DOI: 10.1002/chem.200701521

Synthesis of a Novel Pentagastrin-Drug Conjugate for a Targeted Tumor Therapy

Lutz F. Tietze,* Olaf Panknin, Felix Major, and Birgit Krewer[a]

Dedicated to Professor Peter Hofmann on the occasion of his 60th birthday

Abstract: The synthesis of the novel pentagastrin seco-CBI conjugate **3**, which is based on the highly cytotoxic antitumor antibiotic (+)-duocarmycin SA (**1**), is reported. A key step in the synthesis is the palladium-catalyzed carbonylation of aryl bromide **7** to give the benzyl ester **16**, which is transformed into the new seco-CBI derivative **21** bearing a carboxylic acid ester moiety. Subsequent transformation of **21** into an activated ester followed by the introduction of β-alanine and tetragastrin led to the new pentagastrin drug **3** that contains a peptide moiety for targeting cancer cells expressing CCK-B/gastrin receptors.

Keywords: antibiotics · antitumor agents · carbonylation · duocarmycins · pentagastrin · targeting

Introduction

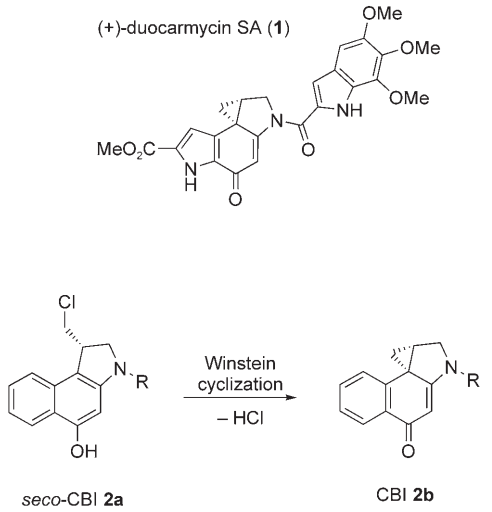
One of the main problems in anticancer therapy is the usually low differentiation between normal and malignant cells by the known antiproliferating agents, thus causing severe side effects. An approach to overcome this problem is the antibody-directed enzyme prodrug therapy (ADEPT).[1,2] Another promising concept is the use of ligands of low molecular weight for tumor targeting that are able to transport diagnostic or antineoplastic agents to the tumor. Among these ligands, small peptides play an important role, which is a result of their better tumor penetration and lower immunogenicity relative to antibodies as well as their high specifities and affinities to receptors that are often overexpressed on certain cancer cells.[3] Some of these peptides that are already successfully applied in cancer therapy belong to the gastrin family. For example, radio labeled gastrin derivatives have shown a high therapeutic and diagnostic potential in targeting cholecystokinin (CCK-B)/gastrin receptor expressing tumors.[4] In addition, a gastrin analogue was linked to a triazene alkylating agent.[5] However, the observed receptor-mediated cytotoxicity was quite low. Better results were obtained with heptagastrin linked to a potently cytotoxic ellipticine derivative.[6] A high receptor-mediated cytotoxicity could also be achieved with the anthracyclines daunorubicin, doxorubicin, and 2-pyrrolinodoxorubicin as well as other cytotoxic agents such as melphalan, cisplatin, or methotrexate coupled to analogues of peptides like LHRH,[3,7] bombesin,[3,7a,8] somatostatin,[3,7a,9] and neuropeptide Y.[3,10] This is in agreement with our observations that only highly potent anticancer agents are suitable for such an approach.

Here we describe the synthesis of a gastrin derivative based on the naturally occurring antibiotic (+)-duocarmycin SA (**1**), which is a particularly potent cytotoxic compound with an IC_{50} value of 10 pM (L1210).[11]

The antiproliferative effect of **1** and its analogues, such as CBI **2b**, derives most probably from a selective alkylation of the N-3 atom of adenine in DNA by nucleophilic attack at the spirocyclopropyl–cyclohexadienone moiety as the pharmacophoric group.[12] To improve the accessibility of a potential prodrug based on this concept, we decided not to use CBI **2b** but the corresponding seco-compound **2a** for conjugation with the peptide. It has been shown by us and others in in vitro experiments that seco-compound **2a** has nearly the same cytotoxicity as the corresponding CBI compound **2b** as it can easily cyclize under basic conditions in a so-called Winstein cyclization to give **2b** (Scheme 1).[1,12,13] Furthermore, we decided not to use the whole heptadecapeptide gastrin but the shorter β-alanine modified pentagastrin

[a] Prof. Dr. L. F. Tietze, Dr. O. Panknin, Dr. F. Major, Dipl.-Chem. B. Krewer
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstraße 2, 37077 Göttingen (Germany)
Fax: (+49) 551-39-9476
E-mail: ltietze@gwdg.de

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.



Scheme 1. Structures of (+)-duocarmycin SA (**1**), seco-CBI **2a**, and CBI **2b**.

because its β-Ala-Trp-Met-Asp-Phe-NH_2 sequence representing the C-terminal amide of the natural peptides restores the whole biological activity of gastrin in a comparable order of magnitude.[3e,14] As a consequence, the cytotoxic agent had to be attached to the N-terminal amino function of pentagastrin. This resulted in the requirement of a seco-CBI derivative with a carboxylic acid moiety by which an amide linkage to the peptide could be achieved. This linkage should be located in a position that neither the receptor affinity nor the drug's mode of action should be influenced. Therefore, we decided to prepare molecule **3**, the synthetic strategy of which is outlined in Scheme 2.

Thus, coupling of the central seco-CBI unit **5** with TMI-CO_2H **6** as the DNA-binding subunit and finally with pentagastrin (**4**) should provide **3**. The introduction of the carboxylic acid moiety in **5** could be performed by means of a palladium-catalyzed carbonylation of bromide **7**.

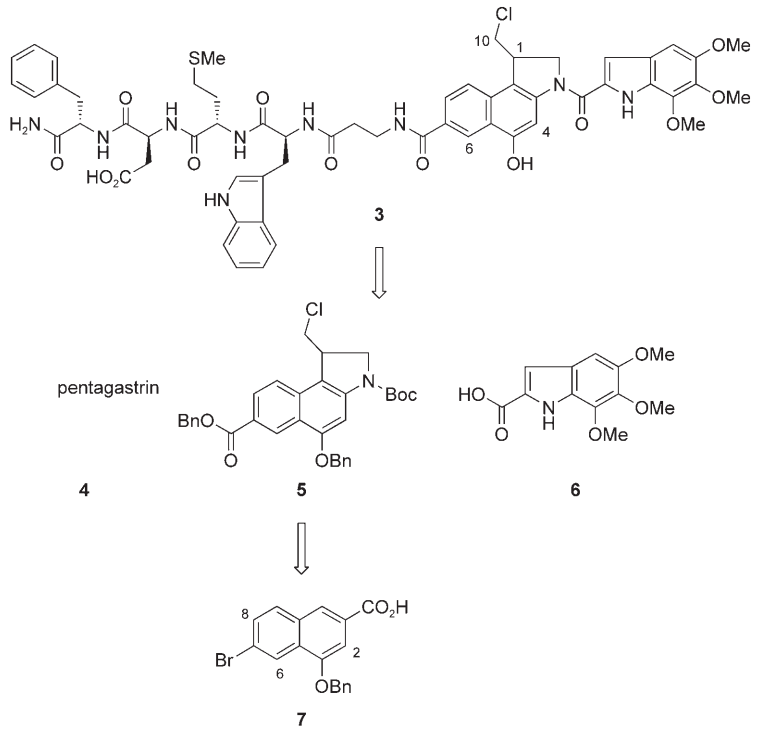
Results and Discussion

The synthesis of the necessary substrate **7** was performed according to an approach developed by Boger et al. for a similar system.[15] Thus, a Horner–Wadsworth–Emmons reaction between the commercially available 4-bromobenzaldehyde (**8**) and phosphonate **9**[16] with NaH in THF provided the *E*-configurated styrene **10** in 74% yield (Scheme 3).

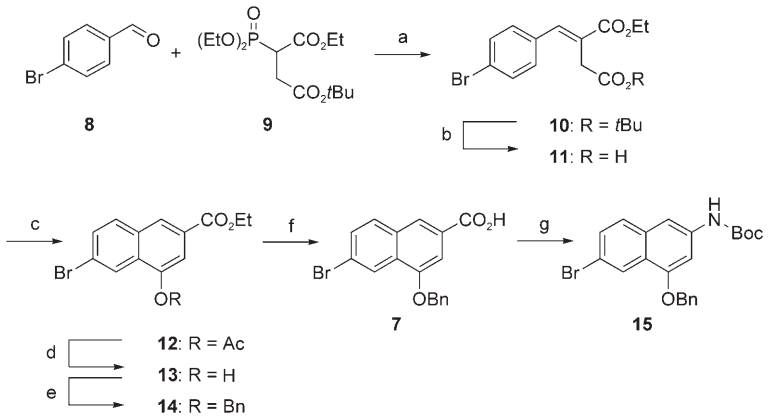
Selective hydrolysis of the *tert*-butyl ester in **10** with a TFA/water mixture followed by a Friedel–Crafts acylation by using Ac_2O and NaOAc yielded **12** in 78% via **11** over two steps. Then, deprotection of the O-acetate moiety in **12** with K_2CO_3 in EtOH and reprotection under standard conditions by using benzyl bromide, K_2CO_3, and catalytic amounts of TBAI in DMF afforded benzyl ether **14** via **13** in 95% yield over two steps. After this, ethyl ester **14** was hydrolyzed with $LiOH{\cdot}H_2O$ to give carboxylic acid **7** in 85% yield. Finally, a Curtius rearrangement of **7** with DPPA and NEt_3 in *t*BuOH led directly to the protected naphtholamine **15** in 85% yield.

