EFFICIENT SYNTHESIS OF (±)-*seco*-CYCLOPROPANEINDOLINE ANALOGS OF CC-1065

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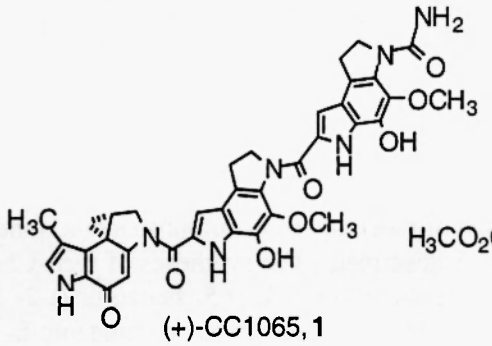
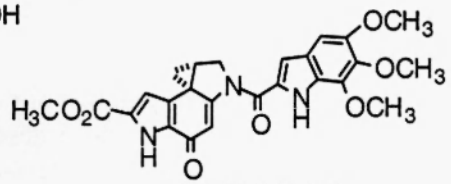
Abstract: An efficient method for the preparation of racemic *seco*-cyclopropaneindoline, or *seco*-CI, analogs of the anticancer agent CC1065 is described. The syntheses of *seco*-CI compounds containing either 5,6,7-trimethoxyindole-2-carbonyl, **4**, or 5-(benzofuran-2-carboxamido)indole-2-carbonyl, **10**, or 2-(4-N,N-diethyl)aminophenyl)benzimidazole-6-carbonyl, **11**, or 4-(4-butanamido-1-methylpyrrole-2-carboxamido)-1-methylpyrrole-2-carbonyl, **12**, subunit are detailed. At μM concentrations, compounds **4**, **10-12** inhibited the growth of human leukemic K562 cells in culture.

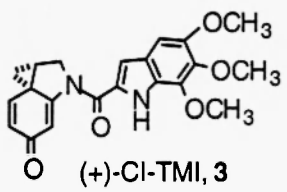
Introduction

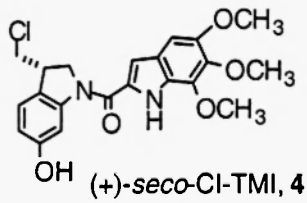
(+)-CC-1065 **I**[1,2] and duocarmycin SA (or DUMSA, **2**)[3] are natural products that exhibit extremely potent cytotoxicity, with IC_{50} values in the picomolar range, against the growth of murine leukemia L1210 cells *in vitro*. Consequently, this class of compounds has received a lot of attention, and a number of total syntheses as well as the biological and biochemical properties of these and related compounds have been published.[4] Upon selective binding to the minor groove of DNA at AT-rich sequences, the cyclopropane moiety of DUMSA[3,4,5] and CC-1065[4,6] becomes more reactive toward covalent reaction with nucleophiles, such as purine N3 groups on the floor of the minor groove. Both DUMSA[3,4,7] and CC-1065[4,6,8] generally show similar sequence preference: 5'-AAA = 5'-TTA > 5'-TAA > 5'-ATA (the alkylation site is denoted by the underlined base).

From structure-activity relationship studies concerning the DNA alkylating subunit of CC-1065 and the duocarmycins, Boger and others, have demonstrated that the CI pharmacophore is one of the simplest analog of the CPI (cyclopropanepyrroloindoline) subunit.[4] CI (cyclopropaneindoline) analogs, including (+)-CI compound **3**, exhibited significant cytotoxic activity and covalent sequence specificity.[4,9,10] Further studies revealed that the *seco*-prodrug form of these compounds,[9,10] including the (+)-*seco*-CI compound **4**,[4,10c,d] have similar biochemical and biological properties to the corresponding ring closed agents themselves.[4,9,10c,d] It has been suggested that the *seco*-CI compounds undergo elimination of HCl in cells to form the ultimate cyclopropane-containing CI drug which bind to, and covalently modify DNA.[4,9,10c,d] Interestingly, the (+)- and (-)-enantiomers of compound **4** show similar cytotoxicity against L1210 mouse leukemia cell in culture.[4a]







