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Convolutamydine A: the first authenticated absolute configuration and enantioselective synthesis

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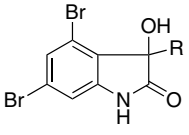
Abstract—The absolute configuration of (+)-convolutamydine A **1** isolated from *Amathia convoluta* has been unambiguously established as (*R*) by enantioselective synthesis, based on chiral auxiliary-directed π-face discrimination in an allyl metal addition to (1*R*,2*S*,5*R*)-8-phenylmenthyl ester **7**. For an independent and unequivocal proof, the absolute stereochemistry of synthetic precursor **11** en route to **1** was determined by X-ray crystallography.

1. Introduction

The rapidly growing domain of natural products isolated from marine organisms has caused widespread interest because of their intriguing structural features and bioactivities.[1] Recently, a number of oxindole alkaloids, for example, convolutamydines A–E **1**–**5** along with some distantly related metabolites (e.g., bryostatins), have been isolated by Pettit from the bryozoan *Amathia convoluta* Lamarck, collected off the Northeastern Gulf of Mexico (Fig. 1).[2,3]

These compounds share an unprecedented structural feature, viz. the 4,6-dibromo-3-hydroxyindoline motif that bears a quaternary stereocentre at C-3. Interestingly, convolutamydine A **1**, one of the simplest members of the oxindole subfamily, exhibited a potent inhibitory activity on the differentiation of HL-60 human promyelocytic leukaemia cells @ 12.5–25 μg/mL. Its structure was deduced from spectroscopic data and confirmed by synthesis, although its absolute configuration remained unknown. The discovery of this unique structure has spurred the development of several synthetic routes, recently crowned by the synthesis of (±)-convolutamydines A and C **1** and **3**, respectively, via Rh(II)-promoted cyclization of diazoamides,[4] Claisen rearrangement of 2-allyloxy indolin-3-ones[5] and aldol condensation of 4,6-dibromoisatin with acetone.[6] Within this context, Tomasini et al. recently reported an interesting dipeptide-catalyzed enantioselective aldol reaction with isatins.[7] While the present manuscript was in preparation, Kobayashi reported the first enantioselective synthesis of convolutamydines B and E (**2** and **5**, respectively) via a vinylogous Mukaiyama aldol reaction; the absolute configuration of natural compound **2** was assigned as (*R*) by its chiroptical properties.[8] Previously, Aimi[9] had tried to predict the absolute configuration of convolutamydines A–D **1**–**4** by comparing their CD spectra in the 225–250 nm range with the corresponding CD spectra of 3(*R*)–3-hydroxy-L-tryptophan. Because the absolute configurations of convolutamydines have been inferred by empirical CD methods, the need was felt for an independent, unequivocal verification of these assignments.



1	R = CH_2COCH_3	(A)
2	R = CH_2CH_2Cl	(B)
3	R = CH_3	(C)
4	R = $CH{=}CH_2$	(D)
5	R = CH_2CH_2OH	(E)

Figure 1.

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Herein, we report the first enantioselective synthesis of (+)-convolutamydine A **1** and the X-ray diffraction analysis of a strictly related compound, thus providing unambiguous proof of the previous configurational assignment.

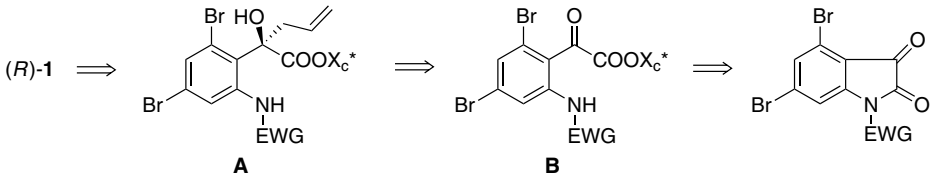
2. Results and discussion

Our approach to the synthesis of (+)-**1** involved enantiocontrolled access to alcohol A, which was to be unmasked and oxidized (Wacker) (Scheme 1). The homoallylic alcohol functionality (viz. the latent 2-oxopropyl moiety in **1**) was to be installed in **A** by the addition to **B** of an allyl anion after ring opening of an *N*-EWG-substituted 4,6-dibromoisatin **C** in the presence of an enantiopure alcohol as a chiral auxiliary. For the sake of expediency, we opted for *N*-BOC-4,6-dibromoisatin **6**[10] as the starting material; (−)-(1*R*,2*S*,5*R*)-8-phenylmenthol was chosen with the intent of favourably influencing the chiral-auxiliary-directed π-face discrimination in the subsequent addition step (see Scheme 2).[11]