For the introduction of the carboxylic acid moiety in **15**, which is necessary for coupling with pentagastrin, we tried to perform a palladium-catalyzed carbonylation of **15**. However, this gave only a moderate yield, probably due to the high electron density of the substrate resulting in a low reaction rate of the oxidative addition as the first step. We, therefore, used bromide **7** which contains an electron-withdrawing group (Scheme 4). But when using **7** as the substrate, the new carboxylic ester group had to be introduced as an easily cleavable ester to enable a differentiation between the two carboxyl moieties then existing in the molecule. However, a corresponding published carbonylation of an aryl bromide by using benzyl alcohol gave the corresponding benzyl ester in only 30% yield.[17]

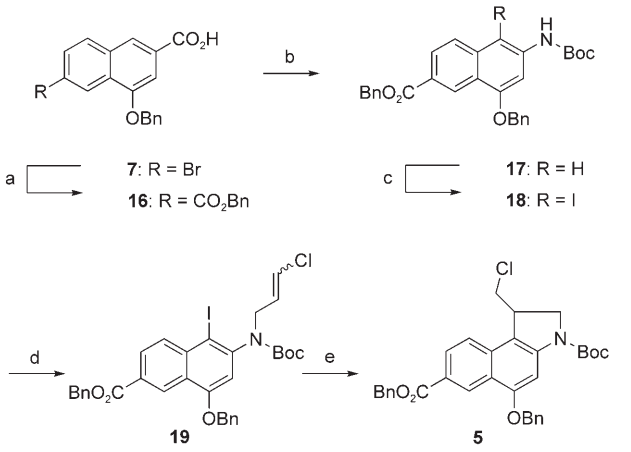
Fortunately, heating **7** under a CO atmosphere (1 bar) with $[PdBr_2(PPh_3)_2]$ as the catalyst and dppf[18] and $N(n\mathrm{Bu})_3$



Scheme 2. Retrosynthetic analysis of drug **3**.



Scheme 3. Synthesis of precursors **7** and **15**: a) NaH, THF, 0–20 °C, 22.5 h, 74 %; b) TFA/H_2O, 20 °C, 4.5 h, quant.; c) Ac_2O, NaOAc, reflux, 1 h, 78 %; d) K_2CO_3, EtOH, reflux, 1.5 h, 95 %; e) K_2CO_3, BnBr, TBAI, DMF, 20 °C, 1 d, quant.; f) LiOH·H_2O, THF/MeOH/H_2O, 20 °C, 3 d, 85 %; g) DPPA, *t*BuOH, NEt_3, MS (4) Å), reflux, 2.5 d, 85 %. DPPA = diphenylphosphoryl azide; TBAI = tetrabutylammonium iodide; TFA = trifluoroacetic acid.

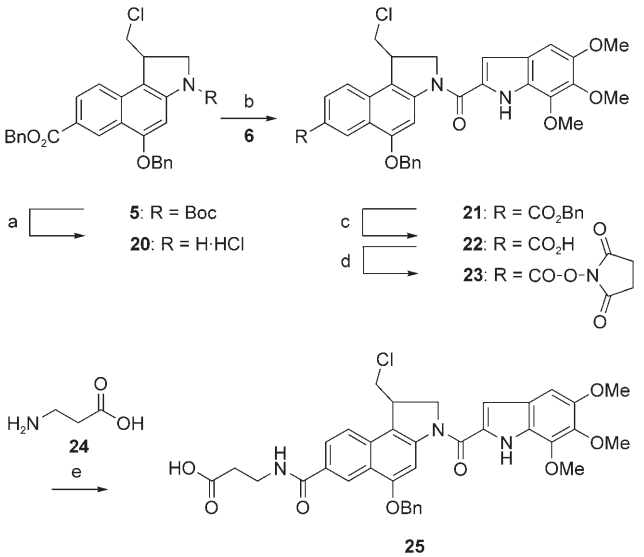


Scheme 4. Synthesis of seco-CBI compound **5**: a) 1 bar CO, 5 mol % [$PdBr_2(PPh_3)_2$], 20 mol % dppf, N(*n*Bu)$_3$, BnOH, 85–130 °C, 95 min, 82 %; b) DPPA, *t*BuOH, NEt_3, MS (4) Å, reflux, 3.5 d, 65 %; c) NIS, TsOH·H_2O, THF/MeOH, 50 °C, 40 min, 99 %; d) NaH, 1,3-dichloropropene, DMF, 20 °C, 20.5 h, 85 %; e) HSi(SiMe$_3$)$_3$, AIBN, benzene, reflux, 3 h, 87 %. AIBN = azo-bis-isobutyronitrile; Boc = *tert*-butoxycarbonyl; dppf = bis(diphenylphosphino)ferrocene; NIS = N-iodosuccinimide; Ts = tosyl.

in benzylic alcohol as the solvent afforded the benzyl ester **16** in an excellent yield of 82 %.[19] After Curtius rearrangement under the aforementioned conditions to give **17** and iodination, employing NIS[15,20] and by using TsOH·H_2O as the catalyst, the iodide **18** was obtained in 64 % yield over two steps. N-Alkylation of the generated sodium salt of **18** by using 1,3-dichloropropene afforded an *E*/*Z* mixture of alkene **19**. This alkene was submitted to a 5-*exo*-*trig* radical cyclization[21] by using the comparatively untoxic tris(trimethylsilyl)silane (TTMSS)[22] as the hydride source and AIBN as the radical starter, providing seco-CBI derivative **5** in 74 % yield over two steps.

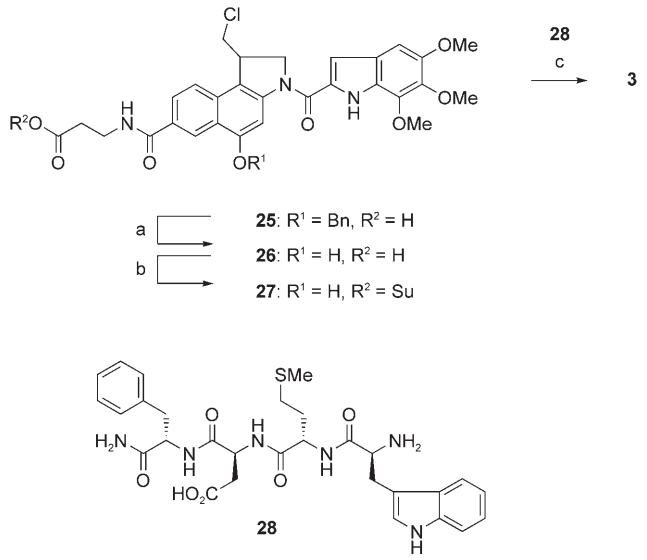
For the coupling reaction with the DNA-binding indole subunit, the Boc group in **5** was cleaved under acidic conditions in an aqueous HCl/EtOAc mixture with Et_3SiH as the cation scavenger[23] (Scheme 5). The obtained hydrochloride **20** was directly coupled with TMI-CO_2H **6**,[24] employing EDC·HCl as the coupling reagent to give **21** in 63 % yield over two steps. To connect **21** with the peptide, the benzyl ester was selectively cleaved with LiOH·H_2O to afford **22** in 79 % yield without any loss of the primary chloride.

Coupling with pentagastrin was performed in a stepwise manner. Earlier attempts to couple pentagastrin directly to the aromatic carboxylic acid **22** were not successful. To diminish complications, we decided to couple the seco-CBI scaffold with β-alanine (**24**) first. This amino acid is part of the pentagastrin sequence and should at the same time serve as a spacer unit. To avoid protection steps we first synthesized the active ester of **22**. As activator HOSu[5] was used, which gave active ester **23** upon coupling with acid **22** by using EDC·HCl. This ester was reacted without further purification with unprotected β-alanine (**24**), employing NEt*i*Pr$_2$ as the base to give **25** in 69 % yield over two steps. At this stage, the benzyl ether moiety in **25** had to be cleaved because any attempts to cleave the ether group after the introduction of the pentagastrin



Scheme 5. Synthesis of **25**: a) HCl/EtOAc, Et_3SiH, 20 °C, 3 h; b) **6**, EDC·HCl, DMF, 20 °C, 1 d, 63 % (two steps); c) LiOH·H_2O, THF/MeOH/H_2O, 0–20 °C, 3.5 h, 79 %; d) HOSu, EDC·HCl, THF, 0–20 °C, 13 h; e) NEt*i*Pr$_2$, H_2O/MeCN, 20 °C, 7 h, 69 % (two steps). EDC·HCl = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOSu = *N*-hydroxysuccinimide.

moiety were not successful. The debenzylation was achieved under transfer hydrogenolytic conditions with an aqueous ammonium formate solution and with palladium on charcoal as the catalyst[25] to afford the phenol **26**, which was used in the next reaction step without any purification. Thus, **26** was transferred into the active ester **27** with HOSu under the aforementioned conditions; then, **27** was directly coupled with the fully unprotected tetrapeptide **28**[26] to give pentagastrin seco-CBI drug **3** in 27% yield over three steps (Scheme 6).



Scheme 6. Synthesis of seco-CBI pentagastrin drug **3**: a) Pd/C, NH_4HCO_2, THF/MeOH, 20 °C, 2.5 h; b) HOSu, EDC·HCl, THF/CH_2Cl_2/DMF, 0–20 °C, 28.5 h; c) NE*t*Pr_2, DMF, 20 °C, 57 h, 27% (three steps).

Both reactions, the activation step and the coupling step, showed only slow conversion with the last transformation giving the lowest yields, but no significant formation of side products was observed, although the phenolic hydroxyl group was unprotected. We assume that this is due to the low nucleophilicity of the phenol moiety; however, under basic conditions, a fast cyclization of the seco-CBI to the CBI-pharmacophore takes place.

Conclusions

We have designed the new cytotoxic compound **3** for a selective treatment of cancer based on the assumption that the pentagastrin moiety allows a selective incorporation of **3** into cancer cells which overexpress the CCK-B/gastrin receptor. To guaranty a high reactivity of the drug, we used a seco-duocarmycin analogue with a carboxylic acid moiety at one of the aromatic rings of the CBI pharmacophore to allow the introduction of the pentagastrin by an amide bond. The biological activity of this new type of anticancer agent is currently being investigated in our cell-culture lab by using cancer cell lines expressing the gastrin receptor.

