A Concise and Efficient Synthesis of *seco*-Duocarmycin SA

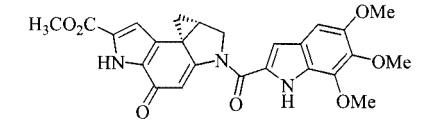
Lutz F. Tietze,*[a] Frank Haunert,[a] Tim Feuerstein,[a] and Tobias Herzig[a]

Keywords: Cyclization / Indoles / Natural products / Radicals / Synthetic methods

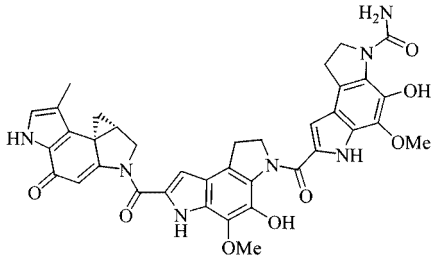
A short and efficient synthesis of *seco*-duocarmycin SA (**3**), a highly potent cytostatic agent and direct precursor of the natural product duocarmycin SA (**1**), has been achieved. Starting from commercially available 2-methoxy-4-nitroaniline (**4**) the synthetic protocol contains a Fischer indole synthesis to introduce the heterocyclic scaffold and a radical 5-*exo*-*trig* cyclization to furnish the (chloromethyl)indoline ring system as key reactions.

Introduction

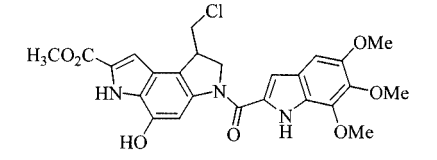
It has been shown in various studies that the natural antibiotic (+)-duocarmycin SA (**1**), which was first isolated from *Streptomyces* DO-113 in 1990,[1] is a highly potent cytostatic agent (Scheme 1).[2] Compound **1** exhibits an extraordinarily high cytotoxicity with an IC_{50} of 10 pM (cancer line L1210)[3] and is thus considered to be a powerful candidate for cancer treatment. The cytotoxicity of **1** as the structurally and biologically related (+)-CC-1065[4] (**2**) is caused by an alkylation of N-3 of adenine in AT-rich parts of the minor groove of the DNA by reaction with the spiro-[cyclopropane-cyclohexadienone] moiety in **1** and **2**.[3]



1: (+)-duocarmycin SA



2: (+)-CC-1065



3: *seco*-duocarmycin SA

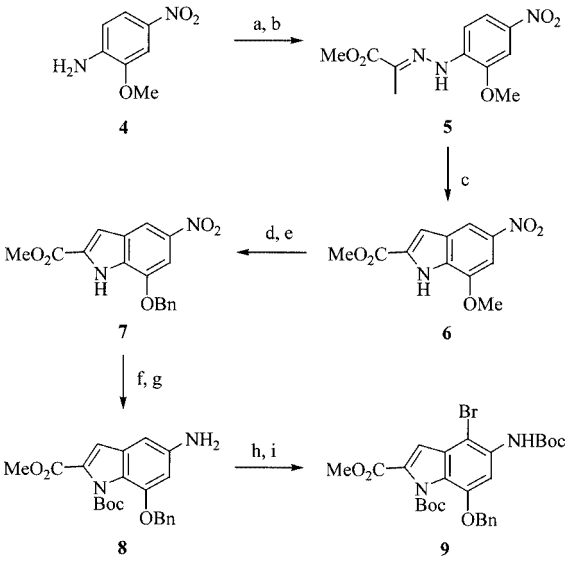
Scheme 1. Structures of (+)-duocarmycin SA (**1**), (+)-CC-1065 (**2**) and *seco*-duocarmycin SA (**3**)

Duocarmycin SA (**1**) seems to be superior to CC-1065 (**2**) due to the lack of a delayed fatal hepatotoxicity associated with (+)-CC-1065.[3] Moreover, (+)-duocarmycin SA is the most stable member of this class of agents and, according to a correlation between solvolytic stability and cytotoxic potency, it is also the most potent one. However, *seco* compounds of **1** or **2**, such as **3**, possess a similar alkylating selectivity and efficiency as the corresponding natural products[5] since they can form the spiro[cyclopropane] moiety in situ by an intramolecular Winstein cyclization.[6] In studies that culminated in the total synthesis of (+)- and *ent*-(−)-*seco*-duocarmycin SA (**1**) the corresponding *seco* compounds were the direct precursors.[7,8] On the other hand, glycosylated *seco* analogues of duocarmycin and CC-1065 are highly promising compounds for the selective treatment of cancer in an antibody-directed enzyme prodrug therapy.[9−12] Therefore, *seco* compounds are also highly interesting and promising synthetic targets. However, so far a concise and practical approach towards **3** starting from cheap, commercially available substrates is still missing. Here we describe a facile and efficient preparation of *seco*-duocarmycin SA (**3**) starting from 2-methoxy-4-nitroaniline (**4**).