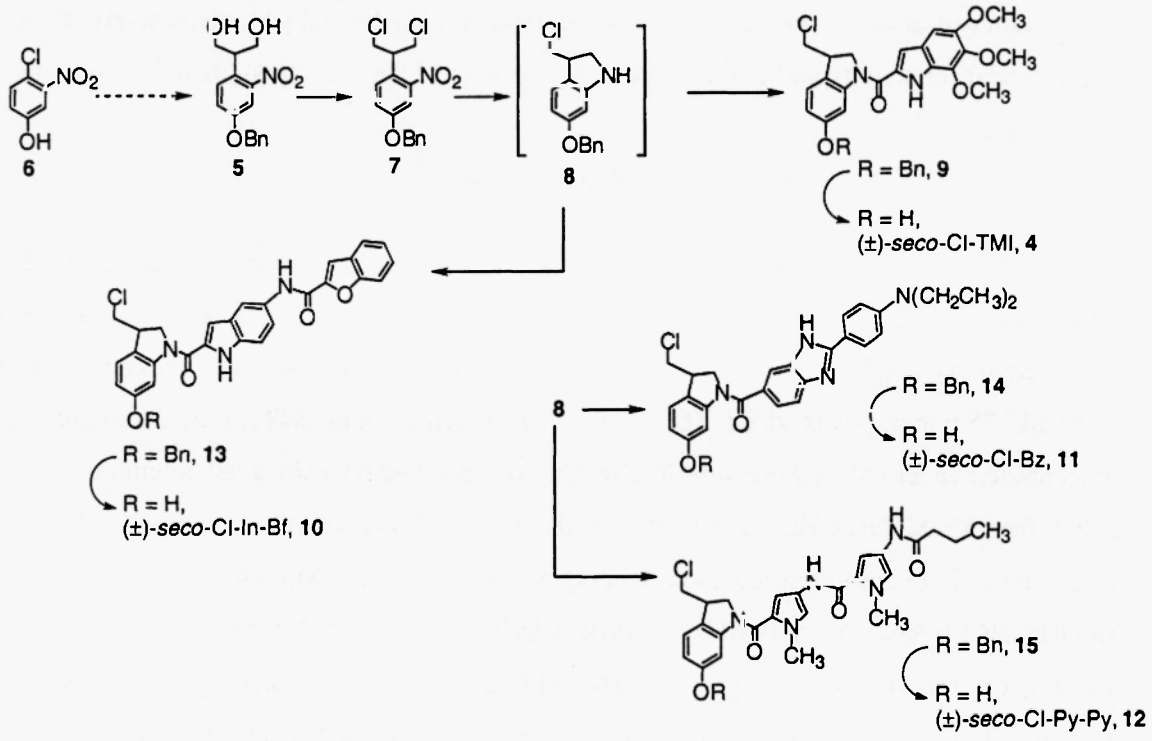


Since the CI analogs have interesting biochemical and pharmacological properties, several synthetic approaches to construct this pharmacophore have been reported.[9a,10,11] Preparation of the optically active forms of the CI pharmacophore has been achieved either through chemical resolution and chromatography (HPLC)[10b], or by enzymatic resolution of prochiral intermediates.[11d]

Results and Discussion

In this paper, we report an efficient method to synthesize compound **4** and related compounds in essentially three separate steps from a readily available diol intermediate **5**[2c] as

