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Synthesis of Inducamides A and B

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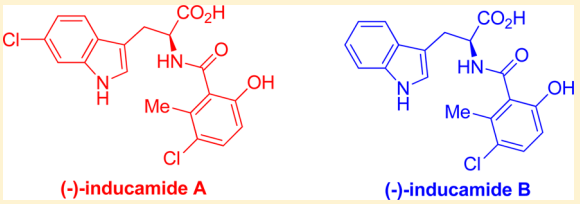
Supporting Information

ABSTRACT: The inducamides are a family of chlorinated alkaloids featuring an amide arising from union of an L-tryptophan to a rare chlorosalicylic acid unit, the production of which is linked to a chemically induced mutation in the RNA polymerase of *Streptomyces* sp. (SNC-109-M3). The synthesis of inducamides A and B has been accomplished by the coupling of 6-hydroxy-3-chloro-2-methylbenzoic acid with L-6-chlorotryptophan and L-tryptophan, respectively, followed by ester hydrolysis. The spectroscopic data and optical rotation for each synthetic sample confirm the structures of these silent secondary metabolites and their biosynthesis from L-tryptophan.



The introduction of mutations into the ribosome or RNA polymerase of actinomycetes can be used to activate biosynthetic pathways that trigger the production of silent secondary metabolites.[1] A pertinent example is inducamides A–C (**1**–**3**, Figure 1), chlorinated alkaloids recently isolated from the RNA polymerase (RNAP) mutant strain of *Streptomyces* sp. named SNC-109-M3.[2] The natural products **1**–**3** are assembled by the acylation of an L-tryptophan unit with 6-hydroxy-3-chloro-2-methylbenzoic acid (**4**), followed by lactonization in the case of inducamide C (**3**). As these natural products are produced only by the mutant strains, it is likely that the RNAP mutation triggers the chlorosalicylic acid production, and interestingly, the arene **4** is also present in the spirotetronate antibiotic chlorothricin.[4]

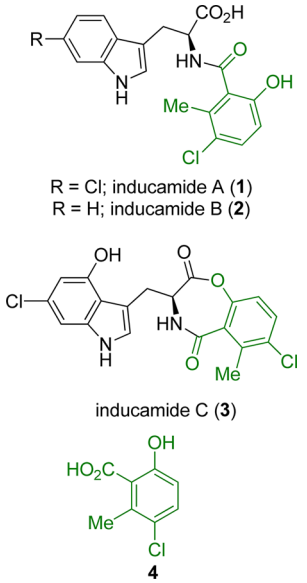
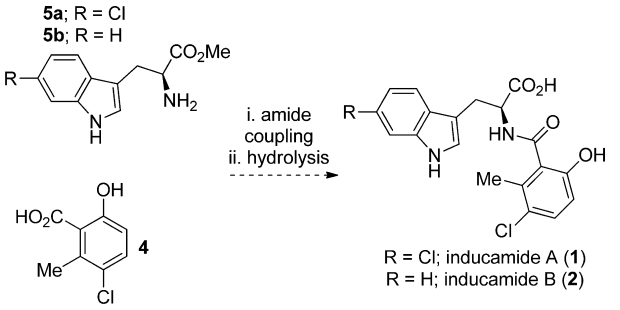


Figure 1. Inducamides A–C (**1**–**3**) and 6-hydroxy-3-chloro-2-methylbenzoic acid (**4**).

An ongoing interest in the synthesis of halogenated alkaloids[3] and the unique framework present in the inducamides led us to pursue their synthesis, initially targeting inducamides A and B (**1** and **2**) by the coupling of 6-hydroxy-3-chloro-2-methylbenzoic acid (**4**) with the tryptophan methyl esters **5a** and **5b**, respectively, followed by ester hydrolysis (Scheme 1).

Scheme 1. Proposed Assembly of Inducamides A and B (1 and 2)



RESULTS AND DISCUSSION

Using a literature chlorination of a related substrate as a guide,[5,6] the chlorination of the known arene **6**[7] with NCS proceeded with the desired regioselectivity to give **7**, confirmed by NOE analysis and the splitting of the two aromatic protons (J 8.9 Hz) (Scheme 2). Demethylation of **7** gave **8**, which upon ester hydrolysis delivered the desired salicylic acid **4**.