Experimental Section

General: All reactions were performed in flame-dried glassware under an argon atmosphere. Solvents were dried and purified according to standard procedures and redistilled prior to use. TLC chromatography was performed on precoated aluminum silica gel SIL G/UV254 plates (Macherey–Nagel) and silica gel 60 (0.040–0.063 mm) (Merck) was used for column chromatography. IR spectroscopy: Bruker Vector 22. UV/VIS: Perkin–Elmer Lambda 2. ^{1}H NMR spectroscopy: Varian Mercury-200, Unity-300 (300 MHz), Unity Inova-600 (600 MHz). ^{13}C NMR spectroscopy: Varian Mercury-200 (50 MHz), Unity-300 (75 MHz), Unity Inova-600 (150 MHz). For ^{1}H and ^{13}C NMR spectroscopy, $CDCl_3$, [D_6]DMSO, and [D_7]DMF were used as solvents. Chemical shifts are reported on a δ scale. Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), m_c (centered multiplet), and br (broad). MS: Finnigan MAT 95, TSQ 7000, LCQ. HRMS was carried out by using, among others, a modified peak matching technique, error ± 2 ppm, with a resolution of ca. 10,000. Elemental analysis: Mikroanalytisches Labor des Institutes für Organische und Biomolekulare Chemie der Universität Göttingen.

***tert*-Butyl-(*E*)-3-(ethoxycarbonyl)-4-(4-bromophenyl)-3-butenoate (10)**: NaH (13.0 g, 60% in oil, 326 mmol) was washed with dry *n*-pentane, dried for ca. 15 min under reduced pressure, and then suspended in THF (500 mL). Phosphonate **9** (296 mmol, 100 g) was added dropwise at 0 °C and stirring was continued at 20 °C for 4.5 h. The mixture was again cooled to 0 °C and added by cannula to a solution of 4-bromobenzaldehyde (**8**) (60.3 g, 326 mmol) in THF (250 mL) also maintained at 0 °C. The reaction mixture was warmed to 20 °C, stirred for a further 18 h, and the solvent removed under reduced pressure. The ensuing red residue was dissolved in CH_2Cl_2 (300 mL), washed with water (3×100 mL), brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product (81.0 g, 74%) was used for the next reaction without further purification. An analytically pure sample was obtained after column chromatography by using pentane/Et_2O (10:1) as the eluent. $R_f = 0.44$ (pentane/Et_2O 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 1.33 (t, $J = 7.0$ Hz, 3H; OCH_2CH_3), 1.45 (s, 9H; $C(CH_3)_3$), 3.40 (s, 2H; 2-H_2), 4.27 (q, $J = 7.0$ Hz, 2H; OCH_2CH_3), 7.20–7.25 (m, 2H; Ar-H), 7.49–7.54 (m, 2H; Ar-H), 7.76 ppm (s, 1H; 4-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.85$ (OCH_2CH_3), 27.54 ($C(CH_3)_3$), 34.36 (C-2), 60.64 (OCH_2CH_3), 80.52 ($C(CH_3)_3$), 122.54 (C-3), 127.17 (C-4′), 130.16, 131.32 (C-2′, C-3′, C-5′, C-6′), 133.65 (C-1′), 139.34 (C-4), 166.58 (*C*(O)OEt), 169.48 ppm (C-1); MS (DCI, NH_3, 200 eV): *m*/*z* (%): 754 (4) $[2M+NH_4]^+$, 386 (100) $[M+NH_4]^+$, 369 (12) $[M+H]^+$.

(*E*)-3-Ethoxycarbonyl-4-(4-bromophenyl)-but-3-enoic acid (11): Crude **10** (75.0 g, 203 mmol) was dissolved in 9:1 TFA/H_2O (145 mL) and stirred for 4.5 h at 20 °C. The solvent was removed under reduced pressure and the resulting residue treated with toluene (2×100 mL) and then again concentrated under reduced pressure. After cooling to 0 °C, the residue was treated with $NaHCO_3$ (150 mL, saturated solution), adjusted to pH 1 with HCl (2 N) and extracted with EtOAc (4×100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product (76.0 g, quant.) was afforded as a yellow oil and used for the next reaction without further purification. An analytically pure sample was obtained after column chromatography by using pentane/EtOAc 2:1 as the eluent. $R_f = 0.30$ (pentane/EtOAc 2:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J =$ 7.3 Hz, 3H; OCH_2CH_3), 3.54 (s, 2H; 2-H_2), 4.31 (q, $J = 7.3$ Hz, 2H; OCH_2CH_3), 7.22–7.26 (m, 2H; Ar-H), 7.53–7.57 (m, 2H; Ar-H), 7.84 (s, 1H; 4-H), 10.05 ppm (br s, 1H; CO_2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 14.15 (OCH_2CH_3), 33.54 (C-2), 61.53 (OCH_2CH_3), 123.40 (C-3), 126.12 (C-4′), 130.51, 131.95 (C-2′, C-3′, C-5′, C-6′), 133.58 (C-1′), 141.07 (C-4), 167.14 (*C*(O)OEt), 176.77 ppm (C-1); MS (DCI, NH_3, 200 eV): *m*/*z* (%): 642 (2) $[2M+NH_4]^+$, 347 (12) $[M+NH_3+NH_4]^+$, 330 (65) $[M+NH_4]^+$, 286 (100) $[M-CO_2+NH_4]^+$.

Ethyl-1-acetoxy-7-bromo-3-naphthalene carboxylate (12): A solution of the crude acid **11** (63.6 g, 203 mmol) in acetic anhydride (1.20 L) was treated with sodium acetate (29.9 g, 305 mmol) and stirred for 1 h under reflux. The hot reaction mixture was poured into water (2.00 L) and

cooled to 20 °C. The precipitated product (54.0 g, 78 %) was collected by filtration and used for the next reaction without further purification. R_f = 0.50 (pentane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 (t, J = 7.1 Hz, 3H; OCH_2CH_3), 2.50 (s, 3H; CH_3), 4.43 (q, J = 7.1 Hz, 2H; OCH_2CH_3), 7.65 (dd, J = 8.4, 1.9 Hz, 1H; 6-H), 7.85 (d, J = 8.4 Hz, 1H; 5-H), 7.86 (d, J = 1.6 Hz, 1H; 2-H), 8.04 (d, J = 1.9 Hz, 1H; 8-H), 8.47 ppm (brs, 1H; 4-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.33 (OCH_2CH_3), 21.00 ($C(O)CH_3$), 61.48 (OCH_2CH_3), 118.78 (C-2), 123.48, 128.21, 129.97 (C-3, C-4a, C-8a), 123.83, 128.59, 130.81, 131.02 (C-4, C-5, C-6, C-8), 132.08 (C-7), 145.62 (C-1), 165.59 (C(O)OEt), 169.08 ppm (C(O)CH_3); MS (EI, 70 eV): m/z (%): 336 (12) $[M]^+$, 294 (100) $[M-C(O)CH_3+H]^+$.

Ethyl-7-bromo-1-hydroxy-3-naphthalene carboxylate (13): A solution of crude **12** (53.3 g, 158 mmol) in ethanol (650 mL) was treated with K_2CO_3 (109 g, 790 mmol) and stirred for 1.5 h under reflux. The reaction mixture was poured into water (1.00 L) and cooled to 20 °C, adjusted to pH 1 with HCl (2 N) and extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting light-brown solid (44.0 g, 95 %) was used for the next reaction without further purification. R_f = 0.36 (pentane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.0 Hz, 3H; OCH_2CH_3), 4.33 (q, J = 7.0 Hz, 2H; OCH_2CH_3), 7.43 (d, J = 1.4 Hz, 1H; 2-H), 7.50 (dd, J = 8.8, 2.0 Hz, 1H; 6-H), 7.67 (d, J = 8.8 Hz, 1H; 5-H), 7.99 (brs, 1H; 4-H), 8.37 (d, J = 2.0 Hz, 1H; 8-H), 9.70 ppm (brs, 1H; OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.20 (OCH_2CH_3), 60.84 (OCH_2CH_3), 108.08 (C-2), 120.99, 128.14, 128.35 (C-3, C-4a, C-8a), 121.40, 124.91, 129.94, 130.29 (C-4, C-5, C-6, C-8), 131.93 (C-7), 152.53 (C-1), 166.49 ppm (C(O)OEt); MS (EI, 70 eV): m/z (%): 294 (100) $[M]^+$, 266 (22) $[M-C_2H_4]^+$, 249 (40) $[M-C_2H_5O]^+$.

Ethyl-1-benzyloxy-7-bromo-3-naphthalene carboxylate (14): A magnetically stirred solution of crude **13** (44.3 g, 150 mmol) in DMF (950 mL) was treated with K_2CO_3 (31.0 g, 225 mmol) and TBAI (2.2 g, 6.0 mmol). Benzyl bromide (21.5 mL, 30.8 g, 180 mmol) was added dropwise with stirring and the resulting mixture was stirred for 1 d at 20 °C. The reaction mixture was poured into water (1.20 L) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with water (1 × 100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product (62.0 g, quant.) was afforded as a brown oil and used for the next reaction without further purification. An analytically pure sample was obtained after column chromatography by using pentane/EtOAc 15:1 as the eluent. R_f = 0.59 (pentane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (t, J = 7.2 Hz, 3H; OCH_2CH_3), 4.44 (q, J = 7.2 Hz, 2H; OCH_2CH_3), 5.29 (s, 2H; CH_2Ph), 7.35–7.58 (m, 6H; 5 × Ph-H, 2-H), 7.62 (dd, J = 8.6, 1.7 Hz, 1H; 6-H), 7.77 (d, J = 8.6 Hz, 1H; 5-H), 8.18 (brs, 1H; 4-H), 8.48 ppm (d, J = 1.7 Hz, 1H; 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.38 (OCH_2CH_3), 61.28 (OCH_2CH_3), 70.47 (CH_2Ph), 105.10 (C-2), 122.10, 128.33, 128.82 (C-3, C-4a, C-8a), 123.32, 124.88, 128.22, 130.49, 130.61 (C-4, C-5, C-6, C-8, Ph-C_p), 127.69, 128.68 (Ph-C_o, Ph-C_m), 131.88 (C-7), 136.30 (Ph-C_i), 153.62 (C-1), 166.50 ppm (C(O)OEt); MS (DCI, NH_3, 200 eV): m/z (%): 419 (15) $[M+NH_3+NH_4]^+$, 402 (39) $[M+NH_4]^+$.