shown in Scheme 1. The synthetic strategy takes advantage of a key set of three transformations. The transformations are: (i) reduction of a nitro group on compound **5**, followed by (ii) intramolecular nucleophilic substitution to produce the *seco*-CI nucleus, and (iii) subsequent coupling to a carboxylic acid group of a specific DNA binding subunit. Treatment of diol **5** with triphenylphosphine and CCl_4 gave dichloride **7** in 77% yield as a brownish solid. Several attempts of using hydrogen over Pd-C or PtO_2 were tried to reduce the nitro group of compound **7** to an amine. The amino group was expected to undergo a 5-*exo-tet* intramolecular S_N2 ring closure to produce the CI pharmacophore. In each of these attempts, the amino product underwent significant degradation, and no desired CI product was obtained. However, reduction of the nitro group in compound **7** with stannous chloride and hydrochloric acid in THF, followed by sodium hydroxide workup, gave indoline **8** in 66% yield. Because indoline **8** was chemically unstable, it was directly reacted with 5,6,7-trimethoxyindole-2-carboxylic acid and EDCI in DMF to give the desired product **9** in 52% yield from compound **7**. Subsequent removal of the benzyl protecting group by catalytic hydrogenation provided (±)-*seco*-CI-TMI **4** in 76% yield, whose ^{1}H-NMR spectrum was similar to that reported in the literature.[10c]



Scheme 1.

This method for preparing *seco*-CI containing compounds was further demonstrated through the synthesis of agents **10-12**. The indole-benzofuran subunit which is the non-covalent component of adozelesin, a clinically investigated analog of CC-1065,[12] was selected for compound **10**. The benzimidazole and dipyrrole groups in agents **11** and **12** are related to the DNA reading components of Hoechst 33258[13] and netropsin,[14] respectively. Indoline **8** was coupled to 5-(benzofuran-2-carboxamido)indole-2-carboxylic acid[2c] with EDCI in DMF to afford compound **13** in 35% yield, which was isolated as a white solid from precipitation of the crude product with chloroform. Removal of the benzyl group with 25% aqueous ammonium formate in THF and 10% Pd/C gave the target compound **10** in 87% yield, which was essentially homogeneous by TLC analysis. Reaction of indoline **8** with 2-(4-(N,N-diethyl)aminophenyl)benzimidazole-6-carboxylic acid[15] and 4-(4-butanamido-1-methylpyrrole-2-carboxamido)-1-methylpyrrole-2- carboxylic acid,[15] and EDCI produced compounds **14** and **15** in 55 and 59% yield, respectively. Subsequent catalytic hydrogenation of **14** and **15** furnished the desired compounds **11** and **12** in 56 and 59 percent yields, accordingly.

The cytotoxicity of compounds **4, 10-12** against the K562 human chronic myeloid leukemia cells, following 3-day continuous exposure of the drugs, was determined using a MTT tetrazolium dye assay.[16] Their IC_{50} values were 0.010, 0.14, 1.59, 3.0 μM, respectively. Details of the anticancer activity and DNA interaction properties of these compounds will be reported in due course.

Experimental

2-[4-Benzyloxy-2-nitrophenyl]-1,3-dichloropropane (7). Diol **5** (1.90 g, 6.28 mmol), prepared according to published procedures,[2c] and triphenylphosphine (6.60 g, 25.2 mmol) were dissolved in dry CH_2Cl_2 (32 mL). The solution was placed under a positive N_2 pressure, and CCl_4 (7.30 mL, 75.6 mmol) was added. The solution was stirred at room temperature overnight, then concentrated under reduced pressure. The residue was purified on a silica gel column using $CHCl_3$ then 5% MeOH/$CHCl_3$ as eluents, and the product **7** was obtained as a brown oil (1.65 g, 4.85 mmol, 77 %) that solidified upon standing in the refrigerator. Mp = 48-50°C. TLC (5% MeOH/$CHCl_3$): R_f = 0.62. 500 MHz ^{1}H-NMR ($CDCl_3$): δ = 7.37 (d, 2.0, 1H), 7.28 (m, 6H), 7.10 (dd, 2,0, 8.5, 1H), 4.98 (s, 2H), 3.80 (m, 5H). MS (EI): *m/z* (relative intensity) = 339, (M^+, 6). Isotope pattern for M^+ cluster matches that for 2 chlorine atoms. HRMS (EI) Calcd. for $C_{16}H_{15}NO_3{}^{35}Cl_2$: 339.0429. Found: 339.0418.