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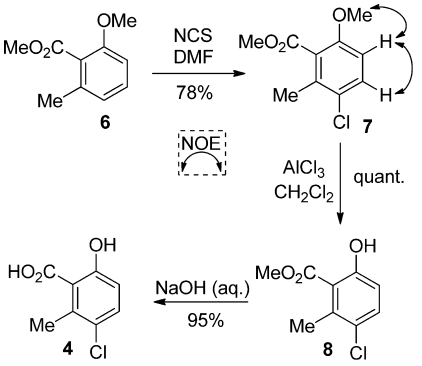
Scheme 2. Synthesis of 6-Hydroxy-3-chloro-2-methylbenzoic Acid (4)



The synthesis of inducamide A (**1**) commenced with subjecting the known 6-aminotryptophan **9**[8] to a Sandmeyer reaction to give **10**[9] in 32% yield, accompanied by significant amounts of dechlorination. Removal of both Boc groups from **10** gave 6-chlorotryptophan methyl ester **5a**[10,11] (Scheme 3). Coupling of **5a** with **4** gave amide **11**, which upon ester hydrolysis gave inducamide A (−)-**1**. Employing L-tryptophan methyl ester **5b** in the same coupling−hydrolysis sequence delivered inducamide B (−)-**2** via amide **12**.[12,13] The NMR spectroscopic data of synthetic **1** and **2** were in excellent agreement with those reported for the natural products (Table 1). The optical rotation of synthetic inducamide A (**1**) correlated well with that of the natural product {$[\alpha]_D^{24}$ −12.0 (*c* 0.10, MeOH); lit.[2] $[\alpha]_D^{24}$ −18.0 (*c* 0.10, MeOH)}, whereas the optical rotation of synthetic inducamide B (**2**) was in near perfect agreement {$[\alpha]_D^{22}$ −9.5 (*c* 0.10, MeOH; lit.[2] $[\alpha]_D^{24}$ −10.0 (*c* 0.05, MeOH)}.

In summary, the synthesis of inducamides A (−)-**1** and B (−)-**2** has been achieved, confirming both the structure of these silent secondary metabolites and their biosynthesis from L-tryptophan. Synthetic studies toward the unusual 4-hydroxy-6-chlorotryptophan[14] present in inducamide C (and the alkaloid itself) are in progress.

EXPERIMENTAL SECTION

Methyl 3-Chloro-6-methoxy-2-methylbenzoate (7). To a stirred solution of methyl 2-methoxy-6-methylbenzoate (**6**)[7] (67 mg, 0.37 mmol) in *N,N,*-dimethylformamide (1 mL) was added *N*-chlorosuccinimide (60 mg, 0.45 mmol). After stirring for 3 days at room temperature, the solution was diluted with ether (10 mL) and washed with water (10 mL). The aqueous layer was then further extracted with ether (2 × 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel eluting with hexanes−toluene (1:9) to afford the title compound (62 mg, 0.29 mmol, 78%) as a pale yellow oil: HRMS found $[M + Na]^+$ 237.0291, $[C_{10}H_{11}{}^{35}ClO_3 + Na]^+$ requires 185.0011; IR (neat) 2953, 1733, 1436, 1289, 1262, 1084, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (1 H, d, *J* 8.9, ArH), 6.71 (1 H, d, *J* 8.9, ArH), 3.91 (3 H, s, Me), 3.80 (3 H, s, Me), 2.28 (3 H, s, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1 (C═O), 155.0 (C), 134.1 (C), 130.7 (CH), 126.6 (C), 125.6 (C), 109.9 (CH), 56.2 (Me), 52.6 (Me), 17.3 (Me).

Methyl 3-Chloro-6-hydroxy-2-methylbenzoate (8). To a solution of **7** (84 mg, 0.39 mmol) in dichloromethane (4 mL) was added aluminum trichloride (209 mg, 1.57 mmol), and the resulting solution heated to reflux for 12 h. The reaction mixture was quenched with 1 M HCl (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with hexanes−ethyl acetate (4:1) to afford the title compound (79 mg, 0.39 mmol, 100%) as a light brown solid: mp 25−30 °C; HRMS found $[M + Na]^+$ 223.0132, $[C_9H_9{}^{35}ClO_3 + Na]^+$ requires 223.0139; IR (neat) 2954, 2925, 2854, 1665, 1439, 1211, 824, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.84 (1 H, s, OH), 7.40 (1 H, d, *J* 8.9, ArH), 6.81 (1 H, d, *J* 8.9, ArH), 3.98 (3 H, s, Me), 2.59 (3 H, s, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C═O), 160.8 (C), 137.8 (C), 135.1 (CH), 126.1 (C), 116.7 (CH), 114.3 (C), 52.6 (Me), 19.6 (Me).