1-Benzyloxy-7-bromo-3-naphthalene carboxylic acid (7): A solution of crude **14** (57.8 g, 150 mmol) in 3:1:1 THF/MeOH/H_2O (1.25 L) was treated with LiOH·H_2O (31.5 g, 750 mmol) and stirred for 3 d at 20 °C. The resulting mixture was adjusted to pH 1 with HCl (2 N) and the precipitated crude product was collected by filtration. The filtrate was extracted with EtOAc (3 × 100 mL), the combined organic phases dried ($MgSO_4$), and concentrated under reduced pressure to give an additional amount of crude product. The combined crude products were recrystallized (EtOAc) to afford acid **7** (45.7 g, 85 %) as a white solid. R_f = 0.17 (pentane/EtOAc 2:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.34 (s, 2H; CH_2Ph), 7.32–7.45 (m, 3H; 3 × Ph-H), 7.51–7.56 (m, 3H; 2 × Ph-H, 2-H), 7.70 (dd, J = 8.8, 1.8 Hz, 1H; 6-H), 8.01 (d, J = 8.8 Hz, 1H; 5-H), 8.20 (s, 1H; 4-H), 8.28 (d, J = 1.8 Hz, 1H; 8-H), 13.00 ppm (brs, 1H; CO_2H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 69.83 (CH_2Ph), 105.62 (C-2), 121.30, 127.90, 129.20 (C-3, C-4a, C-8a), 122.89, 123.62, 127.93, 130.22, 131.31 (C-4, C-5, C-6, C-8, Ph-C_p), 127.51, 128.49 (Ph-C_o, Ph-C_m), 131.63 (C-7), 136.53 (Ph-C_i), 152.85 (C-1), 167.08 ppm (C(O)OH); MS (EI, 70 eV): m/z (%): 356 (11) $[M]^+$, 91 (100) $[C_7H_7]^+$.

3-Amino-1-benzyloxy-7-bromo-*N*-(*tert*-butoxycarbonyl)naphthalene (15): A suspension of acid **7** (12.4 g, 34.7 mmol) in dry *tert*-butanol (850 mL) was treated with activated molecular sieves 4 Å (70 g), triethylamine (5.80 mL, 4.20 g, 41.6 mmol), and DPPA (9.00 mL, 11.4 g, 41.6 mmol) and heated for 2.5 d at reflux without stirring. After cooling to 20 °C, the molecular sieves were filtered off and washed thoroughly with EtOAc. The filtrate was concentrated under reduced pressure and the resulting residue was dissolved in EtOAc (300 mL). The organic phase was washed with HCl (2 N, 2 × 100 mL), $NaHCO_3$ (1 × 100 mL, saturated solution), and brine (100 mL), and then dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallization of the resulting residue gave the title compound along with a brown oil which was purified by column chromatography (pentane/EtOAc 7:1) to yield further product. The protected amine **18** (12.7 g, 85 %) was afforded as a white solid. R_f = 0.27 (pentane/EtOAc 10:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.55 (s, 9H; $C(CH_3)_3$), 5.22 (s, 2H; CH_2Ph), 6.61 (brs, 1H; NH), 7.06 (d, J = 1.8 Hz, 1H; 2-H), 7.30–7.60 (m, 8H; 5 × Ph-H, 4-H, 5-H, 6-H), 8.34 ppm (d, J = 1.8 Hz, 1H; 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.35 ($C(CH_3)_3$), 70.34 ($C(CH_3)_3$), 80.87 (CH_2Ph), 99.95 (C-2), 106.66 (C-4), 117.56, 123.52 (C-7, C-8a), 124.50, 128.16, 128.51, 130.39 (C-5, C-6, C-8, Ph-C_p), 127.56, 128.67 (Ph-C_o, Ph-C_m), 133.20 (C-4a), 136.39, 136.64 (C-3, Ph-C_i), 152.65, 154.30 ppm (C-1, C=O); MS (EI, 70 eV): m/z (%): 427 (9) $[M]^+$, 371 (16) $[M-C_4H_8]^+$, 91 (100) $[C_7H_7]^+$, 57 (24) $[C_4H_9]^+$.

1-Benzyloxy-7-benzyloxycarbonyl-3-naphthalene carboxylic acid (16): A magnetically stirred and degassed solution of bromide **7** (100 mg, 280 μmol) and N(nBu)$_3$ (200 μL, 156 mg, 840 μmol) in benzylic alcohol (5.00 mL, 5.20 g, 48.0 mmol) was treated with [$PdBr_2(PPh_3)_2$] (11 mg, 14 μmol) and 1,1′-bis(diphenylphosphino)ferrocene (31 mg, 56 μmol). The reaction mixture was degassed again, set under a carbon monoxide atmosphere (1 bar) and stirred for 45 min at 85 °C and for a further 50 min at 130 °C. The benzylic alcohol and tributylamine were distilled off under reduced pressure and the resulting residue quenched with HCl (2 N) and water (pH 2). The water phase was extracted with EtOAc (4 × 50 mL) and the combined organic phases washed with brine (50 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. The resulting brown oil was adsorbed on silica gel and purified by column chromatography (pentane/EtOAc 1:1 + 0.5 % HOAc). The acid **16** (94 mg, 82 %) was obtained as a white solid. R_f = 0.29 (pentane/EtOAc 4:1 + 0.5 % HOAc); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.40 (s, 4H; 2 × CH_2Ph), 7.35–7.60 (m, 11H; 10 × Ph-H, 2-H), 8.07 (dd, J = 8.7, 1.5 Hz, 1H; 6-H), 8.18 (d, J = 8.7 Hz, 1H; 5-H), 8.26 (s, 1H; 4-H), 8.90 (brs, 1H; 8-H), 13.00 ppm (brs, CO_2H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 66.37 (CH_2Ph-ester), 69.84 (CH_2Ph-ether), 105.43 (C-2), 122.47, 124.09, 125.96, 129.72 (C-4, C-5, C-6, C-8), 126.04, 128.11, 131.17, 135.27, 135.94, 136.51 (C-3, C-4a, C-7, C-8a, 2 × Ph-C_i), 127.37, 127.80, 127.90, 128.02, 128.43 (10 × Ph-C), 154.69 (C-1), 165.29, 167.04 ppm (2 × C=O); MS (EI, 70 eV): m/z (%): 412 (13) $[M]^+$, 91 (100) $[C_7H_7]^+$.

3-Amino-1-benzyloxy-7-benzyloxycarbonyl-*N*-(*tert*-butoxycarbonyl)naphthalene (17): A suspension of acid **16** (802 mg, 1.94 mmol) in dry *tert*-butanol (50 mL) was treated with activated molecular sieves 4 Å (4 g), triethylamine (327 μL, 236 mg, 2.33 mmol), and DPPA (505 μL, 641 mg, 2.33 mmol) and heated for 3.5 d at reflux without stirring. After cooling to 20 °C, the reaction mixture was filtered through a pad of Celite and then it was thoroughly washed with EtOAc. The filtrate was concentrated under reduced pressure and the resulting residue dissolved in EtOAc (100 mL). The organic phase was washed with HCl (2 N, 2 × 50 mL), $NaHCO_3$ (1 × 50 mL, saturated solution), and brine (50 mL), and then dried ($MgSO_4$) and concentrated under reduced pressure to give a light-brown oil. This material then underwent column chromatography (pentane/EtOAc 7:1) to give the protected amine **17** (534 mg, 65 %) as a light-yellow solid. R_f = 0.22 (pentane/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 9H; $C(CH_3)_3$), 5.24 (s, 2H; CH_2Ph-ether), 5.42 (s, 2H; CH_2Ph-ester), 6.81 (brs, 1H; NH), 7.10 (d, J = 1.8 Hz, 1H; 2-H), 7.30–7.55 (m, 11H; 10 × Ph-H, 4-H), 7.69 (d, J = 8.7 Hz, 1H; 5-H), 8.06 (dd, J = 8.7, 2.1 Hz, 1H; 6-H), 9.04 ppm (brs, 1H; 8-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.30 ($C(CH_3)_3$), 66.52 (CH_2Ph-ester), 70.22 (CH_2Ph-ether), 80.98 ($C(CH_3)_3$), 99.56 (C-2), 106.32 (C-4), 121.56, 125.00, 136.28, 136.40, 137.27 (C-4a, C-7, C-8a, 2 × Ph-C_i), 125.70, 126.62, 126.93, 127.26, 127.96, 127.99, 128.05, 128.53, 128.60 (C-5, C-6, C-8, 10 × Ph-C),

138.88 (C-3), 152.53, 156.21 (C-1, C=O), 166.76 ppm (*C*(O)OBn); MS (EI, 70 eV): *m/z* (%): 483 (14) $[M]^+$, 427 (18) $[M-C_4H_8]^+$, 91 (100) $[C_7H_7]^+$, 57 (15) $[C_4H_9]^+$.