6-Benzyloxy-3-(chloromethyl)indoline (8). To an ice-chilled solution of dichloride **7** (0.1837 g, 0.54 mmol) in dry THF (3 mL) was added $SnCl_2.2H_2O$ (1.22g, 5.40 mmol) and concentrated HCl (1.8 mL). The resulting suspension was stirred overnight under positive N_2 pressure. 25% NaOH was slowly added to the suspension until all the precipitate was dissolved. The solution was extracted in $CHCl_3$ (3 x 50 mL each) and the organic layers were collected, dried with sodium sulfate, gravity filtered, and concentrated under reduced pressure to a thick greenish oil that was kept *in vacuo*. Due to the instability of indoline **8**, it was directly used in coupling reactions with carboxylic acids as described below. 300 MHz ^{1}H-NMR ($CDCl_3$): δ = 7.40 (m, 5H), 7.00 (d, 8.4, 1H), 6.50 (dd, 2.4, 8.4, 1H), 6.45 (d, 2.4, 1H), 5.01 (s, 2H), 3.55-3.95 (m, 5H), 3.38 (quintet, 6.3, 1H).

3-Chloromethyl-6-hydroxy-1-(5,6,7-trimethoxyindole-2-carbonyl)indoline (4). Indoline **8** (167 mg, 0.614 mmol) was treated with 5,6,7-trimethoxyindole-2-carboxylic acid[10c,17] (169 mg, 0.675 mmol), EDCI (354 mg, 1.84 mmol), and dry DMF (13 mL). The solution was stirred at room temperature and kept under an atmosphere of nitrogen for 3 days. The DMF was removed using a Kugelrohr apparatus (60 ^{o}C, 1mm Hg), and the oily residue was partitioned between $CHCl_3$ (100 mL) and H_2O (50 mL). The chloroform layer was collected and dried (Na_2SO_4). Purification of the crude product by silica gel column chromatography ($CHCl_3$) afforded the desired substance **9** (160 mg, 51.5%). IR (neat): ν = 3419, 3050, 2940, 1624, 1494, 1461, 1413, 1384, 1307, 1238, 1120, 1048, 999, 827, 745, 696 cm^{-1}. 500 MHz ^{1}H-NMR ($CDCl_3$): δ = 9.42 (s, 1H), 7.30-7.46 (m, 5H), 7.15 (d, 8.3, 1H), 7.13 (s, 1H), 6.95 (d, 3.0, 1H), 6.87 (s, 1H), 6.74 (dd, 3.0, 8.3, 1H), 5.10 (s, 2H), 4.64 (dd, 9.5, 10.0, 1H), 4.46 (dd, 4.5, 10.0, 1H), 4.07 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.80 (m, 2H), 3.57 (m, 1H).

A suspension of compound **9** (0.160 g, 0.316 mmol), 25% aqueous ammonium formate (1.3 mL), and 10% Pd/C (0.100 g) in chilled THF (10 mL) was stirred overnight at room temperature and kept under an atmospheric pressure of hydrogen. Removal of the catalyst and solvent gave an oily residue that was purified by silica gel column chromatography using a solvent system that started with $CHCl_3$. The percentage of EtOAc was increased by 10% every 50 mL until 40% EtOAc/ $CHCl_3$. Fractions showing the product were collected and concentrated to give the known compound (±)-**4** as a white solid (0.100 g, 76.0%) whose ^{1}H-NMR spectrum was similar to that reported in reference 10c. 500 MHz ^{1}H-NMR ($CDCl_3$ and 2 drops of DMSO-d_6): δ = 9.50 (s br, 1H), 8.87 (s br, 1H), 7.98 (s br, 1H), 7.08(d, 8.3, 1H), 6.95 (d, 2.5, 1H), 6.88 (s, 1H), 6.62 (dd, 2.5, 8.3, 1H), 4.62 (t, 9.1, 1H), 4.45 (dd, 4.5, 9.1, 1H), 4.08 (s, 3H), 3.94 (s,

3H), 3.91 (s, 3H), 3.79 (m, 2H), 3.53 (t, 9.1, 1H). Anal. Calcd. for $C_{21}H_{21}N_2O_5Cl$. 3/4H_2O: C, 58.55; H, 5.23; N, 6.51%. Found: C, 58.96; H, 5.67; N, 6.17%.