3-Chloro-6-hydroxy-2-methylbenzoic Acid (4). A solution of **8** (80 mg, 0.40 mmol) in aqueous sodium hydroxide (1.4 M, 3.8 mL, 5.2 mmol) was heated to reflux for 2 h. After cooling to room temperature, the reaction mixture was washed with ethyl acetate (10 mL), and the organic layer discarded. The remaining aqueous solution was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the title compound (71 mg, 0.38 mmol, 95%), as a colorless solid: mp 154−157 °C; HRMS found $[M - H]^-$ 185.0018, $[C_8H_7{}^{35}ClO_3 - H]^-$ requires 185.0011; IR

Scheme 3. Synthesis of Inducamides A (−)-1 and B (−)-2

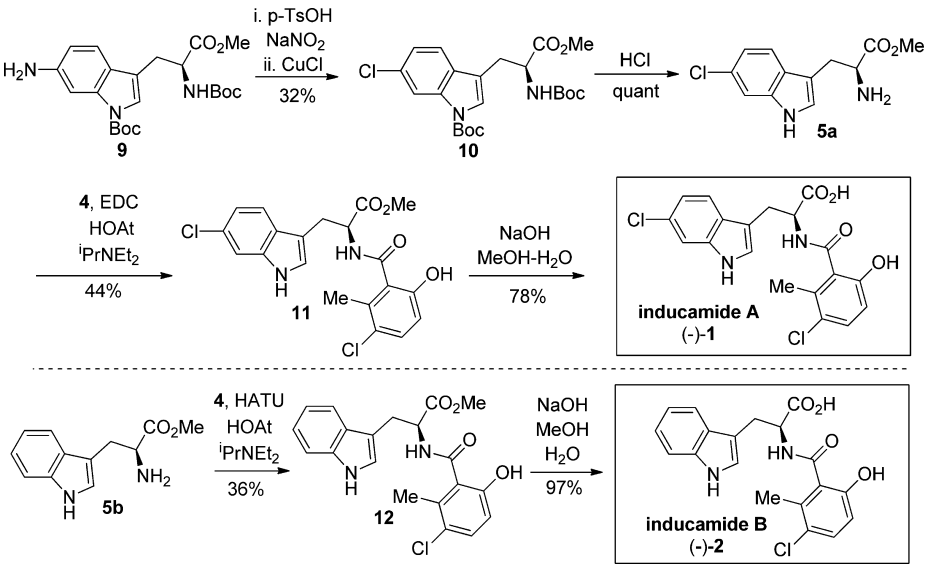


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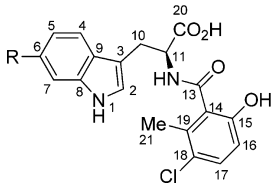
Table 1. NMR Spectroscopic Data for Inducamides A (1) and B (2) in CD_3OD[a]