2-Amino-4-benzyloxy-6-benzyloxycarbonyl-*N*-(*tert*-butoxycarbonyl)-1-iodonaphthalene (18): A magnetically stirred solution of **17** (1.56 g, 3.23 mmol) in 1:1 THF/MeOH (44 mL) was treated with a solution of TsOH·H_2O (61 mg, 0.32 mmol) in THF (2 mL) and *N*-iodosuccinimide (1.45 g, 6.46 mmol). The resulting mixture was warmed to 50 °C, and stirred for a further 40 min. The reaction mixture was quenched with $NaHCO_3$ (20 mL, saturated solution) and water and extracted with EtOAc (2×40 mL). The combined organic phases were washed with $Na_2S_2O_3$ (1×50 mL, saturated solution) and brine (50 mL), dried ($MgSO_4$) and then concentrated under reduced pressure. The afforded pale-yellow solid (1.94 g, 99%) was used for the next reaction without further purification. R_f=0.40 (pentane/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.60 (s, 9H; $C(CH_3)_3$), 5.31 (s, 2H; CH_2Ph-ether), 5.42 (s, 2H; CH_2Ph-ester), 7.32–7.59 (m, 10H; 10×Ph-H), 8.04 (dd, J=8.7, 0.6 Hz, 1H; 8-H), 8.12 (dd, J=8.7, 1.8 Hz, 1H; 7-H), 8.14 (s, 1H; 3-H), 9.01 ppm (d, J=1.8 Hz, 1H; 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 28.29 ($C(CH_3)_3$), 66.67 (CH_2Ph-ester), 70.46 (CH_2Ph-ether), 79.14 (*C*-$(CH_3)_3$), 81.57 (C-1), 100.13 (C-3), 122.71, 125.67, 136.13, 136.17, 137.18 (C-4a, C-6, C-8a, 2×Ph-C_i), 125.94, 127.67, 127.97, 128.09, 128.10, 128.12, 128.57, 128.59, 131.45, (C-5, C-7, C-8, 10×Ph-C), 140.69 (C-2), 152.50, 156.58 (C-4, C=O), 166.28 ppm (*C*(O)OBn); UV/Vis (CH_3CN): λ_{max} (lg ε)=224 (4.099), 268 (4.477), 340 nm (3.557); IR (KBr): $\tilde{\nu}$=3396 (NH), 1720 (C=O), 1602, 1518, 1385, 1235, 1155, 731 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 609 (38) $[M]^+$, 553 (26) $[M-C_4H_8]^+$, 426 (6) $[M-C_4H_8-I]^+$, 91 (100) $[C_7H_7]^+$, 57 (16) $[C_4H_9]^+$.

(*E*/*Z*)-2-Amino-4-benzyloxy-6-benzyloxycarbonyl-*N*-(*tert*-butoxycarbonyl)-*N*-(3-chloro-2-propenyl)-1-iodonaphthalene (19): A magnetically stirred solution of **18** (1.51 mmol, 921 mg) in DMF (22 mL) was treated with NaH (151 mg, 60% in oil, 3.78 mmol). Stirring was continued for 1.5 h at 20 °C. (*E*/*Z*)-1,3-Dichloropropene (279 μL, 335 mg, 3.02 mmol) was then added dropwise and the mixture was stirred for a further 19 h at 20 °C. The ensuing mixture was then quenched with NH_4Cl (10 mL, saturated solution) and extracted with EtOAc (4×20 mL). The combined organic phases were washed with water (3×25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a red oil. Purification of this material by column chromatography (pentane/EtOAc 7:1) gave iodide **19** (875 mg, 85%) as a pale-yellow foam. R_f= 0.28, 0.36 (pentane/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30/1.58 (2×s, 9H; $C(CH_3)_3$), 3.70–4.00 (m, 1H; 1′-H_a), 4.40–4.65 (m, 1H; 1′-H_b), 5.31 (brs, 2H; CH_2Ph-ether), 5.45 (brs, 2H; CH_2Ph-ester), 5.90–6.15 (m, 2H; 2′-H, 3′-H), 6.65–6.85 (m, 1H; 3-H), 7.32–7.54 (m, 10H; 10×Ph-H), 8.19 (d, J=9.0 Hz, 1H; 8-H), 8.25 (dd, J=9.0, 1.8 Hz, 1H; 7-H), 9.04–9.15 ppm (m, 1H; 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.18/28.44 ($C(CH_3)_3$), 45.74/48.95 (C-1′), 66.87/66.89 (CH_2Ph-ester), 70.47/70.56 (CH_2Ph-ether), 80.93 ($C(CH_3)_3$), 94.62 (C-1), 107.98/108.58 (C-3), 120.94/122.01 (C-3′), 124.72/124.77, 127.67/127.76, 137.63 (C-4a, C-6, C-8a), 125.71, 127.03/127.07, 127.93/127.98, 128.05, 128.15, 128.22, 128.42/128.59, 128.73/128.76, 133.15/133.17 (C-5, C-7, C-8, C-2′, 10×Ph-C), 135.89/135.95 (2×Ph-C_i), 145.12 (C-2), 153.35/153.57 (C-4), 156.01 (C=O), 166.07/166.10 ppm (*C*(O)OBn); MS (EI, 70 eV): *m/z* (%): 683 (3) $[M]^+$, 500 (38) $[M-2\times C_7H_7-H]^+$, 91 (100) $[C_7H_7]^+$, 57 (36) $[C_4H_9]^+$.

(1*R*/*S*)-5-Benzyloxy-3-(*tert*-butoxycarbonyl)-1-chloromethyl-2,3-dihydro-1*H*-benz[*e*]indole-7-carboxylic acid benzyl ester (5): Through a magnetically stirred solution of iodide **19** (471 mg, 688 μmol) in benzene (20 mL) was bubbled argon for 1.5 h. The oxygen-free solution was then treated with tris(trimethylsilyl)silane (229 μL, 183 mg, 736 μmol) and AIBN (26.0 mg, 158 μmol) and stirred for 3 h under reflux. The ensuing mixture was adsorbed on silica gel and purified by column chromatography (pentane/EtOAc 7:1) to afford CBI system **5** (336 mg, 87%) as a colorless foam. R_f=0.27 (pentane/EtOAc 10:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.61 (s, 9H; $C(CH_3)_3$), 3.45 (dd, J=10.4, 9.6 Hz, 1H; 10-H_b), 3.84–4.05 (m, 2H; 1-H, 10-H_a), 4.15 (dd, J=11.4, 9.6 Hz, 1H; 2-H_b), 4.21–4.35 (m, 1H; 2-H_a), 5.29 (s, 2H; CH_2Ph-ether), 5.41 (s, 2H; CH_2Ph-ester), 7.32–7.60 (m, 10H; 10×Ph-H), 7.65 (d, J=8.8 Hz, 1H; 9-H), 7.88 (brs, 1H; 4-H), 8.11 (dd, J=8.8, 1.6 Hz, 1H; 8-H), 9.09 ppm (d, J=1.6 Hz, 1H; 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=28.42 ($C(CH_3)_3$), 41.45 (C-1), 46.36 (C-10), 53.14 (C-2), 66.57 (CH_2Ph-ester), 70.38 (CH_2Ph-ether), 81.06 (*C*-$(CH_3)_3$), 97.00 (C-4), 121.48, 124.33, 132.51 (C-3a, C-5a, C-7, C-9a, C-9b), 121.81 (C-9), 127.14 (C-6), 127.27 (C-8), 127.43, 127.94, 128.04, 128.08, 128.56, 128.62 (10×Ph-C), 136.24, 136.33 (2×Ph-C_i), 152.42 (C-5), 157.27 (C=O), 166.57 ppm (*C*(O)OBn); UV/Vis (CH_3CN): λ_{max} (lg ε)=205 (4.496), 272 (4.757), 355 nm (4.184); IR (KBr): $\tilde{\nu}$=3403 (NH), 2976, 1704 (C=O), 1373, 1327, 1248, 1141, 848, 761 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 557 (16) $[M]^+$, 501 (25) $[M-C_7H_7+H]^+$, 91 (60) $[C_7H_7]^+$, 56 (76) $[C_4H_8]^+$, 41 (100) $[CH_3CN]$; elemental analysis calcd (%) for $C_{33}H_{32}ClNO_5$ (558.06): C 71.02, H 5.78; found: C 70.98, H 5.98.

(1*R*/*S*)-5-Benzyloxy-1-chloromethyl-3-(5,6,7-trimethoxyindole-2-carbonyl)-2,3-dihydro-1*H*-benz[*e*]indole-7-carboxylic acid benzyl ester (21): A solution of the protected amine **5** (275 mg, 493 μmol) in CH_2Cl_2 (2 mL) was treated with HCl (14 mL of a 4 M solution in EtOAc) and Et_3SiH (80.0 μL, 57.0 mg, 493 μmol) and stirred for 3 h at 20 °C. The solvent was removed under reduced pressure and the ensuing residue was treated with toluene (2×10 mL) and then concentrated under reduced pressure again.

The resulting crude hydrochloride **20** was dried under reduced pressure and then treated with 5,6,7-trimethoxyindole-2-carboxylic acid (**6**) (136 mg, 543 μmol), EDC·HCl (284 mg, 1.48 mmol), and DMF (12 mL) and stirred for 1 d at 20 °C. The reaction mixture was adjusted to pH 2 with HCl (2 N) and extracted with EtOAc (4×15 mL). The combined organic phases were washed with water (3×20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a green solid. This material was adsorbed on silica gel and purified by column chromatography (pentane/EtOAc 2:1) to yield TMI-derivative **21** (214 mg, 63% over two steps) as a yellow solid. R_f=0.39 (pentane/EtOAc 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ=3.44 (dd, J=11.4, 10.2 Hz, 1H; 10-H_b), 3.86–4.06 (m, 11H; 3×OCH_3, 1-H, 10-H_a), 4.58 (dd, J=10.2, 9.0 Hz, 1H; 2-H_b), 4.72 (dd, J=10.2, 1.8 Hz, 1H; 2-H_a), 5.25–5.31 (m, 2H; CH_2Ph-ether), 5.37–5.42 (m, 2H; CH_2Ph-ester), 6.86 (s, 1H; 4′-H), 6.97 (d, J= 2.4 Hz, 1H, 3′-H), 7.33–7.52 (m, 10H; 10×Ph-H), 7.62 (d, J=9.0 Hz, 1H; 9-H), 8.10 (dd, J=9.0, 1.8 Hz, 1H; 8-H), 8.21 (brs, 1H; 4-H), 9.08 (d, J= 1.8 Hz, 1H; 6-H), 9.65 ppm (d, J=2.4 Hz, 1H; indole-NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=42.80 (C-1), 45.91 (C-10), 55.15 (C-2), 56.19, 61.08, 61.43 (3×OCH_3), 66.63 (CH_2Ph-ester), 70.36 (CH_2Ph-ether), 97.58 (C-4′), 98.95 (C-4), 106.81 (C-3′), 116.03, 123.52, 125.69, 131.94, 144.57 (C-3a, C-5a, C-7, C-9a, C-9b), 122.14 (C-9), 122.57, 125.14, 129.48, 138.79, 140.65 (C-2′, C-3a′, C-6′, C-7′, C-7a′), 126.94 (C-6), 127.29 (C-8), 127.31, 127.92, 128.00, 128.09, 128.54, 128.59 (10×Ph-C), 136.12, 136.26 (2×Ph-C_i), 150.20 (C-5′), 156.82 (C-5), 160.58 (C=O), 166.36 ppm (*C*(O)OBn); UV/Vis (CH_3CN): λ_{max} (lg ε)=208 (4.618), 229 (4.450), 272 (4.409), 315 (4.384), 365 nm (4.453); IR (KBr): $\tilde{\nu}$=3459 (NH), 2932 (CH_2), 1714 (C= O), 1624, 1526, 1458, 1407, 1308, 1107, 834, 746 cm^{-1}; MS (ESI): *m/z* (%): 713 (100) $[M+Na]^+$, 1403 (44) $[2M+Na]^+$, 689 (100) $[M-H]^-$; elemental analysis calcd (%) for $C_{40}H_{35}ClN_2O_7$ (691.17): C 69.51, H 5.10; found: C 69.68, H 5.19.