6-Benzyloxy-3-chloromethyl-1-[5-(benzofuran-2-carboxamido)indole-2-carbonyl]indoline (13). Indoline **8**, prepared from dichloride **7** (2.15 g, 6.32 mmol), was dissolved in dry DMF (51.5 mL) and EDCI (3.82 g, 19.93 mmol) and 5-(benzofuran-2-carboxamido)indole-2-carboxylic acid[2c,18] (3.96 g, 12.38 mmol) were added to the solution while stirring on an ice bath. The reaction mixture was stirred overnight at room temperature under a positive nitrogen pressure. The DMF was removed using a Kugelrohr apparatus (40°C, 0.1 mm Hg) to give a brown oil which was dissolved in $CHCl_3$ (250 mL) and washed with 5% aqueous $NaHCO_3$ (50 mL). The organic layer was collected, dried with sodium sulfate, gravity filtered, and concentrated under reduced pressure to give an orange/brown sludge. Addition of chloroform (5 mL) to the sludge gave an off-white precipitate that was collected by suction filtration and dried *in-vacuo* to afford compound **13** as a beige solid (1.29 g, 2.24 mmol, 35.4 %). Mp = 238-240 °C. TLC (10% MeOH/$CHCl_3$): R_f = 0.50. 500 MHz ^{1}H-NMR (DMSO-d_6): δ = 11.76 (d, 1.5, 1H), 10.47 (s, 1H), 8.19 (d, 1.0, 1H), 7.88 (s, br, 1H), 7.81 (d, 7.5, 1H), 7.71(d, 9.0, 1H), 7.59 (dd, 2.0, 9.0, 1H), 7.3-7.5 (m, 9H), 7.17 (d, 2.5 2H), 6.76 (dd, 2.5, 8.0, 1H), 5.10 (s, 2H), 4.72 (t, 10.5, 1H), 4.37 (dd, 4.5, 10.5, 1H), 3 97 (m, 1H), 3.86 (m, 2H). 75 MHz ^{13}C-NMR (DMSO-d_6): δ = 160.1, 158.5, 156.4, 149.1, 144.9, 137.1, 133.4, 131.2, 131.0, 128.5 (2Cs), 127.9, 127.6, (2Cs), 127.0, 125.2, 124.4, 123.8, 122.9, 119.4, 113.3, 112.2, 112.0, 110.2, 110.0, 105.8, 104.5, 79.2, 69.5, 54.3, 47.9, 41.7. MS (FAB-NBA): *m/z* (relative intensity) = 576 ($M+H^+$, 6). HRMS (FAB-NBA) Calcd. for $C_{34}H_{27}N_3O_4{}^{35}Cl$: 576.1690. Found: 576.1689. Anal. Calcd. for $C_{34}H_{26}N_3O_4Cl$. H_2O: C, 68.74; H, 4.75; N, 7.07%. Found: C, 69.06; H, 5.08; N, 6.86%.

3-Chloromethyl-6-hydroxy-1-[5-(benzofuran-2-carboxamido)indole-2-carbonyl]indoline (10). A suspension of **13** (1.80 g, 3.18 mmol) and 10% Pd/C (1.08 g) in a chilled solution of 25 % aqueous ammonium formate (3.5 mL) and THF (105 mL) was stirred overnight under an atmosphere of hydrogen. The mixture was filtered, and the filtrate was concentrated to give a yellow solid. The solid was suspended in $CHCl_3$ and suction filtered leaving compound **10** as a white solid (1.32 g, 2.72 mmol, 86.9%). Mp = 235-237°C. TLC (10% MeOH/$CHCl_3$): R_f = 0.54. 500 MHz ^{1}H-NMR (DMSO-d_6): δ = 11.73 (d, 1.5, indole-NH), 10.46 (s, OH), 9.50 (s, NH), 8.20 (d, 1.5, 1H), 7.83 (d, 8.0, 1H), 7.77 (s, 1H), 7.73 (d, 8.0, 1H), 7.73 (s br, 1H), 7.61 (d, 2.0, 8.5, 1H), 7.51 (t, 7.5, 1H), 7.47 (d, 8.5, 1H), 7.38 (t, 7.5, 1H), 7.22 (d, 7.5, 1H), 7.16 (d, 1.5, 1H), 6.51 (dd, 2.0, 7.5, 1H), 4.71 (t, 9.5, 1H), 4.36 (dd, 4.5, 9.5,