Results and Discussion

Diazotation of commercially available 2-methoxy-4-nitroaniline (**4**) followed by instantaneous reduction of the formed diazonium salt provided the corresponding hydrazine (Scheme 2). Further treatment with methyl pyruvate yielded the hydrazone **5** very cleanly with an overall yield of 69%.

[a] Institut für Organische Chemie der Georg August Universität Göttingen,
Tammannstrasse 2, 37077 Göttingen, Germany
Fax: (internat.) + 49-551/399476
E-mail: ltietze@gwdg.de

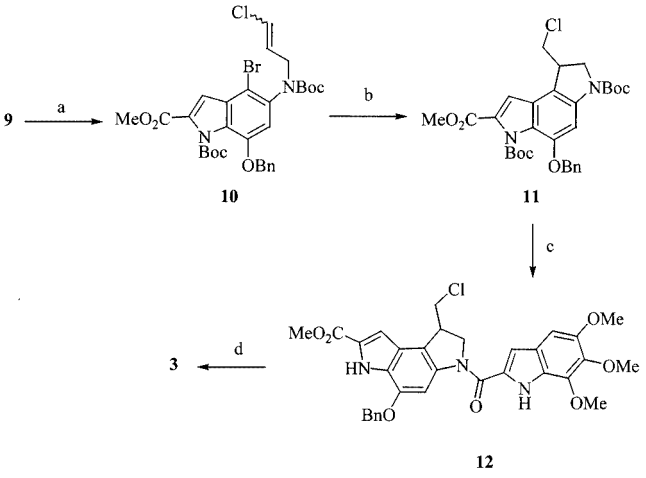


Scheme 2. (a) $NaNO_2$; HCl, −10 °C, 5 min, $SnCl_2$, −20 °C, 1 h, 70%; (b) NaOAc, methyl pyruvate, MeOH, room temp., 16 h, 99%; (c) PPA, xylene, 120 °C, 18 h, 64%; (d) $AlCl_3$, CH_2Cl_2, room temp., 72 h, 70%; (e) BnBr, K_2CO_3, acetone, 40 °C, 8 h, 88%; (f) Boc_2O, DMAP, THF, room temp., 1 h, 98%; (g) Lindlar catalyst, quinoline, EtOAc, H_2, room temp., 18 h, 91%; (h) Boc_2O, THF, room temp., 18 h, 89%; (i) NBS, THF, −78 °C, 4 h, 88%

A subsequent Fischer indole cyclization occurred on heating **5** at 120 °C for 18 h in the presence of polyphosphoric acid and xylene as co-solvent to give **6** in 64% yield.[13] During our investigations we encountered difficulties to hydrolyse the methyl ether by standard procedures at a later stage of the synthesis; therefore, we cleaved the methyl ether with $AlCl_3$ at this early point to switch to a benzyl ether as a more feasible protecting group. The *O*-benzyl-protected indole **7** was then treated with di-*tert*-butyl dicarbonate to give the corresponding *N*-Boc-protected indole, which, on reduction of the nitro group with Lindlar catalyst and quinoline, led to **8** in 89% yield over two steps. The protection of the amino moiety as its carbamate and subsequent regioselective bromination with NBS at −78 °C provided **9** in 78% overall yield. The bromination occurred completely regioselectively at C-4 of the indole moiety without the formation of any by-products.

After deprotonation of the NHBoc group in **9** with NaH, alkylation with (*E*/*Z*)-1,3-dichloro-2-propene furnished the corresponding *N*-(3-chloropropenyl)indole **10**. This compound was treated with tris(trimethylsilyl)silane[14] and catalytic amounts of AIBN in deoxygenated benzene at 80 °C in a radical 5-*exo*-*trig* cyclization[15] to generate the fully functionalized *seco*-duocarmycin scaffold **11** in 73% over two steps (Scheme 3). Radical cyclization with Bu_3SnH as radical donor is less suitable due to the high toxicity of the reagent and the tedious separation of tin-containing compounds from the final product.

Coupling with the DNA-binding subunit of duocarmycin SA − the trimethoxyindole (TMI) moiety − proceeded under standard conditions. First, both Boc groups were removed under acidic conditions to give the corresponding



Scheme 3. (a) NaH, DMF, room temp., 30 min; (*E*/*Z*)-1,3-dichloropropene, room temp., 12 h, 92%); (b) TTMSS, AIBN, benzene, 80 °C, 3 h, 79%; (c) 4 M HCl/EtOAc, 2 h, room temp.; TMI-CO_2H, EDC, DMF, room temp., 18 h, 51%; (d) NH_4HCO_2, Pd/C, THF, 40 °C, 2 h, 91%

amine hydrochloride, which was then directly coupled with 5,6,7-trimethoxyindolecarboxylic acid in the presence of EDC in DMF to give **12** in 51% yield. Finally, the benzyl protecting group was removed by transfer hydrogenolysis with NH_4HCO_2 as hydrogen donor and palladium on charcoal as catalyst to give *seco*-duocarymcin SA (**3**) in 91% yield.