(1*R*/*S*)-5-Benzyloxy-1-chloromethyl-3-(5,6,7-trimethoxyindole-2-carbonyl)-2,3-dihydro-1*H*-benz[e]indole-7-carboxylic acid (22): A magnetically stirred solution of **21** (176 mg, 255 μmol) in 3:1:1 THF/MeOH/H_2O (4.5 mL) at 0 °C was treated with LiOH·H_2O (32.0 mg, 765 μmol). The reaction mixture was warmed to 20 °C and stirring was continued for 3.5 h. The ensuing solution was then adjusted to pH 1–2 with HCl (2 N) and extracted with EtOAc (4×10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting brownish solid was adsorbed on silica gel and purified by column chromatography (CH_2Cl_2/MeOH 30:1+0.5% HOAc) to afford acid **22** (121 mg, 79%) as a yellow solid. R_f=0.58 (CH_2Cl_2/MeOH 10:1+0.5% HOAc); ^{1}H NMR (300 MHz, [D_6]DMSO): δ=3.80–3.94 (m, 10H; 3×OCH_3, 10-H_b), 4.04 (dd, J=10.8, 2.9 Hz, 1H; 10-H_a), 4.22–4.27 (m, 1H; 1-H), 4.52 (d, J=9.9 Hz, 1H; 2-H_b), 4.75 (dd, J=10.5, 9.9 Hz, 1H; 2-H_a), 5.27 (brs, 2H; CH_2Ph), 6.97 (s, 1H; 4′-H), 7.08 (d, J=1.5 Hz, 1H; 3′-H), 7.35–7.54 (m, 5H; 5×Ph-H), 7.94–8.05 (m, 3H; 4-H, 8-H, 9-H), 8.84 (d, J=0.9 Hz, 1H; 6-H), 11.49 ppm (brs, 1H; indole-NH); ^{13}C NMR (75 MHz, [D_6]DMSO): δ=40.81 (C-1), 47.40 (C-10), 55.06 (C-2), 55.94, 60.89, 61.05 (3×OCH_3), 69.87 (CH_2Ph), 98.07 (C-

4′), 98.68 (C-4), 106.37 (C-3′), 116.69, 123.13, 125.88, 131.66, 144.37 (C-3a, C-5a, C-7, C-9a, C-9b), 121.53, 125.52, 130.58, 139.03, 140.01 (C-2′, C-3a′, C-6′, C-7′, C-7a′), 123.15 (C-9), 125.25 (C-6), 126.95 (C-8), 127.59 (2×Ph-C), 128.07 (Ph-C_p), 128.56 (2×Ph-C), 136.41 (Ph-C_i), 149.24 (C-5′), 155.52 (C-5), 160.48 (C=O), 167.38 ppm (*C*(O)OH); MS (ESI): *m*/*z* (%): 623 (100) $[M+Na]^+$, 645 (68) $[M-H+2Na]^+$, 599 (100) $[M-H]^-$.

(1*R*/*S*)-5-Benzyloxy-1-chloromethyl-3-(5,6,7-trimethoxyindole-2-carbonyl)-2,3-dihydro-1*H*-benz[*e*]indole-7-carboxylic acid (*N*-hydroxysuccinimide) ester (23): A magnetically stirred solution of acid **22** (121 mg, 200 μmol) and *N*-hydroxysuccinimide (34.5 mg, 300 μmol) in THF (14 mL) at 0°C was treated with EDC·HCl (57.5 mg, 300 μmol). The reaction mixture was warmed to 20°C and stirring was continued for 13 h. The ensuing solution was then adjusted to pH 1–2 with HCl (2 N) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give active ester **23** as orange solid which was used for the next reaction without further purification. R_f=0.89 (CH_2Cl_2/MeOH 10:1+0.5% HOAc); ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.92 (brs, 4H; 2×CH_2C(O)), 3.48 (dd, *J*=11.0, 10.6 Hz, 1H; 10-H_b), 3.90–4.17 (m, 11H; 3×OCH_3, 1-H, 10-H_a), 4.69 (dd, *J*=10.7, 8.6 Hz, 1H; 2-H_b), 4.80 (dd, *J*=10.7, 1.8 Hz, 1H; 2-H_a), 5.27–5.40 (m, 2H; CH_2Ph), 6.88 (s, 1H; 4′-H), 7.03 (d, *J*=1.6 Hz, 1H; 3′-H), 7.30–7.56 (m, 5H; 5×Ph-H), 7.75 (d, *J*=9.0 Hz, 1H; 9-H), 8.12 (dd, *J*=9.0, 1.7 Hz, 1H; 8-H), 8.26 (brs, 1H; 4-H), 9.18 (d, *J*=1.7 Hz, 1H; 6-H), 9.45 ppm (brs, 1H; indole-NH); MS (ESI): *m*/*z* (%): 720 (100) $[M+Na]^+$, 1417 (50) $[2M+2Na]^+$, 696 (100) $[M-H]^-$.

(1*R*/*S*)-5-Benzyloxy-1-chloromethyl-3-(5,6,7-trimethoxyindole-2-carbonyl)-2,3-dihydro-1*H*-benz[*e*]indole-7-carboxylic acid β-alanyl amide (25): A magnetically stirred solution of β-alanine (**24**) (27.0 mg, 300 μmol) in water (2 mL) was treated with NE*ti*Pr_2 (52.0 μL, 39.0 mg, 300 μmol) and dropwise with a solution of crude **23** (140 mg, 200 μmol) in MeCN (5 mL). The reaction mixture was stirred for 7 h at 20°C, then adjusted to pH 2 with HCl (2 N) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting brownish solid was adsorbed on silica gel and purified by column chromatography (CH_2Cl_2/MeOH 30:1+0.5% HOAc) to afford amide **25** (93 mg, 69% over two steps) as a pale-yellow solid. R_f=0.54 (CH_2Cl_2/MeOH 10:1+0.5% HOAc); ^{1}H NMR (300 MHz, [D_6]DMSO): δ=2.56 (t, *J*=7.0 Hz, 2H; 2″-H_2), 3.50–3.56 (m, 2H; 1″-H_2), 3.80–3.94 (m, 10H; 3×OCH_3, 10-H_b), 4.05 (m_c, 1H; 10-H_a), 4.26 (m_c, 1H; 1-H), 4.51 (d, *J*=9.9 Hz, 1H; 2-H_b), 4.76 (dd, *J*=10.3, 9.9 Hz, 1H; 2-H_a), 5.30 (brs, 2H; CH_2Ph), 6.98 (s, 1H; 4′-H), 7.08 (brs, 1H, 3′-H), 7.31–7.55 (m, 5H; 5×Ph-H), 7.95–8.01 (m, 3H; 4-H, 8-H, 9-H), 8.70 (t, *J*=5.1 Hz, 1H; NH), 8.74 (brs, 1H; 6-H), 11.47 ppm (brs, 1H; indole-NH); ^{13}C NMR (75 MHz, [D_6]DMSO): δ=33.94 (C-2″), 35.75 (C-1″), 40.81 (C-1), 47.42 (C-10), 54.98 (C-2), 55.95, 60.87, 61.01 (3×OCH_3), 69.73 (CH_2Ph), 98.08 (C-4′), 98.68 (C-4), 106.24 (C-3′), 116.64, 123.11, 125.45, 130.65, 143.59 (C-3a, C-5a, C-7, C-9a, C-9b), 121.66, 129.49, 130.85, 139.00, 139.96 (C-2′, C-3a′, C-6′, C-7′, C-7a′), 122.64/122.91 (C-9), 125.21/125.59 (C-6), 127.34 (2×Ph-C), 127.91/128.09 (C-8), 128.50 (2×Ph-C), 128.79 (Ph-C_p), 136.50 (Ph-C_i), 149.21 (C-5′), 155.27 (C-5), 160.39 (C=O_{TMI}), 166.16 (C-7-*C*=O), 172.92 ppm (*C*(O)OH); MS (ESI): *m*/*z* (%): 694 (58) $[M+Na]^+$, 717 (100) $[M-H+2Na]^+$, 670 (100) $[M-H]^-$.