1H), 3.97 (dd, 3.5, 10.0, 1H), 3.83 (dd, 7.0, 10.0, 1H), 3.81 (m, 1H). MS (FAB-NBA): *m/z* (relative intensity) = 486 ($M+H^+$, 10). HRMS (FAB-NBA) Calcd. for $C_{27}H_{21}N_3O_4{}^{35}Cl$: 486.1221. Found: 486.1230. Anal. Calcd. for $C_{27}H_{20}N_3O_4Cl$: C, 66.74; H, 4.15; N, 8.65%. Found: C, 66.78; H, 4.23; N, 8.61%.

6-Benzyloxy-3-chloromethyl-1-[2-(4-diethylaminophenyl)benzimidazole-5 (or 6)-carbonyl]indoline (14). Indoline **8** (0.167 g, 0.614 mmol), 2-(4-(N,N-diethyl)aminophenyl)benzimidazole-6-carboxylic acid,[15] (0.209 g, 0.675 mmol), and EDCI (0.354 g, 1.84 mmol) were dissolved in dry DMF (13 mL) and allowed to stir at room temperature under N_2 for 3 days. The reaction mixture was worked up using the procedure given for the synthesis of compound **13**. The oily residue was purified by silica gel column chromatography using a solvent system that started with $CHCl_3$ and then switched to 10% EtOAc/$CHCl_3$. The desired product **14** was isolated as a colorless, oily residue (0.19 g, 54.9%). 500 MHz ^{1}H-NMR ($CDCl_3$): δ = 8.20 (s br, 1H), 7.92 (s br, 1H), 7.90 (d, 9.0, 2H), 7.2-7.5 (m, 9H), 7.14 (d, 8.0, 1H), 6.75 (d, 9.0, 2H), 6.68 (d, 8.0, 1H), 4.52 (m, 1H), 4.32 (t br, 1H), 3.73 (m, 1H), 3.62 (m, 1H), 3.55 (m, 1H), 3.44 (q, 7.5, 4H), 1.22 (t, 7.5, 6H). MS (FAB-NBA): *m/z* (relative intensity) = 565 ($M+H^+$, 15). HRMS Calcd. for $C_{34}H_{34}N_4O_2{}^{35}Cl$: 565.2370. Found: 565.2351.

3-Chloromethyl-6-hydroxy-1-[2-(4-diethylaminophenyl)benzimidazole-5 (or 6)-carbonyl]indoline (11). Compound **14** (0.190 g, 0.337 mmol) and 10% Pd/C (0.100 g) were suspended in a chilled solution of 25% aqueous ammonium formate (1.3 mL) and THF (10 mL). The suspension was stirred under an atmosphere of hydrogen overnight at room temperature and atmospheric pressure. Removal of the catalyst and solvent gave a foamy residue that was co-evaporated twice with dry CH_2Cl_2 (5 mL each). The resulting yellowish solid was purified through column chromatography using $CHCl_3$ as a solvent system and then switching to a 10-40% EtOAc/$CHCl_3$ solvent, to afford the product (±)-**11** as a white solid (0.90 g. 56.4 % yield). Mp = 225 °C. 500 MHz ^{1}H-NMR ($CDCl_3$ and 2 drops of DMSO-d_6): δ = 8.90 (s br, 1H), 8.79 (s br, 1H), 8.06 (s br, 1H), 8.02 (d, 9.0, 2H), 7.90 (s br, 1H), 7.73 (s br, 1H), 7.40 (s, 1H), 7.05 (d, 8.0, 1H), 6.75 (d, 8.0, 1H), 6.74 (d, 9.0, 2H), 4.30 (dd, 7.5, 10.5, 1H), 4.11 (m, 1H), 3.98 (dd, 6.8, 10, 1H), 3.74 (m, 1H), 3.59 (m, 1H), 3.44 (q, 7.5, 4H), 1.23 (t, 7.5, 6H). MS (FAB-NBA): *m/z* (relative intensity) = 475 ($M+H^+$, 10). HRMS Calcd. for $C_{27}H_{28}N_4O_2{}^{35}Cl$: 475.1901. Found: 475.1900. Anal. Calcd. for $C_{27}H_{27}N_4O_2Cl$. 1/2H_2O: C, 66.94; H, 5.79; N, 11.57%. Found: C, 66.51; H, 5.88; N, 11.21%.