The structures of the newly formed compounds were mainly determined by NMR spectroscopy. The identity of the final product was verified by comparison with the spectroscopic data found in the literature.[7]

Conclusion

The combination of a Fischer indole synthesis and a 5-*exo*-*trig* radical cyclization has been shown to allow an efficient generation of the tricyclic duocarmycin scaffold. With this new synthetic protocol an excellent access to *seco*-duocarmycin SA (**3**) has been developed.

Experimental Section

General: All reactions were performed under nitrogen or argon in flame-dried flasks, and the reactants were introduced by syringe. All solvents were dried by standard methods. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography was performed on precoated silica gel SIL G/UV_{254} plates (Macherey−Nagel GmbH & Co. KG), and silica gel 32−63 (0.032−0.064 mm) (Macherey−Nagel GmbH & Co. KG) was used for column chromatography. UV/Vis spectra were taken in CH_3CN with a Perkin−Elmer Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films with a Bruker IFS 25 spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Varian XL 200, VXR 200 and VXR 500 or a Bruker AMX-300 with tetramethylsilane (TMS) as internal standard in [D_6]acetone, [D]chloroform or [D_6]DMSO. The multiplicities of the ^{13}C NMR peaks were determined with the APT pulse sequence.

Mass spectra were measured at 70 eV with a Varian MAT 311A, high-resolution mass spectra with a Varian MAT 731 instrument. The following abbreviations are used in the text: EtOAc = ethyl acetate, PE = petroleum ether.

Methyl 2-[(2-Methoxy-4-nitrophenyl)hydrazono]propanoate (5): A suspension of 2-methoxy-4-nitroaniline (**4**) (500 mg, 3.0 mmol) in concd. HCl (150 mL) was treated carefully with $NaNO_2$ (216 mg, 3.0 mmol) in water (150 mL) at −10 °C internal temperature. The resulting yellow solution was added to a −30 °C cold solution of tin(II) chloride dihydrate (2.0 g, 9.0 mmol) in concd. HCl (100 mL) and stirred for an additional hour at −20 °C. The reaction mixture was then allowed to warm to room temperature and the precipitate was filtered off and dried. The filtrate was dissolved in methanol and treated with NaOAc (297 mg, 3.6 mmol) and methyl pyruvate (0.31 mg, 0.26 mL, 3.0 mmol). After vigorous stirring for 18 h, the yellow precipitate was filtered off, washed with cold methanol and dried in vacuo to afford 553 mg of **5** (2.1 mmol, 69%). IR (KBr): $\tilde{\nu}$ = 3333 (NH), 2956 (C−H), 1732 (C=O), 1579 (C=C), 1527, 1501, 1473 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 201 (4.3), 239 (3.8), 247 (3.8), 292 (3.8), 382 (4.4), 385 (4.4) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.18 (s, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 7.62 (d, *J* = 9.0 Hz, 1 H, 6-H), 7.76 (d, *J* = 2.2 Hz, 1 H, 3-H), 7.95 (dd, *J* = 9.0, 2.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.8 (CH_3), 52.7 (OCH_3), 56.3 (4-OCH_3), 105.8 (C-3), 112.2 (C-5), 118.7 (C-6), 137.4 (C-1), 138.2 (C-4), 141.5 (C-2), 145.1 (C=N), 165.2 (C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 267 (100) [M^+]. $C_{11}H_{13}N_3O_5$ (267.24): calcd. C 49.43, H 4.90; found C 49.12, H 4.84.

Methyl 7-Methoxy-5-nitro-1*H*-indole-2-carboxylate (6): A stirred suspension of polyphosphoric acid (PPA) (3 g) in xylene (100 mL) was treated with **5** (2.0 g, 7.5 mmol) and heated at 120 °C for 18 h. The solvent was decanted and the residue thoroughly washed with xylene and CH_2Cl_2. The combined organic layers were then washed with water and dried with Na_2SO_4. Removal of the solvent and purification by column chromatography (EtOAc/PE, 1:1) yielded 1.2 g (4.8 mmol, 64%) of **6** as an orange solid. IR (KBr): $\tilde{\nu}$ = 3314 (N−H), 3103, 2952 (C−H), 1708 (C=O), 1588 (C=C), 1526, 1434 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 213 (4.3), 265 (4.2), 282 (4.2), 329 (3.7), 382 (3.7) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 7.33 (d, *J* = 2.5 Hz, 1 H, 3-H), 7.61 (d, *J* = 1.5 Hz, 1 H, 6-H), 8.34 (d, *J* = 1.5 Hz, 1 H, 4-H), 9.32 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 52.4 (OCH_3), 56.1 (4-OCH_3), 99.5 (C-3), 110.9 (C-6), 113.0 (C-4), 126.7, 129.7, 130.9 (C-2, C-3a, C-7a), 143.6, 146.2 (C-5, C-7), 161.4 (C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 250 (100) [M^+]. $C_{11}H_{10}N_2O_5$ (250.21): calcd. C 250.0590; found 250.0600.