(1*R*/*S*)-1-Chloromethyl-5-hydroxy-3-(5,6,7-trimethoxyindole-2-carbonyl)-2,3-dihydro-1*H*-benz[*e*]indole-7-carboxylic acid β-alanyl amide (26): A magnetically stirred solution of benzyl ether **25** (101 mg, 150 μmol) in 3:1 THF/MeOH (5.6 mL) was treated with 10% Pd/C (41 mg) and dropwise with NH_4HCO_2 (393 μL of a 25% solution in water, 1.56 mmol) and stirring was continued for 2.5 h at 20°C. The reaction mixture was filtered through a pad of Celite and was then thoroughly washed with MeOH and THF. The filtrate was treated with toluene (10 mL) and concentrated under reduced pressure to give **26** as light-yellow solid which was used for the next reaction without further purification. R_f=0.39 (CH_2Cl_2/MeOH 10:1+0.5% HOAc); ^{1}H NMR (300 MHz, [D_6]DMSO): δ=2.53 (t, *J*=7.1 Hz, 2H; 2″-H_2), 3.49–3.56 (m, 2H; 1″-H_2), 3.80–3.91 (m, 7H; 2×OCH_3, 10-H_b), 3.94 (s, 3H; OCH_3), 4.01 (dd, *J*=10.8, 2.6 Hz, 1H; 10-H_a), 4.19 (m_c, 1H; 1-H), 4.46 (d, *J*=9.9 Hz, 1H; 2-H_b), 4.72 (dd, *J*=10.8, 9.9 Hz, 1H; 2-H_a), 6.93/6.96 (2×s, 1H; 4′-H), 7.06 (m_c, 1H; 3′-H), 7.85–8.06 (m, 3H; 4-H, 8-H, 9-H), 8.64 (t, *J*=5.0 Hz, 1H; NH), 8.68 (brs, 1H; 6-H), 11.35/11.40 ppm (2×brs, 1H; indole-NH); ^{13}C NMR (150 MHz, [D_6]DMSO): δ=34.35 (C-2″), 35.86 (C-1″), 40.86 (C-1), 47.42 (C-10), 55.08 (C-2), 55.97, 60.87, 61.03 (3×OCH_3), 98.07/98.10 (C-4′), 100.65 (C-4), 106.16/106.19 (C-3′), 114.93, 123.11, 125.41, 130.86, 143.75 (C-3a, C-5a, C-7, C-9a, C-9b), 121.16, 128.64, 131.05, 139.02, 139.91 (C-2′, C-3a′, C-6′, C-7′, C-7a′), 122.64/122.76 (C-9), 123.02 (C-6), 125.46 (C-8), 149.21 (C-5′), 155.31 (C-5), 160.31 (C=O_{TMI}), 166.25 (C-7-*C*=O), 173.64 ppm (*C*(O)OH); MS (ESI): *m*/*z* (%): 604 (100) $[M+Na]^+$, 1185 (26) $[2M+Na]^+$, 544 (100) $[M-H-HCl]^-$, 580 (32) $[M-H]^-$.

(1*R*/*S*)-1-Chloromethyl-5-hydroxy-3-(5,6,7-trimethoxyindole-2-carbonyl)-2,3-dihydro-1*H*-benz[*e*]indole-7-carboxylic acid [2-(*N*-succinimidyloxycarbonyl)ethyl] amide (27): A magnetically stirred solution of crude acid **26** (119 mg, 204 μmol) and *N*-hydroxysuccinimide (141 mg, 1.22 mmol) in 4:1:1 THF/CH_2Cl_2/DMF (30 mL) at 0°C was treated with EDC·HCl (117 mg, 612 μmol). The reaction mixture was warmed to 20°C and stirring was continued for 18 h. Another batch of *N*-hydroxysuccinimide (47.0 mg, 408 μmol) and EDC·HCl (78.0 mg, 408 μmol) was added and stirring was continued for a further 10.5 h at 20°C. The ensuing solution was then adjusted to pH 1–2 with HCl (2 N) and extracted with EtOAc (4×15 mL). The combined organic phases were washed with water (2×15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford **27** as orange solid which was used for the next reaction without further purification. R_f=0.55 (CH_2Cl_2/MeOH 10:1+0.5% HOAc); MS (ESI): *m*/*z* (%): 701 (35) $[M+Na]^+$, 733 (44) $[M+MeOH+Na]^+$, 677 (44) $[M-H]^-$, 709 (100) $[M-H+MeOH]^-$.

(1*R*/*S*)-1-Chloromethyl-5-hydroxy-3-(5,6,7-trimethoxyindole-2-carbonyl)-2,3-dihydro-1*H*-benz[*e*]indole-7-carboxylic acid [β-alanyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanineamidyl] amide (3): A magnetically stirred suspension of tetragastrin (**28**)[26] (114 mg, 192 μmol) in DMF (3 mL) was treated with NE*ti*Pr_2 (33.5 μL, 24.8 mg, 192 μmol) and dropwise with a solution of crude **27** (147 mg, 216 μmol) in DMF (12 mL). Stirring was continued for 57 h at 20°C. The ensuing mixture was adjusted to pH 2 with HCl (2 N) and extracted with EtOAc (5×10 mL). The combined organic phases were washed with water (2×10 mL) and brine (10 mL), treated with toluene (10 mL), and concentrated under reduced pressure. The resulting brownish solid was adsorbed on silica gel and subjected to column chromatography (CH_2Cl_2/MeOH 30:1+0.5% HOAc→5:1+0.5% HOAc) to give **3** (67 mg, 27% over three steps, 33% based on recovery, 1:1 mixture of both diastereomeres) as a light-yellow solid. Further purification was achieved by HPLC. R_f=0.13 (CH_2Cl_2/MeOH 10:1+0.5% HOAc); ^{1}H NMR (600 MHz, [D_7]DMF): δ=1.90–1.98 (m, 1H; 2c-H_b), 2.01–2.06 (m, 4H; 2c-H_a, SCH_3), 2.37–2.42 (m, 1H; 3c-H_b), 2.44–2.50 (m, 1H; 3c-H_a), 2.59–2.70 (m, 2H; 1e-H_2), 2.75 (m_c, 1H; 2b-H_b), 2.81 (m_c, 1H; 2b-H_a), 3.02 (dd, *J*=13.7, 9.2 Hz, 1H; 2a-H_b), 3.20–3.26 (m, 2H; 2d-H_b, 2a-H_a), 3.33 (dd, *J*=15.0, 4.8 Hz, 1H; 2d-H_a), 3.67 (m_c, 2H; 1f-H_2), 3.88 (s, 3H; OCH_3), 3.90 (s, 3H; OCH_3), 3.93 (dd, *J*=11.2, 8.1 Hz, 1H; 10-H_b), 4.03 (s, 3H; OCH_3), 4.11 (dd, *J*=11.2, 2.9 Hz, 1H; 10-H_a), 4.29 (m_c, 1H; 1-H), 4.39 (m_c, 1H; 1c-H), 4.55 (m_c, 1H; 1a-H), 4.64–4.68 (m, 3H; 1b-H, 1d-H, 2-H_b), 4.84 (t, *J*=9.9 Hz, 1H; 2-H_a), 6.98 (t, *J*=7.8 Hz, 1H; 5d′-H), 7.04 (s, 1H; 4′-H), 7.07 (t, *J*=7.8 Hz, 1H; 6d′-H), 7.14–7.17 (m, 1H; 1×Ph-H), 7.18 (d, *J*=1.5 Hz, 1H; 3′-H), 7.26 (m_c, 2H; 2×Ph-H), 7.32–7.33 (m, 3H, 2d′-H; 2×Ph-H), 7.39 (d, *J*=7.8 Hz, 1H, 7d′-H), 7.61 (d, *J*=7.8 Hz, 1H; 4d′-H), 7.83 (m_c, 1H; NH), 7.95 (d, *J*=8.9 Hz, 1H; 9-H), 8.00–8.02 (m, 3H; 8-H, 2×NH), 8.06 (brs, 1H; 4-H), 8.21 (d, *J*=7.2 Hz, 1H; NH), 8.37 (m_c, 2H; 2×NH), 8.66 (m_c, 1H; NH), 8.84 (s, 1H; 6-H), 10.84 (m_c, 2H; indole-NH_{Trp}, C(O)OH), 11.31 ppm (brs, 1H; indole-NH_{TMI}); ^{13}C NMR (150 MHz, [D_7]DMF): δ=14.93 (SCH_3), 27.84 (C-2d), 30.52 (C-3c), 31.52 (C-2c), 36.11 (C-2b), 36.53 (C-1e), 37.03 (C-1f), 38.12 (C-2a), 42.26 (C-1), 47.97 (C-10), 51.37 (C-1b), 54.15 (C-1c), 55.45 (C-1a), 55.88/55.93 (C-1d), 55.98 (C-2), 56.48, 61.34, 61.42 (3×OCH_3), 98.87 (C-4′), 101.66 (C-4), 107.07 (C-3′), 110.83/110.84 (C-3d′), 111.98 (C-7d′), 115.94, 124.33, 126.53, 131.85, 144.96 (C-3a, C-5a, C-7, C-9a, C-9b), 118.95 (C-4d′), 119.04 (C-5d′), 121.60 (C-6d′), 122.27, 129.70, 132.15, 139.94, 141.09 (C-2′, C-3a′, C-6′, C-7′, C-7a′), 123.38 (C-9), 123.91 (C-6), 124.57/124.59 (C-2d′), 126.15/126.17 (C-8), 126.83 (Ph-C_p), 128.35 (C-3ad′), 128.75 (2×Ph-C), 129.91 (2×Ph-C), 137.33 (C-7ad′), 138.94 (Ph-C_i), 150.51 (C-5′), 156.42 (C-5), 161.26 (C=

O_{TMI}), 162.33 (C=O_{Ala}), 167.59 (C-7-*C*=O), 171.20, 172.72/172.75, 173.24/173.27, 173.70, 173.94 ppm (4×C=O, (*C*(O)OH); MS (ESI): *m/z* (%): 1182 (29) $[M+Na]^+$, 1204 (64) $[M-H+2Na]^+$, 1158 (100) $[M-H]^-$; HRMS: calcd for $C_{58}H_{62}ClN_9O_{13}S$: 1182.37685 $[M+Na]^+$; found: 1182.37679; HPLC (preparative): column: Kromasil 100 C18; eluent: 75% MeOH, 25% H_2O+0.05% TFA; flow: 12 mL min^{-1}; R_t: 14–20 min.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. F.M. thanks the Studienstiftung des deutschen Volkes (German National Academic Foundation) for a PhD scholarship. B.K. is grateful to the Deutsche Telekom Foundation for a PhD scholarship.