3-Chloromethyl-6-hydroxy-1-[4-(4-butanamido-1-methylpyrrole-2-carboxamido)-1-methylpyrrole-2-carbonyl]indoline (12). A mixture of indoline **8** (89.2 mg, 0.328 mmol), EDCI (0.19 g, 1.0 mmol) and 4-(4-butanamido-1-methylpyrrole-2-carboxamido)-1-methylpyrrole-2-carboxylic acid[16] (0.093g, 0.240 mmol) was dissolved in dry DMF (5 mL). This reaction was stirred under nitrogen overnight. Upon work-up, the brown residue was purified by silica gel column chromatography using a gradient that gradually went form 2 to 10% MeOH in $CHCl_3$. Compound **15** was obtained as a thick brown oil (0.58 g, 27 % yield). TLC (10% MeOH/$CHCl_3$): Rf = 0.42. 500 MHz ^{1}H-NMR ($CDCl_3$): δ = 7.65 (s br, 2H), 7.41 (d, 7.5, 2H), 7.36 (t, 7.5, 2H), 7.33 (s, 1H), 7.32 (t, 7.5, 1H), 7.12 (d, 7.5, 1H), 7.09 (s, 1H), 6.67 (dd, 2.0, 7.5, 1H), 6.64 (s, 1H), 6.52 (s, 1H), 5.10 (s, 2H), 4.44 (t, 10.0, 1H), 4.24 (dd, 4.0, 10.5, 1H), 3.83 (s, 3H), 3.65 (s, 3H), 3.49 (dd, 4.0, 10.0, 1H), 3.63 (m, 1H), 3.53 (dd, 10.0, 10.5, 1H), 2.30 (T, 6.0, 2H), 1.74 (sextet, 6.0, 2H), 0.96 (t, 6.0, 3H). MS (FAB-NBA): m/z (relative intensity) = 588 ($M+H^+$, 8).

A suspension of compound **15** and 10% Pd-C (0.055 g) in chilled THF (10 mL) was hydrogenated overnight at room temperature and atmospheric pressure. Removal of the catalyst and solvent yielded a beige solid **12** (0.031g, 59 %) that was homogeneous by TLC analysis. Mp = 155 °C. TLC (10% MeOH/$CHCl_3$): R_f = 0.29. 500 MHz ^{1}H-NMR ($CDCl_3$): δ = 8.60 (s br. 1H), 8.40 (s br, 2H), 7.40 (s, 1H), 7.27 (d, 1.5, 1H), 7.07 (s, 1H), 6.96 (d, 7.0, 1H), 6.72 (s, 1H), 6.51 (s, 1H), 6.57 (dd, 2.0, 7.0, 1H), 4.36 (T, 10.5, 1H), 4.18 (dd, 4.0, 10.0, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.70 (m, 2H), 3.57 (m, 2H), 3.47 (dd, 10.0, 10.5, 1H), 2.26 (t, 6.0, 2H), 1.70 (sextet, 6.0, 2H), 0.95 (t, 6.0, 3H). MS (FAB-NBA): *m/z* (relative intensity) = 498 ($M+H^+$, 1). HRMS Calcd. for $C_{25}H_{29}N_5O_4Cl$: 497.1830. Found: 497.1806.

Acknowledgements

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