Methyl 7-(Benzyloxy)-5-nitro-1*H*-indole-2-carboxylate (7)

1. Cleavage of the Methyl Ether: A solution of **6** (50 mg, 200 μmol) in CH_2Cl_2 (50 mL) was treated with $AlCl_3$ (134 mg, 1.0 mmol) at room temp. and stirred for 72 h. The reaction was quenched by careful addition of ice/water and extracted with ethyl acetate. After drying of the extracts with Na_2SO_4, the solvents were removed in vacuo and the residue purified by column chromatography (EtOAc/PE, 1:2) to afford the corresponding phenol (33 mg, 139 μmol, 70%) as a brown solid.

Methyl 7-Hydroxy-5-nitro-1*H*-indole-2-carboxylate: IR (KBr): $\tilde{\nu}$ = 3303 (N−H), 1711 (C=O), 1523, 1404 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 215 (4.2), 267 (4.2), 283 (4.3) nm. ^1H NMR (200 MHz, [D_6]DMSO): δ = 3.87 (s, 3 H, OCH_3), 7.38 (d, *J* = 2.0 Hz, 1 H, 6-H), 7.43 (d, *J* = 2.2 Hz, 1 H, 4-H), 8.19 (d, *J* = 1.8 Hz, 1 H, 3-H), 10.54 (s, 1 H, NH), 12.25 (s, 1 H, OH) ppm. ^{13}C NMR (50.3 MHz, [D_6]DMSO): δ = 51.9 (OCH_3), 102.0 (C-3), 110.6 (C-6), 110.8 (C-4), 126.8 (C-2), 129.9 (C-7a), 131.0 (C-3a), 142.2 (C-7), 144.2 (C-5), 160.8 (C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 236 (100) [M^+].

2. Protection as the Benzyl Ether: K_2CO_3 (55 mg, 400 μmol) and, dropwise, benzyl bromide (0.02 mL, 200 μmol) were added at room temp. to a solution of the phenol (45 mg, 190 μmol) in acetone (15 mL). The reaction mixture was stirred for 8 h at 40 °C, washed with brine (100 mL) and extracted with ethyl acetate. After drying of the extracts with Na_2SO_4, the solvents were removed in vacuo and the residue purified by column chromatography (EtOAc/PE, 1:4) to afford **7** (55 mg, 167 μmol, 88%) as a yellow oil. IR (film): $\tilde{\nu}$ = 3327, 3295 (N−H), 2924, 2853 (C−H), 1704 (C=O), 1522, 1440 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 209 (4.4), 266 (4.3), 282 (4.3), 368 (3.7) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, OCH_3), 5.29 (s, 2 H, OCH_2), 7.35 (d, *J* = 2.2 Hz, 1 H, 3-H), 7.42−7.51 (m, 5 H, Ar-H), 7.72 (d, *J* = 1.9 Hz, 1 H, 4-H), 8.36 (d, *J* = 1.9 Hz, 1 H, 6-H), 9.34 (br. s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 52.4 (OCH_3), 71.0 (OCH_2), 100.3 (C-6), 110.9 (C-4), 113.1 (C-3), 126.6 (C-2*), 128.2, 128.8, 128.9 (Ar−C−H), 129.6 (C-3a*), 130.8 (C-7a*), 135.2 (Ar-C), 143.1 (C-5), 145.1 (C-7), 161.3 (C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 326 (10) [M^+], 91 (100) [$C_7H_7^+$]. $C_{17}H_{14}N_2O_5$ (326.30): calcd. C 62.57, H 4.32; found C 62.89, H 4.03.

Methyl 5-Amino-7-(benzyloxy)-1-(*tert*-butoxycarbonyl)indole-2-carboxylate (8)

1. Protection of the Indole: A solution of **7** (720 mg, 2.20 mmol) in THF (50 mL) was treated with di-*tert*-butyl dicarbonate (720 mg, 3.30 mmol) and catalytic amounts of DMAP and stirred for 1 h at room temp. The mixture was then quenched with brine and extracted with ethyl acetate, and the extracts were washed with water and brine and dried with Na_2SO_4. The solution was concentrated under reduced pressure and the residue purified by flash chromatography (EtOAc/PE, 1:2) to afford the *N*-Boc-protected indole (855 mg, 2.16 mmol, 98%) as a yellow oil.

