal X-ray analysis of compounds **11**, **13**, and **18**; tabular comparison of the $^{13}C\{^1H\}$ NMR spectral data obtained on synthetically derived compound **6** with those reported in the literature for notoamide N; $^1H$ and $^{13}C\{^1H\}$ NMR spectra of compounds **6** and **9**–**26**.

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