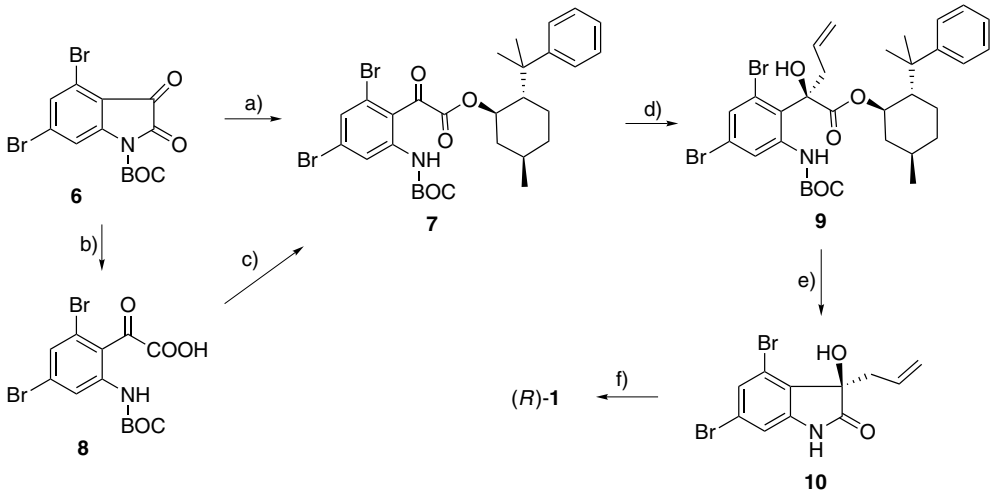
Our initial efforts on the preparation of isatinic ester **7** from **6** proved less straightforward than expected. The use of coupling reagents proved critical for achieving esterification with (−)-8-phenylmenthol of isatinic acid **8**, obtained by hydrolysis of **6** with LiOH in THF–MeOH–H_2O, 3:1:1 [rt, 1 h, followed by acidification with AcOH]. After an extensive screening of coupling conditions, we found that 8-phenylmenthyl chloroformate[12] (1.1 equiv) in the presence of DMAP (0.22 equiv) in MeCN at 40 °C for 3 h could achieve conversion of **8** to **7**[10,13] (through the intermediacy of a mixed carboxylic-carbonic anhydride),[14] albeit in modest yields (22%).[15]

As the esterification approach did not appear viable, we turned to the regioselective base-catalyzed ring opening ($B_{AC}2$ mechanism) of *N*-BOC protected lactams (e.g., isatins[16] and pyroglutamates[17]) successfully employed by several authors, and decided to react **6**[18] per se with (−)-8-phenylmenthol according to the protocol developed by Schoenfelder and Mann.[19]

In our initial experiments, we added tetrabutylammonium cyanide or KCN, together with the chiral auxiliary, to a solution of **6** in dry THF at room temperature (24 h). Under these conditions, we detected the formation of **7**, but the yield was less than 10%. The use of other bases (e.g., K_2CO_3, K_3PO_4 and Cs_2CO_3[20]) as catalysts for the ring opening reaction did not significantly improve yields. These results were attributed to the poor nucleophilicity of the hydroxyl group in the chiral auxiliary. Accordingly, we resorted to using the preformed alkoxide of (−)-8-phenylmenthol as nucleophile. After screening many combinations of bases [*n*-BuLi, NaH/15-crown-5, potassium bis(trimethylsilyl)amide (KHMDS), *t*-BuOK, CsOH, phosphazene base (BEMP)[21]] and solvents, we found that the most successful procedure was the formation of potas-



Scheme 1.



Scheme 2. Reagents and conditions: (a) (−)-8-phenylmenthol, KH, 18-crown-6, THF, rt; (b) LiOH, THF–MeOH–H_2O, rt; then AcOH; (c) (−)-8-phenylmenthyl chloroformate, MeCN, DMAP, 40 °C; (d) In, allyl bromide, KI, DMF, rt; (e) TFA, CH_2Cl_2, rt or 6 M HCl, DME, reflux; (f) O_2, $CuCl_2$, $PdCl_2$ (cat.), MeCN–H_2O, 40 °C.