Methyl 7-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-5-nitroindole-2-carboxylate: IR (film): $\tilde{\nu}$ = 3425 (N−H), 3101, 2982, 2951 (C−H), 1768, 1724 (C=O), 1516 (C=C), 1438, 1372 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 211 (4.4), 276 (4.4) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 3.94 (s, 3 H, OCH_3), 5.32 (s, 2 H, OCH_2), 7.34−7.39 (m, 6 H, 3-H, Ar-H), 7.46 (d, *J* = 1.9 Hz, 1 H, 4-H), 8.26 (d, *J* = 1.9 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.1 [$C(CH_3)_3$], 52.4 (OCH_3), 71.1 (OCH_2), 86.4 [$C(CH_3)_3$], 101.9 (C-6), 112.3 (C-4), 112.5 (C-3), 126.2 (C-7a*), 127.9, 128.5, 128.6 (Ar-CH), 129.8 (C-2*), 129.9 (C-3a*), 134.9 (Ar-C), 143.3, 145.4 (C-5, C-7), 149.1, 160.3 (C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 426 (63) [M^+], 91 (100) [$C_7H_7^+$].

2. Reduction of the Nitro Group: The nitroindole (900 mg, 2.10 mmol) was dissolved in ethyl acetate (150 mL), and Lindlar catalyst (294 g) and quinoline (0.30 mL, 294 mg, 2.28 mmol) were added. The suspension was stirred under hydrogen at room temp. for 16 h. The solid was removed by filtration through Celite and the solution was concentrated in vacuo. Purification by column chromatography (EtOAc/PE, 1:1) yielded **8** (756 mg, 1.91 mmol, 91%) as a brown oil. IR (film): $\tilde{\nu}$ = 3367 (N−H), 3004, 2978 (C−H), 1764, 1716, 1628 (C=O), 1581 (C=C), 1437, 1370 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 209 (4.5), 229 (4.3), 246 (4.4), 291 (4.1), 361 (3.5) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.38 [s, 9 H, $C(CH_3)_3$], 3.88 (s, 3 H, OCH_3), 5.13 (s, 2 H, OCH_2), 7.04 (s, 1 H, 3-H), 7.11 (s, 1 H, 4-H), 7.26−7.41 (m, 6 H, 6-H, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.2 [$C(CH_3)_3$], 51.9

(OCH_3), 70.3 (OCH_2), 84.6 [$C(CH_3)_3$], 98.1 (C-6), 100.0 (C-4), 110.4 (C-3), 122.5 (C-7a), 127.4, 127.7 (Ar-CH), 127.9 (C-2*), 128.5 (Ar-CH), 128.5 (C-3a*), 136.5 (Ar-C), 141.7 (C-5), 146.2 (C-7), 150.7, 161.24 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 396 (36) [M^+], 296 (100) [$M^+ - C_5H_8O_2$]. $C_{22}H_{24}N_2O_5$ (396.44): calcd. 396.1685; found 396.1685.

Methyl 7-(Benzyloxy)-4-bromo-1-(*tert*-butoxycarbonyl)-5-[(*tert*-butoxycarbonyl)amino]indole-2-carboxylate (9)

1. Protection of the Amino Group: A solution of **8** (475 mg, 1.2 mmol) in THF (150 mL) was treated with di-*tert*-butyl dicarbonate (786 mg, 3.60 mmol) and stirred for 18 h at room temp. The mixture was quenched with brine, extracted with ethyl acetate, and the extracts were washed with water and brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (EtOAc/PE, 1:2) to yield the corresponding carbamate (529 mg, 1.07 mmol, 89%) as a yellow oil.

Methyl 7-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-5-[(*tert*-butoxycarbonyl)amino]indole-2-carboxylate: IR (film): $\tilde{\nu}$ = 3356 (N−H), 2979 (C−H), 1769, 1722 (C=O), 1590 (C=C), 1531, 1456, 1369 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 217 (4.4), 251 (4.6), 292 (4.1), 333 (3.5), 288 (4.1) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 1.51 [s, 9 H, $C(CH_3)_3$], 3.89 (s, 3 H, OCH_3), 5.21 (s, 2 H, OCH_2), 6.42 (br. s, 1 H, NH), 6.82 (d, *J* = 1.5 Hz, 1 H, 4-H), 7.09 (s, 1 H, 3-H), 7.27−7.42 (m, 6 H, 6-H, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.2, 28.4 [$C(CH_3)_3$], 51.9 (OCH_3), 70.5 (OCH_2), 80.4, 84.9 [$C(CH_3)_3$], 101.6 (C-6), 103.7 (C-4), 111.2 (C-3), 124.4 (C-7a), 127.7 (Ar-CH), 127.9 (C-2*), 128.0 (Ar-CH), 128.1 (C-3a*), 128.5 (Ar-CH), 133.1 (Ar-C), 136.2 (C-5), 145.7 (C-7), 150.3, 153.0, 161.24 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 496 (18) [M^+], 396 (25) [$M^+ - C_5H_8O_2$], 91 (100) [$C_7H_7^+$].