[1] Reviews: a) W. A. Denny, *Cancer Invest.* **2004**, *22*, 604–619; b) L. F. Tietze, T. Feuerstein, *Curr. Pharm. Des.* **2003**, *9*, 2155–2175; c) L. F. Tietze, T. Feuerstein, *Aust. J. Chem.* **2003**, *56*, 841–854; d) W. A. Denny, *Eur. J. Med. Chem.* **2001**, *36*, 577–595; e) M. Jung, *Mini-Rev. Med. Chem.* **2001**, *1*, 399–407; f) G. Xu, H. L. McLeod, *Clin. Cancer Res.* **2001**, *7*, 3314–3324; g) K. N. Syrigos, A. A. Epenetos, *Anticancer Res.* **1999**, *19*, 605–613; h) G. M. Dubowchik, M. A. Walker, *Pharmacol. Ther.* **1999**, *83*, 67–123; i) C. J. Springer, I. Niculescu-Duvaz, *Adv. Drug Delivery Rev.* **1997**, *26*, 151–172; j) L. N. Jungheim, T. A. Shepherd, *Chem. Rev.* **1994**, *94*, 1553–1566.

[2] a) L. F. Tietze, F. Major, I. Schuberth, D. A. Spiegl, B. Krewer, K. Maksimenka, G. Bringmann, J. Magull, *Chem. Eur. J.* **2007**, *13*, 4396–4409; b) L. F. Tietze, F. Major, I. Schuberth, *Angew. Chem.* **2006**, *118*, 6724–6727; *Angew. Chem. Int. Ed.* **2006**, *45*, 6574–6577; c) L. F. Tietze, B. Krewer, H. Frauendorf, F. Major, I. Schuberth, *Angew. Chem.* **2006**, *118*, 6720–6724; *Angew. Chem. Int. Ed.* **2006**, *45*, 6570–6574; d) L. F. Tietze, F. Major, *Eur. J. Org. Chem.* **2006**, 2314–2321; e) K. D. Bagshawe, *Br. J. Cancer* **1987**, *56*, 531–532.

[3] Reviews: a) J. C. Reubi, H. R. Mäcke, E. P. Krenning, *J. Nucl. Med.* **2005**, *46*, 67S-75S; b) M. Dyba, N. I. Tarasova, C. J. Michejda, *Curr. Pharm. Des.* **2004**, *10*, 2311–2334; c) J. C. Reubi, *Endocr. Rev.* **2003**, *24*, 389–427; d) J. C. Reubi, B. Waser, *Eur. J. Nucl. Med.* **2003**, *30*, 781–793; e) M. Langer, A. G. Beck-Sickinger, *Curr. Med. Chem.* **2001**, *1*, 71–93; f) W. A. P. Breeman, M. de Jong, D. J. Kwekkeboom, R. Valkema, W. H. Bakker, P. P. M. Kooij, T. J. Visser, E. P. Krenning, *Eur. J. Nucl. Med.* **2001**, 28, 1421–1429; g) A. Heppeler, S. Froidevaux, A. N. Eberle, H. R. Maecke, *Curr. Med. Chem.* **2000**, *7*, 971–994; h) A. V. Schally, A. Nagy, *Eur. J. Endocrinol.* **1999**, *141*, 1–14; i) G. S. Baldwin, A. Shulkes, *Gut* **1998**, *42*, 581–584.

[4] a) B. A. Nock, T. Maina, M. Béhé, A. Nikolopoulou, M. Gotthardt, J. S. Schmitt, T. M. Behr, H. R. Macke, *J. Nucl. Med.* **2005**, *46*, 1727–1736; b) M. Béhé, T. M. Behr, *Biopolymers* **2002**, *66*, 399–418; c) T. M. Behr, N. Jenner, M. Béhé, C. Angerstein, S. Gratz, F. Raue, W. Becker, *J. Nucl. Med.* **1999**, *40*, 6, 1029–1044; d) T. M. Behr, M. Béhé, C. Angerstein, S. Gratz, R. Mach, L. Hagemann, N. Jenner, M. Stiehler, K. Frank-Raue, F. Raue, W. Becker, *Clin. Cancer Res.* **1999**, *5*, 3124 s-3138 s; e) T. M. Behr, N. Jenner, S. Radetzky, M. Béhé, S. Gratz, S. Yücekent, F. Raue, W. Becker, *Eur. J. Nucl. Med.* **1998**, *25*, 424–430.

[5] B. F. Schmidt, L. Hernandez, C. Rouzer, G. Czerwinski, G. Chmurny, C. J. Michejda, *J. Med. Chem.* **1994**, *37*, 3812–3818.

[6] G. Czerwinski, N. I. Tarasova, C. J. Michejda, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 11520–11525.

[7] a) S. Buchholz, G. Keller, A. V. Schally, G. Halmos, F. Hohla, E. Heinrich, F. Koester, B. Baker, J. B. Engel, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 10403–10407; b) A. Nagy, A. V. Schally, *Biol. Reprod.* **2005**, *73*, 851–859; c) A. Nagy, A. V. Schally, P. Armatis, K. Szepesházi, G. Halmos, M. Kovács, M. Zarandi, K. Groot, M. Miyazaki, A. Jungwirth, J. Horvath, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 7269–7273.

[8] a) J. B. Engel, G. Keller, A. V. Schally, G. Halmos, B. Hammann, A. Nagy, *Clin. Cancer Res.* **2005**, *11*, 2408–2415; b) A. Nagy, P. Armatis, R. Z. Cai, K. Szepesházi, G. Halmos, A. V. Schally, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 652–656.

[9] a) K. Szepesházi, A. V. Schally, G. Halmos, P. Armatis, F. Hebert, B. Sun, A. Feil, H. Kiaris, A. Nagy, *Cancer Res.* **2002**, *62*, 781–788; b) A. Nagy, A. V. Schally, G. Halmos, P. Armatis, R. Z. Cai, V. Csernus, M. Kovács, M. Koppán, K. Szepesházi, Z. Kahán, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 1794–1799.

[10] a) M. Langer, F. Kratz, B. Rothen-Rutishauser, H. Wunderli-Allenspach, A. G. Beck-Sickinger, *J. Med. Chem.* **2001**, *44*, 1341–1348.

[11] a) D. L. Boger, D. S. Johnson, *Angew. Chem.* **1996**, *108*, 1542–1580; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1438–1474; b) M. Ichimura, T. Ogawa, S. Katsumata, K. Takahashi, I. Takahashi, H. Nakano, *J. Antibiot.* **1991**, *44*, 1045–1053; c) M. Ichimura, T. Ogawa, K. Takahashi, E. Kobayashi, I. Kawamoto, T. Yasuzawa, I. Takahashi, H. Nakano, *J. Antibiot.* **1990**, *43*, 1037–1038.

[12] a) D. L. Boger, B. Bollinger, D. L. Hertzog, D. S. Johnson, H. Cai, P. Mésini, R. M. Garbaccio, Q. Jin, P. A. Kitos, *J. Am. Chem. Soc.* **1997**, *119*, 4987–4998; b) D. L. Boger, D. S. Johnson, *Angew. Chem.* **1996**, *108*, 1542–1580; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1438–1474; c) L. H. Hurley, D. R. Needham-VanDevanter, *Acc. Chem. Res.* **1986**, *19*, 230–237.

[13] a) L. F. Tietze, F. Haunert, T. Feuerstein, T. Herzig, *Eur. J. Org. Chem.* **2003**, *3*, 562–566; b) R. Baird, S. Winstein, *J. Am. Chem. Soc.* **1963**, *85*, 567–578.

[14] a) J. S. Morley, H. J. Tracy, R. A. Gregory, *Nature* **1965**, *207*, 1356–1359; b) H. J. Tracy, R. A. Gregory, *Nature* **1964**, *204*, 935–938.

[15] D. L. Boger, N. Han, C. M. Tarby, C. W. Boyce, H. Cai, Q. Jin, P. A. Kitos, *J. Org. Chem.* **1996**, *61*, 4894–4912.

[16] W. M. Owton, P. T. Gallagher, A. Juan-Montesinos, *Synth. Commun.* **1993**, *23*, 2119–2125.

[17] A. Huth, I. Beetz, I. Schumann, K. Thielert, *Tetrahedron* **1987**, *43*, 1071–1074.

[18] a) W. Mägerlein, A. F. Indolese, M. Beller, *J. Organomet. Chem.* **2002**, *641*, 30–40; b) W. Mägerlein, A. F. Indolese, M. Beller, *Angew. Chem.* **2001**, *113*, 2940–2943; *Angew. Chem. Int. Ed.* **2001**, *40*, 2856–2859; c) M. Beller, W. Mägerlein, A. F. Indolese, C. Fischer, *Synthesis* **2001**, 1098–1109.

[19] On a larger scale (2.0 g) the yields dropped to 44–66%.

[20] a) D. L. Boger, S. R. Brunette, R. M. Garbaccio, *J. Org. Chem.* **2001**, *66*, 5163–5173; b) D. L. Boger, J. A. McKie, H. Cai, B. Cacciari, P. G. Baraldi, *J. Org. Chem.* **1996**, *61*, 1710–1729.

[21] a) D. L. Boger, C. W. Boyce, R. M. Garbaccio, M. Searcey, *Tetrahedron Lett.* **1998**, *39*, 2227–2230; b) V. F. Patel, S. L. Andis, J. K. Enkema, D. A. Johnson, J. H. Kennedy, F. Mohamadi, R. M. Schultz, D. J. Soose, M. M. Spees, *J. Org. Chem.* **1997**, *62*, 8868–8874; c) D. L. Boger, J. A. McKie, *J. Org. Chem.* **1995**, *60*, 1271–1275.

[22] a) A. Studer, S. Amrein, *Angew. Chem.* **2000**, *112*, 3196–3198; *Angew. Chem. Int. Ed.* **2000**, *39*, 3080–3082; b) C. Chatgilialoglu, *Acc. Chem. Res.* **1992**, *25*, 188–194.

[23] A. Mehta, R. Jaouhari, T. J. Benson, K. T. Douglas, *Tetrahedron Lett.* **1992**, *33*, 5441–5444.

[24] D. L. Boger, S. A. Munk, H. Zarrinmayeh, *J. Am. Chem. Soc.* **1991**, *113*, 3980–3983.

[25] a) S. Ram, L. D. Spicer, *Tetrahedron Lett.* **1987**, *28*, 515–516; b) T. Bieg, W. Szeja, *Synthesis* **1985**, 76–77.

[26] Tetragastrin (**28**) was purchased from *Bachem*.

Received: September 25, 2007
Published online: January 23, 2008