sium (−)-8-phenylmenthoxide with KH in THF.[22] Gratifyingly, isatinic ester **7** was obtained in 65% yield by treating (−)-8-phenylmenthol with a suspension of oil-free KH (2.1 equiv) in the presence of 18-crown-6 (5 mol %), and subsequently adding the resulting product to a 0.2 M solution of **6** (1.1 equiv) in THF at rt. The desired functionalization of ester **7** was then achieved by a carbonyl allylation reaction. Several methods currently exist to obtain homoallylic alcohols by allylmetal addition reactions to a carbonyl group.[23] We opted for indium-mediated allylation because the procedure is simple, the reaction conditions are mild, the product yields were high and the metal to be employed was not toxic.[24] Thus, the reaction in DMF of **7** with $(allyl)_3In_2Br_3$ [generated in situ by In metal (99.99%, 100 mesh, 2 equiv) and allyl bromide(3 equiv)] in the presence of KI (3.1 equiv) at rt for 45 min, followed by quenching with aq NH_4Cl, afforded alcohol **9**[10] (55% yield) essentially as a single diastereomer, as indicated by its clean ^1H and ^{13}C NMR spectra.[10] At this stage, we were unable to assign the configuration at C(3) from the NMR data, while attempts to obtain suitable crystals for X-ray analysis proved fruitless. The amino functionality release required for γ-lactam formation with concomitant detachment of the chiral inductor was achieved [TFA (5 equiv), CH_2Cl_2, rt, 12 h or 6 M HCl, DME, reflux, 5 h[25]] to provide **10**[10] in nearly quantitative yield and >95% ee (by chiral-HPLC[26]). In particular, this procedure allowed a 95% recovery of pure (−)-8-phenylmenthol (97% ee), which could be reused offsetting the expense met in employing it. Enantiopure **10** exhibited a CD spectrum (MeOH) with a negative Cotton effect (CE) in the long-wave region (285–245 nm, due to $^1L_a/^1L_b$ transitions) and a positive CE in the short-wave region (245–210 nm, due to ^1B_b transitions); according to Aimi's estimation, this would unequivocally prove the *R* configuration.

As we also wished to evaluate the reactivity and diastereofacial selection capability for other commercially available chiral auxiliaries [viz., (1*S*,2*R*,5*S*)-(+)-menthol, (1*S*)-*endo*-(−)-borneol, (1*R*,2*S*)-*trans*-(−)-2-phenyl-1-cyclohexanol and (1*S*,2*S*,3*S*,5*R*)–(+)-isopinocampheol], we studied the allylindation of the corresponding α-oxo esters carried out in a similar way as the one just described. In all cases the homoallylic alcohols were not isolated, but directly converted to the γ-lactam **10**. Overall yields (from **6**) fell in the 35–56% range but selectivities were insignificant (ee in the 4–26% range, by chiral HPLC).

Finally, in order to convert the allyl group in **10** to the 2-oxopropyl group, a Wacker reaction under ligandless aerobic conditions was employed using $CuCl_2$ as a co-catalyst. Thus, treatment of **10** (>95% ee) with $PdCl_2$ (0.2 equiv) and $CuCl_2$ (3 equiv) in MeCN–H_2O 3:1 in an oxygen atmosphere (balloon) (40 °C, 4 h) afforded virtually enantiopure (+)-convolutamydine **1**[10] (68% yield; >98% ee by chiral HPLC[26]). Apart from the discrepancy between $[\alpha]_D^{26} = +27.4$ (*c* 0.06, MeOH)[2a] and our specific rotation for (+)-**1**, $[\alpha]_D^{20} = +48.2$ (*c* 0.20, MeOH), ^1H, ^{13}C NMR and CD spectra [negative CE (285-245 nm), positive CE (245–210)] exactly matched those of the natural product, leading us to assign the (*R*)-configuration to natural (+)-convolutamydine.

However, as crystallographic evidence was lacking for the absolute configuration of (+)-convolutamydine, we decided to fill the gap by preparing crystalline derivatives. The racemic lactam **10**[27] proved to be particularly suitable for resolution by diastereomer formation with a resolving agent.[28] From the chemical and configurational points of view, this convolutamydine precursor was completely stable in the conditions that were required for introducing and cleaving off a chiral resolving agent (Fig. 2).

The resolving agent of choice was (*S*)–*O*-methyl mandelic acid which, by coupling with *rac*-**10** (DCC, DMAP, MeCN, rt), gave esters **11**[10] and **12**[10] in 64% yield. These were easily separated by standard silica flash chromatography (separation factor α of 1.45 ± 0.05). The high-R_f diastereomer **11** was crystalline, and its single-crystal X-ray study unequivocally established the absolute configuration at C-3 as (*S*) (Fig. 3).[29] Interestingly, the (*S*)-*O*-methyl mandelate subunit was used as an internal standard for the X-ray determination of absolute configuration; moreover **11**, containing two heavy atoms (Br), made it possible to assess the absolute configuration by the Bijvoet method. Thus, the absolute configuration of **11** was determined independently by two crystallographic methods.