2. Bromination: The carbamate (450 mg, 907 μmol) was dissolved in THF (150 mL) and *N*-bromosuccinimide was slowly added with stirring at −78 °C. The reaction mixture was allowed to warm to room temperature, and then extracted with EtOAc and dried with Na_2SO_4. Concentration in vacuo and purification by column chromatography yielded **9** (459 mg, 798 μmol, 88%) as a light yellow oil. IR (film): $\tilde{\nu}$ = 3342 (N−H), 2978 (C−H), 1761, 1728 (C=O), 1579 (C=C), 1545, 1455, 1368 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 216 (4.4), 249 (4.6), 295 (4.1), 327 (3.7) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 1.53 [s, 9 H, $C(CH_3)_3$], 3.90 (s, 3 H, OCH_3), 5.24 (s, 2 H, OCH_2), 6.89 (br. s, 1 H, NH), 7.17 (s, 1 H, 3-H), 7.32−7.46 (m, 5 H, Ar-H), 7.87 (s, 1 H, 6-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.1, 28.3 [$C(CH_3)_3$], 52.1 (OCH_3), 70.9 (OCH_2), 80.9, 85.5 [$C(CH_3)_3$], 101.9 (C-4), 102.0 (C-6), 110.8 (C-3), 123.9, 127.8, 127.9 (C-2, C-3a, C-7a), 128.2, 128.5, 128.5 (Ar-CH), 131.2 (Ar-C), 135.8 (C-5), 145.4 (C-7), 149.7, 152.7, 160.7 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 574 (10) [M^+], 474 (15) [$M^+ - C_5H_8O_2$], 91 (100) [$C_7H_7^+$]. $C_{27}H_{31}BrN_2O_7$ (575.45): calcd. 574.1314; found 574.1314.

Methyl (1*R*/*S*)-1-(Chloromethyl)-5-hydroxy-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (3)

1. Alkylation: Compound **9** (408 mg, 709 μmol) was dissolved in DMF (15 mL) and treated with NaH (60% in oil, 51.1 mg, 2.13 mmol). After stirring at room temperature for 30 min, 1,3-dichloro-2-propene (157 mg, 1.42 mmol) was added. The mixture was quenched with saturated aq. NH_4Cl after 12 h at room temperature. It was then extracted several times with ethyl acetate, and the extracts were washed with water and brine and dried with Na_2SO_4. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/PE, 1:2). The alkylated indole **10** (423 mg, 652 μmol, 92%) was obtained as a yellow oil as a mixture of rotamers.

Methyl (*E*/*Z*)-7-(Benzyloxy)-4-bromo-1-(*tert*-butoxycarbonyl)-5-[(*tert*-butoxycarbonyl)(3′-chloroprop-2′-enyl)amino]indole-2-carboxylate (10): IR (film): $\tilde{\nu}$ = 3066, 2980 (C−H), 1774, 1726 (C=O), 1575 (C=C), 1543, 1454, 1371 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 249 (4.4), 293 (3.9), 323 (3.5) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25, 1.27 [s, 9 H, $C(CH_3)_3$], 1.29, 1.39 [s, 9 H, $C(CH_3)_3$], 3.83−3.93 (m, 5 H, OCH_3, 1′-H_2), 5.24 (s, 2 H, OCH_2), 5.89−6.10 (m, 2 H, 2′-H, 3′-H), 7.17 (s, 1 H, 3-H), 7.27−7.46 (m, 6 H, 6-H, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.2, 28.1 [$C(CH_3)_3$], 45.9 (C-1′), 52.2 (OCH_3), 70.6 (OCH_2), 80.5, 85.8 [$C(CH_3)_3$], 107.8 (C-4), 109.9 (C-6), 111.8 (C-3), 120.4, 121.5 (C-2′, C-3′), 127.3 (C-7a), 127.4, 128.2, 128.7 (Ar-CH), 135.7 (Ar-C), 135.8 (C-2), 144.5 (C-3a), 149.7 (C-5), 154.3 (C-7), 160.7, 160.7, 171.1 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 648 (5) [M^+], 91 (100) [$C_7H_7^+$].

2. Radical Cyclization: A solution of the alkylated indole **10** (429 mg, 662 μmol) in benzene (20 mL) was degassed thoroughly and treated with tris(trimethylsilyl)silane (TTMSS) (0.22 mL, 176 mg, 707 μmol) and AIBN (25 mg, 153 μmol). After 3 h of stirring at 80 °C, the volatiles were removed in vacuo and the residue was purified by flash chromatography (EtOAc/PE, 1:2) to give **11** (299 mg, 523 μmol, 79%) as a yellow oil.