	Inducamide A (-)-1 (R = Cl)				Inducamide B (-)-2 (R = H)			
	natural product[a]		synthetic[b]		natural product[a]		synthetic[b]	
pos	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
2	125.7	7.21, s	125.71	7.22, s	124.6	7.19, s	124.7	7.19, s
3	111.9		112.0		111.1		111.0	
4	120.5	7.62, d (8.5)	120.5	7.58, d (8.5)	119.3	7.63, d (7.9)	119.3	7.62, d (7.8)
5	120.2	6.97, dd (8.5, 1.8)	120.3	6.99, dd (8.5, 1.8)	119.7	7.00, t (7.3)	119.8	7.01, t (7.4)
6	128.2		128.3		122.3	7.08, t (7.3)	122.4	7.09, t (7.4)
7	111.5	7.31, d (1.8)	111.5	7.33, d (1.8)	112.2	7.32, d (8.1)	112.2	7.33, d (8.0)
8	138.3		138.4		138.0		138.1	
9	127.6		127.7		128.8		128.8	
10	28.3	3.43, dd (14.8, 4.6)	28.3	3.39, dd (14.9, 5.0)	28.4	3.41, dd (14.8, 5.0)	28.4	3.41, dd (14.9, 5.3)
		3.19, dd (14.8, 8.8)		3.22, dd (14.9, 8.5)		3.23, dd (14.8, 8.6)		3.24, dd (14.9, 8.5)
11	55.0	4.87, dd (8.8, 4.6)	54.8	4.93, dd (8.5, 5.0)	55.1	4.93, dd (8.6, 5.0)	54.8	4.93, dd (8.5, 5.3)
13	170.3		170.3		170.3		170.3	
14	127.5		127.6		127.6		127.6	
15	154.3		154.4		154.4		154.4	
16	115.5	6.66, d (8.8)	115.5	6.66, d (8.7)	115.5	6.66, d (8.8)	115.5	6.66, d (9.0)
17	131.2	7.16, d (8.8)	131.2	7.17, d (8.7)	131.2	7.16, d (8.7)	131.2	7.16, d (8.7)
18	125.6		125.70		125.6		125.7	
19	135.2		135.3		135.2		135.3	
20	175.4		175.1		175.5		175.2	
21	17.1	2.07, s	17.1	2.09, s	17.0	2.06, s	17.0	2.07, s

[a] ^1H and ^{13}C NMR run at 600 and 100 MHz, respectively. [b] ^1H and ^{13}C NMR run at 400 and 100 MHz, respectively.

(neat) ν_{max} 3288, 2924, 1702, 1634, 1522, 1439, 1290, 1228, 743 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.26 (1 H, d, J 8.5, ArH), 6.74 (1 H, d, J 8.5, ArH), 2.23 (3 H, s, Me), 2 × OH not observed; ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 172.2 (C), 160.7 (C), 138.1 (C), 134.9 (CH), 126.0 (C), 117.5 (C), 117.2 (CH), 19.2 (Me).

Methyl *N*,1-Bis(*tert*-butoxycarbonyl)-6-chloro-L-tryptophanate (10). To a solution of **9**[8] (348 mg, 0.80 mmol) in acetonitrile (3.3 mL) was added *p*-toluenesulfonic acid monohydrate (457 mg, 2.4 mmol) at 10 °C. After stirring for 10 min, a solution of sodium nitrite (124 mg, 1.8 mmol) in water (0.55 mL) was added dropwise, immediately followed by cuprous chloride (158 mg, 1.6 mmol) in one portion. The reaction mixture was then stirred for 10 min at 10 °C and warmed to room temperature. After stirring for 2 h, a further batch of cuprous chloride (158 mg, 1.6 mmol) was added. The reaction was stopped after stirring for a further 12 h at room temperature by addition to an ice/water mix (30 mL). The aqueous layer was then extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with brine (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel eluting with dichloromethane−ethyl acetate (19:1) to afford the title compound (116 mg, 0.26 mmol, 32%), as pale yellow crystals: mp 80−82 °C; {$[\alpha]_D^{24}$ +40.7 (c 0.14, $CHCl_3$), lit.[10] $[\alpha]_D^{27}$+41.2 (c 1.30, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1 H, br s, ArH), 7.38 (1 H, d, J 8.4, ArH), 7.36 (1 H, s, ArH), 7.22 (1 H, dd, J 8.4, 1.7, ArH), 5.10 (1 H, d, J 7.9, CONH), 4.61−4.64 (1 H, m, CH), 3.69 (3 H, s, Me), 3.12−3.26 (2 H, m, CH_2), 1.67 (9 H, s, 3 × Me), 1.43 (9 H, s, 3 × Me); spectroscopic data consistent with the literature.[10]

Methyl 6-Chloro-L-tryptophanate Hydrochloride (5a). A solution of **10** (58 mg, 0.13 mmol) in 4 M HCl in dioxane (1 mL, 4.0 mmol) was stirred for 18 h at room temperature. The solution was concentrated *in vacuo* to afford the title compound (38 mg, 0.13 mmol, ∼100%), as a pale green solid: ^1H NMR (400 MHz, CD_3OD) δ 7.50 (1 H, d, J 8.5, ArH), 7.40 (1 H, d, J 1.9, ArH), 7.22 (1 H, s, ArH), 7.06 (1 H, dd, J = 8.5, 1.9, ArH), 4.31−4.34 (1 H, m, CH), 3.80 (3 H, s, Me), 3.30−3.46 (2 H, m, CH_2), indole NH and NH_2 not observed; spectroscopic data consistent with the literature.[11]