The CD spectrum of convolutamydine derived from the high-R_f crystalline diastereomer **11** [by hydrolysis (LiOH, THF–H_2O 2:1, 0 °C, 1 h), followed by Wacker oxidation (vide supra)] was roughly enantiomeric [positive CE (285–245 nm), negative CE (245–210 nm)] to that of the natural product. By the sequence of reactions detailed above, the low-R_f amorphous diastereomer **12** was converted to a convolutamydine whose CD spectrum matched that reported by Pettit.

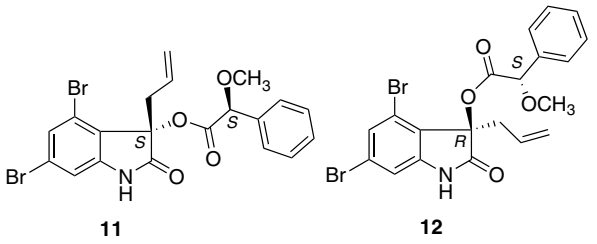


Figure 2.

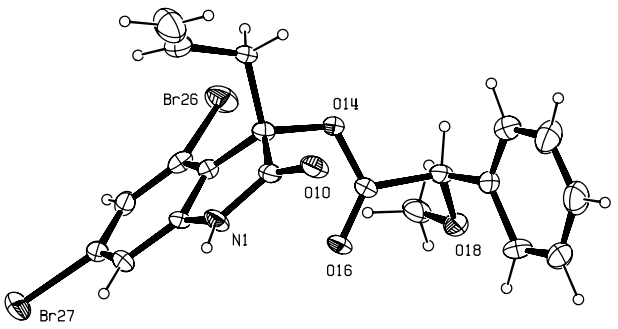


Figure 3.

3. Conclusion

In conclusion, with the present results we achieved the first enantioselective synthesis of natural convolutamydine A **1**, and established beyond any doubt that (+)-**1** has an (*R*)-configuration.