Methyl (1*R*/*S*)-5-(Benzyloxy)-3,6-bis(*tert*-butoxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (11): IR (film): $\tilde{\nu}$ = 3031, 2978, 2929 (C−H), 1771, 1722 (C=O), 1591 (C=C), 1539, 1369 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 251 nm (4.4), 293 (3.9), 332 (3.5) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 1.51 [s, 9 H, $C(CH_3)_3$], 3.80−4.14 (m, 5 H, 1-H, 2-H_2, 9-H_2), 3.90 (s, 3 H, OCH_3), 5.24 (s, 2 H, OCH_2), 7.08−7.21 (m, 3 H, Ar-H), 7.27−7.44 (m, 4 H, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.1, 28.5 [$C(CH_3)_3$], 42.0 (C-1), 46.8 (C-2), 52.1 (OCH_3), 52.9 (C-9), 70.7 (OCH_2), 85.3 [$C(CH_3)_3$], 97.9 (C-6), 107.7 (C-3), 122.3 (C-7a), 123.7 (C-4), 124.5 (C-2), 127.3, 128.1, 128.5 (Ar-CH), 136.1 (Ar-C), 146.3, 150.1, 152.3 (C-3a, C-5, C-7), 160.8, 171.2 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 570 (20) [M^+], 470 (15) [$M^+ - C_5H_8O_2$], 91 (100) [$C_7H_7^+$].

3. Coupling with the TMI Group: Compound **11** (127 mg, 229 μmol) was dissolved in 4 M HCl in EtOAc (10 mL) and stirred for 2 h at room temperature. The solution was concentrated in vacuo, and the residue was thoroughly dried under vacuum. The resulting unstable amine hydrochloride was subsequently dissolved in dry degassed DMF (15 mL) and 5,6,7-trimethoxyindole-2-carboxylic acid (TMI-CO_2H; 172 mg, 687 μmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (131 mg, 687 μmol) were added. The solution was stirred for 20 h at room temp. and poured into brine (100 mL). The product was extracted with ethyl acetate, washed with brine (200 mL) and dried with Na_2SO_4. Concentration and purification by column chromatography (EtOAc/PE, 1:2) afforded **12** (70 mg, 116 μmol, 51%) as a light yellow solid.

Methyl (1*R*/*S*)-5-(Benzyloxy)-1-(chloromethyl)-3-[(5,6,7-trimethoxyindole-2-yl)carbonyl]-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (11): IR (KBr): $\tilde{\nu}$ = 3462, 3300 (N−H), 2925 (C−H), 1713 (C=O), 1526 (C=C), 1492, 1440 (CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 208 (4.7), 236 (4.4), 304 (4.4), 332 (4.4) nm. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.59 (t, *J* = 9.8 Hz, 1 H, 2-H_a), 3.90 (s, 3 H, OCH_3), 3.92 (s, 6 H, 2× OCH_3), 4.07 (s, 3 H,

OCH_3), 4.10 (m, 2 H, 1-H, 2-H_b), 4.58−4.78 (m, 2 H, 9-H_2), 5.26 (s, 2 H, OCH_2), 6.88 (s, 1 H, 4′-H), 6.98 (d, J = 2.2 Hz, 1 H, 8-H), 7.15 (d, J = 2.2 Hz, 1 H, 3′-H), 7.40−7.49 (m, 5 H, Ar-H), 8.19 (s, 1 H, 4-H), 9.17 (s, 1 H, NH), 9.43 (s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 43.6 (C-1), 46.5 (C-2), 52.2 (OCH_3), 55.1 (C-9), 56.3 (OCH_3), 61.1 (OCH_3), 61.5 (OCH_3), 70.6 (OCH_2), 97.6 (C-4′), 98.5 (C-4), 105.8 (C-8), 106.3 (C-3′), 114.3 (C-6′), 123.5, 123.7, 125.4, 126.1, 128.1 (C-3a′, C-5a, C-7a′, C-8a, C-8b), 128.1, 128.12, 128.64 (Ar-CH), 130.1, 136.1, 138.7, 138.8, 140.4 (C-2′, C-3a, C-5′, C-7, C-7′), 145.6 (Ar-C), 150.1 (C-5), 159.8 (NC=O), 161.7 (C=O) ppm. MS (70 eV, EI): m/z (%) = 603 (100) [M^+].

4. Debenzylation: A 25% aq. solution of NH_4HCO_2 (0.60 mL) and 10% Pd/C (60 mg, 57 μmol) were added at 0 °C to a solution of benzyl ether **12** (179 mg, 297 μmol) in THF (25 mL). After stirring for 4 h at 40 °C, the solid was removed by filtration through Celite, which was washed thoroughly with THF. The concentrated filtrate was purified by flash chromatography (EtOAc/PE, 1:2) to afford **3** (138 mg, 270 μmol, 91%) as a pale yellow solid.