(*S*)-Methyl 3-(6-Chloroindol-3-yl)-2-(3-chloro-6-hydroxy-2-methylbenzamido)propanoate (11). To a solution of **4** (6.0 mg, 0.036 mmol) in DMF (0.2 mL) was added 1-hydroxy-7-azabenzotriazol (HOAt, 4.9 mg, 0.036 mmol) and EDC·HCl (10.4 mg, 0.054 mmol) at 0 °C, then warmed to room temperature. After stirring for 2 min, a solution of **5a** (10.0 mg, 0.036 mmol) and triethylamine (0.01 mL, 0.072 mmol) in dichloromethane (0.2 mL) was added, and the resulting solution stirred for 24 h at room temperature. Dichloromethane was added (5 mL), and the reaction mixture washed with saturated $NaHCO_3$ (2 × 5 mL), brine (5 mL), and water (5 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane−ethyl acetate (19:1) to afford the title compound (6.7 mg, 0.016 mmol, 44%), as a yellow oil: $[\alpha]_D^{23}$ +18.8 (c 0.6, $CHCl_3$); HRMS found $[M + Na]^+$ 443.0541, $[C_{20}H_{18}{}^{35}Cl_2N_2O_4 + Na]^+$ requires 443.0536; IR (neat) ν_{max} 3316, 2926, 2854, 1737, 1639, 1440, 1292, 1218, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (1 H, s, OH), 8.12 (1 H, br s, NH), 7.41 (1 H, d, J 8.5, ArH), 7.35 (1 H, d, J 1.7, ArH), 7.28 (1 H, d, J 8.8, ArH), 7.06 (1 H, dd, J 8.5, 1.9, ArH), 7.00 (1 H, d, J 2.4, ArH), 6.77 (1 H, d, J 8.8, ArH), 6.42 (1 H, d, J 7.4, CONH), 5.07−5.12 (1 H, m, CH), 3.78 (3 H, s, OMe), 3.48 (1 H, dd, J 15.0, 5.4, CH_2), 3.38 (1 H, dd, J 15.0, 5.7, CH_2), 2.27 (3 H, s, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (CO), 168.9 (CO), 156.9 (C), 136.6 (C), 133.3 (C), 132.1 (CH), 128.7 (C), 126.2 (C), 126.1 (C), 123.5 (CH), 120.9 (CH), 120.3 (C), 119.5 (CH), 116.6 (CH), 111.5 (CH), 110.1 (C), 53.5 (CH), 53.0 (Me), 27.3 (CH_2), 18.5 (Me).

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(*S*)-Methyl 2-(3-Chloro-6-hydroxy-2-methylbenzamido)-3-(indol-3-yl)propanoate (12). To a suspension of **4** (100 mg, 0.50 mmol) and 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (285 mg, 0.75 mmol) in dichloromethane (15 mL) was added *N*,*N*-diisopropylethylamine (0.26 mL, 1.5 mmol). After stirring for 10 min, L-tryptophan methyl ester (**5b**) (HCl salt, 127 mg, 0.49 mmol) was added in one portion, and the resulting mixture stirred for 3 days at room temperature. Dichloromethane was added (20 mL), and the whole washed with 1 M HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane−ethyl acetate (19:1) to afford the title compound (70 mg, 0.18 mmol, 36%), as a colorless solid: mp 70−73 °C; $[\alpha]_D^{17}$ +100.7 (*c* 1.0, $CHCl_3$); HRMS found $[M + Na]^+$ 409.0927, $[C_{20}H_{19}{}^{35}ClN_2O_4 + Na]^+$ requires 409.0926; IR (neat) ν_{max} 3408, 2953, 1760, 1696, 1435, 1345, 1265, 734 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.99 (1 H, br s, OH), 7.77 (1 H, d, *J* 8.9, ArH), 7.55 (1 H, d, *J* 8.0, ArH), 7.29 (1 H, d, *J* 8.0, ArH), 7.19−7.17 (2 H, m, 2 × ArH), 7.00 (1 H, t, *J* 7.5, ArH), 6.91 (1 H, t, *J* 7.5, ArH), 5.80−5.85 (1 H, dd, *J* 9.6, 5.7, CH), 3.56−3.75 (5 H, m, CH_2 + Me), 2.68 (3 H, s, Me), 2 × NH not observed; ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 160.8 (C), 153.3 (C), 147.7 (C), 140.2 (C), 137.6 (C), 136.9 (CH), 132.5 (C), 128.5 (C), 124.8 (CH), 122.2 (CH), 119.7 (CH), 119.0 (CH), 116.7 (CH), 114.5 (C), 112.3 (CH), 111.0 (C), 56.8 (CH), 52.7 (Me), 24.8 (Me), 17.7 (CH_2).