Acknowledgement

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10. *Analytical data*. Compound **6**, mp 128–131 °C (CH_2Cl_2), R_f 0.75 (hexane/*t*-BuOMe, 3:2), ^{1}H NMR (400 MHz, $CDCl_3$) 8.36 (1H, d, $J = 1.5$), 7.64 (1H, d, $J = 1.5$), 1.65 (9H, s), ^{13}C NMR (100 MHz, $CDCl_3$) 177.2 (C), 154.5 (C), 150.3 (C), 148.3 (C), 134.1 (C), 133.2 (CH), 122.3 (C) 119.6 (CH), 116.7 (C), 28.4 (CH_3). Compound **7**, mp 88–91 °C (hexane–CH_2Cl_2), R_f 0.76 (hexane/*t*-BuOMe, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) 8.49 (1H, d, $J = 1.8$), 8.09 (1H, br s), 7.44 (1H, d, $J = 1.8$), 7.18 (2H, dd, $J = 8.7, 4.3$), 4.99 (1H, dt; $J = 10.8, 4.4$), 2.18 (2H, m), 1.54 (9H, s), 1.42 (3H, s), 1.28 (3H, s), 0.91 (3H, d, $J = 7.0$); ^{13}C NMR (100 MHz, $CDCl_3$) 188.3 (C), 160.7 (C), 152.2 (C), 150.6 (C), 141.6 (C), 129.7 (CH), 128.4 (CH), 128.4 (CH), 126.0 (CH), 125.9 (CH), 122.8 (C), 122.6 (C), 122.6 (C), 82.5 (C), 79.1 (CH), 54.6 (CH), 40.8 (CH_2), 40.4 (C), 35.3 (CH_2), 31.9 (CH), 28.4 (CH_3), 27.5 (CH_2), 24.5 (CH_3), 22.4 (CH_3). Compound **9**, colourless thick oil, R_f 0.62 (hexane/*t*-BuOMe, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 8.95 (1H, br s), 8.41 (1H, d, $J = 2$), 7.32 (1H, d, $J = 2$), 7.26 (6H, m), 5.11 (1H, d, $J = 16$), 5.10 (1H, d, $J = 11$), 4.82 (1H, dd, $J = 11, 4$), 3.02 (1H, dd, $J = 14, 6$), 2.87 (1H, dd, $J = 14, 8$), 1.59 (9H, s), 1.09 (3H, s), 0.93 (3H, d, $J = 7$), 0.88 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6) 172.0 (CO), 152.9 (CO), 147.1 (C), 138.2 (C), 130.0 (CH), 128.2 (C), 128.0 (CH), 125.4 (CH), 125.2 (CH), 123.0 (C), 121.0 (CH_2), 119.1 (CH), 116.5 (C), 80.0 (C), 78.5 (CH), 78.0 (C), 50.5 (CH), 43.0 (CH_2), 39.4 (C) 38.7 (CH_2), 34.5 (CH_2), 30.6 (CH), 28.7 (CH_3), 27.6 (CH_2), 27.5 (CH_3), 25.6 (CH_3), 22.2 (CH_3). Compound **10**, mp 221–223 °C (MeOH); R_f 0.11 (hexane/*t*-BuOMe, 3:2); ^{1}H NMR (400 MHz, DMSO-d_6) 10.62 (1H, br s), 7.35 (1H, d, $J = 1.5$), 6.93 (1H, d, $J = 1.5$), 5.20 (1H, m), 4.97 (1H, dd, $J = 17, 2$), 4.90 (1H, dd, $J = 10, 2$), 3.02 (1H, dd, $J = 13, 7.5$), 2.55 (1H, dd, $J = 13, 7.5$); ^{13}C NMR (100 MHz, DMSO-d_6) 178.6 (C), 146.2 (C), 131.5 (CH), 129.1 (C), 128.0 (CH), 123.2 (C), 120.5 (C), 120.3 (CH_2), 112.7 (CH), 77.8 (C), 41.0 (CH_2). Compound **11**, mp 192 °C (dec) (CH_2Cl_2/hexane); R_f 0.36 (PE/AcOEt, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.61 (1H, br s), ca. 7.50 (5H, m), 7.27 (1H, d, $J = 1.5$), 6.93 (1H, d, $J = 1.5$), 5.31 (1H, ddt, $J = 17.1, 9.8, 7.2$), 5.08 (1H, $J = 17.1, 1.8, 1.1$), 4.99 (1H, $J = 9.8, 1.8, 1.1$); 4.86 (1H, s), 3.33 (3H, s), 3.19 (1H, dd, $J = 13.2, 7.2$), 2.78 (1H, dd, $J = 13.2, 7.2$). Compound **12**, colourless glass, R_f 0.25 (PE/AcOEt, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.66 (1H, br s), 7.45–7.30 (5H, m), 7.16 (1H, d, $J = 1.5$), 6.92 (1H, d, $J = 1.5$), 5.30 (1H, ddt, $J = 17.1, 9.9, 7.2$), 5.08 (1H, $J = 17.1, 1.8, 1.1$), 5.00 (1H, $J = 9.8, 1.8, 1.1$); 4.86 (1H, s), 3.42 (3H, s), 3.15 (1H, dd, $J = 13.2, 7.2$), 2.78 (1H, dd, $J = 13.2, 7.2$). ^{13}C NMR (100 MHz, $CDCl_3$) 174.2 (C), 169.0 (C), 143.6 (C), 135.4 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.6 (CH), 123.9 (C), 121.3 (C), 118.4 (CH_2), 112.8 (CH), 81.7 (CH), 80.8 (C), 57.5 (CH_3), 37.3 (CH_2).
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29. Crystal data for compound **11**: ($C_{20}H_{17}Br_2NO_4$) $M = 495.17$, monoclinic, $P2_1$, $a = 9.814(2)$, $b = 8.629(2)$, $c = 12.602(3)$ Å, $\beta = 110.62(3)°$, $V = 998.8(4)$ Å^3, $Z = 2$, $D_c = 1.646$ g cm^{-3}, $\mu(\text{Mo K}\alpha) = 4.083$ cm^{-1}, $F(000) = 492$; $T = 295(2)$ K; elongated prism, $0.36 \times 0.26 \times 0.16$ mm, Bruker P4 diffractometer; 4548 data collected, 3854 unique, $R_{\text{int}} = 0.0155$, 3134 with $I > \sigma(I)$. Absorption corrections by ψ-scan (Ref. 30), $T_{\min} = 0.369$, $T_{\max} = 0.694$. The structure was solved by direct method (Ref. 31) and refined anisotropically by matrix least-squares based on F^2 (Ref. 32) (to give $R_1 = 0.0543$, $wR_2 = 0.1242$) for 3134 observed reflections and 245 parameters. Supplementary crystallographic data were deposited as CCDC 622273 with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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