Methyl (1*R*/*S*)-1-(Chloromethyl)-5-hydroxy-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (3): IR (KBr): $\tilde{\nu}$ = 3446 (N−H, O−H), 2936, 2836 (C−H), 1718 (C=O), 1587, 1527, 1494 (C=C, CH_2, CH_3) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 207 (3.0), 238 (4.3), 304 (4.5), 329 (4.4) nm. ^{1}H NMR (300 MHz, [D_6]acetone): δ = 3.85 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.88 (m, 1 H, 9-H_a), 3.89 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.13 (d, J = 4.0 Hz, 1 H, 9-H_b), 4.17 (m_c, 1 H, 1-H), 4.58 (dd, J = 10.9, 4.0 Hz, 1 H, 2-H_a), 4.77 (m, 1 H, 2-H_b), 6.96 (d, J = 8.3 Hz, 1 H, 4′-H), 7.05 (dd, J = 8.3, 2.3 Hz, 1 H, 3′-H), 7.21 (s, 1 H, 8-H), 7.96 (s, 1 H, 4-H), 9.01 (br. s, 1 H, OH), 10.21 (br. s, 1 H, NH), 10.75 (br. s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, [D_6]acetone): δ = 34.2 (C-1), 51.6 (OCH_3), 55.7 (C-2), 55.9 (OCH_3), 58.6 (C-9), 60.8 (OCH_3), 60.9 (OCH_3), 97.9 (C-4), 100.5 (C-4′), 105.4 (C-8), 105.8 (C-3′), 118.4 (C-5a), 123.1, 123.6, 124.9, 125.8, 127.6, 131.6, 136.6, 138.9, 139.5, 142.5, 148.9 (C-2′, C-3a, C-3a′, C-5, C-5′, C-7, C-7′, C-7a, C-7a′, C-8a, C-8b), 159.4 (NC=O), 161.3 (C=O) ppm. MS (70 eV, EI): m/z (%) = 513 (12) [M^+]. $C_{25}H_{24}ClN_3O_7$ (513.93): calcd. 513.1303; found 513.1302.

Acknowledgments

This research was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 416) and the Fonds der Chemischen Industrie. F. H. thanks the Fonds der Chemischen Industrie for a Ph.D. fellowship. Gifts of chemicals by BASF AG, Bayer AG, Degussa AG, Dragoco Gerberding & Co. AG and Wacker-Chemie GmbH are gratefully acknowledged.

[1] M. Ichimura, T. Ogawa, K. Takahashi, E. Kobayashi, I. Kawamoto, T. Yasuzawa, I. Takahashi, H. Nakano, *J. Antibiot.* **1990**, *43*, 1037−1038.
[2] M. Ichimura, T. Ogawa, S. Katsumata, K. Takahashi, I. Takahashi, H. Nakano, *J. Antibiot.* **1991**, *44*, 1045−1053.
[3] D. L. Boger, S. Johnson, *Angew. Chem.* **1996**, *108*, 1542−1580; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1438−1474.
[4] L. J. Hanka, A. Dietz, S. A. Gerpheide, S. L. Kuentzel, D. G. Martin, *J. Antibiot.* **1978**, *31*, 1211−1217.
[5] D. L. Boger, D. S. Johnson, W. Yun, *J. Am. Chem. Soc.* **1994**, *116*, 1635−1656.
[6] R. Baird, S. Winstein, *J. Am. Chem. Soc.* **1963**, *85*, 567−578.
[7] D. L. Boger, K. Machiya, D. L. Hertzog, P. A. Kitos, D. Holmes, *J. Am. Chem. Soc.* **1993**, *115*, 9025−9036.
[8] D. L. Boger, C. W. Boyce, R. M. Garbaccio, J. A. Goldberg, *Chem. Rev.* **1997**, *97*, 787−828.
[9] L.F. Tietze, M. Lieb, T. Herzig, F. Haunert, I. Schuberth, *Bioorg. Med. Chem.* **2001**, *9*, 1929−1939.
[10] L. F. Tietze, T. Herzig, A. Fecher, F. Haunert, I. Schuberth, *ChemBioChem* **2001**, 758−765.
[11] L. F. Tietze, T. Feuerstein, A. Fecher, F. Haunert, O. Panknin, U. Borchers, I. Schuberth, F. Alves, *Angew. Chem.* **2002**, *114*, 785−787; *Angew. Chem. Int. Ed.* **2002**, *41*, 759−761.
[12] L. F. Tietze, T. Herzig, T. Feuerstein, *Eur. J. Org. Chem.* **2002**, 1634−1645.
[13] A. Guy, J.-P. Guetté, *Synthesis* **1980**, 222−223.
[14] A. Studer, S. Amrein, *Angew. Chem.* **2000**, *112*, 3196−3198; *Angew. Chem. Int. Ed.* **2000**, *39*, 3080−3082.
[15] V. F. Patel, S. L. Andis, J. K. Endema, D. A. Johnson, J. H. Kennedy, F. Mohamadi, R. M. Schultz, D. J. Soose, M. M. Spees, *J. Org. Chem.* **1997**, *62*, 8868−8874.

Received August 2, 2002
[O02453]