(−)-Inducamide A (1). To a solution of **11** (5.0 mg, 0.012 mmol) in methanol (0.5 mL) was added 1 M NaOH (0.024 mL, 0.024 mmol), and the reaction mixture stirred at room temperature for 2 h. The methanol was removed *in vacuo*, and the aqueous residue diluted with water (1 mL) and then basified to pH 9 with $NaHCO_3$. The resulting mixture was washed with ethyl acetate (2 mL), and the organic phases were discarded. The aqueous layer was then acidified to pH 2 (1 M HCl) and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the title compound (3.8 mg, 0.009 mmol, 78%) as a colorless oil: {$[\alpha]_D^{24}$ −12.0 (*c* 0.10, MeOH); lit.[2] $[\alpha]_D^{24}$ −18.0 (*c* 0.10, MeOH)}; HRMS found $[M - H]^-$ 405.0407, $[C_{19}H_{16}{}^{35}Cl_2N_2O_4 - H]^-$ requires 405.0414; IR (neat) 3318, 2925, 2854, 1716, 1634, 1441, 1290, 805 cm^{-1}; ^1H and ^{13}C NMR data see Table 1.

(−)-Inducamide B (2). To a solution of **12** (70 mg, 0.18 mmol) in methanol (6 mL) was added 1 M NaOH (0.36 mL, 0.36 mmol). After stirring for 2 h, the solution was then basified to pH 9 with $NaHCO_3$, the aqueous layer washed with ethyl acetate (10 mL), and the organic layer discarded. The aqueous layer was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the title compound (65 mg, 0.17 mmol, 97%), as a colorless solid: mp 118−122 °C; {$[\alpha]_D^{22}$ −9.5 (*c* 0.1, MeOH); lit.[2] $[\alpha]_D^{24}$ −10.0 (*c* 0.05, MeOH)}; HRMS found $[M + Na]^+$ 396.0769, $[C_{19}H_{17}{}^{35}ClN_2O_4 + Na]^+$ requires 396.0771; IR (neat) ν_{max} 3288, 2924, 1702, 1634, 1522, 1439, 1290, 1228, 743 cm^{-1}; ^1H and ^{13}C NMR data see Table 1.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b00889.

^1H and ^{13}C NMR spectra for all novel compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professors John Blunt and Murray Munro, of the University of Canterbury, for their pioneering work on bioactive marine natural products.

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(12) The base-mediated ester hydrolysis led exclusively to the desired hydroxy acid, with no lactonization observed (e.g., to the seven-membered ring present in inducamide C).

(13) The low yield for the amide coupling steps can be attributed to the hindered nature of carboxylic acid **4**.

(14) 4-Hydroxy-6-chlorotryptophan is incorporated during the biosynthesis of several nonribosomal peptides isolated from other strains of *Streptomyces* sp.; see: (a) Motohashi, K.; Takagi, M.; Shin-ya, K. *J. Nat. Prod.* **2010**, *73*, 226−228. (b) Muliandi, A.; Katsuyama, Y.; Sone, K.; Izumikawa, M.; Moriya, T.; Hashimoto, J.; Kozone, I.; Takagi, M.; Shin-ya, K.; Ohnishi, Y. *Chem. Biol.* **2014**, *21*, 923−934. (c) Izumikawa, M.; Kawahara, T.; Kagaya, N.; Yamamura, H.; Hayakawa, M.; Takagi, M.; Yoshida, M.; Doi, T.; Shin-ya, K. *Tetrahedron Lett.* **2015**, *56*, 5333−5336.

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