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Low-Valent Titanium Induced Indole Formation: Syntheses of Secofascaplysin, Indolopyridocoline and an Endothelin-Receptor-Antagonist

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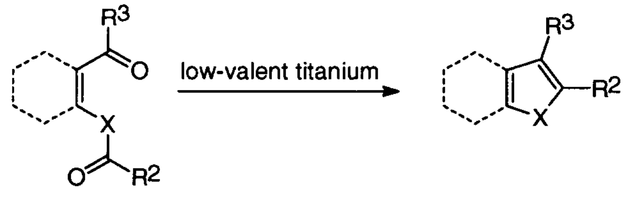
Abstract: The versatility of a titanium-induced reductive oxo-amide coupling reaction is illustrated by the syntheses of the alkaloids secofascaplysin **8** and indolopyridocoline **14** as well as by an efficient and flexible approach to the arylated indole-2-carboxylic acid **4**, which has recently been disclosed as a promising endothelin-receptor-antagonist. Depending on the particular substitution pattern in the substrates, either pre-formed titanium on graphite or low-valent titanium formed in situ ("instant conditions") are the preferred coupling agents for reductive heterocycle syntheses of this type. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

In recent work we have been able to extend the scope of low-valent titanium [Ti] chemistry beyond the classical reductive dimerization of aldehydes and ketones to alkenes (McMurry reaction).[1] Thus, it has been found that [Ti] efficiently promotes the intramolecular coupling of carbonyl groups of distinctly different redox potentials. This has opened up a new and flexible entry into heteroaromatic compounds such as furans, benzo[b]furans, pyrroles and indoles by reductive cyclization of oxo-esters or oxo-amides as depicted in Scheme 1.[2-4]

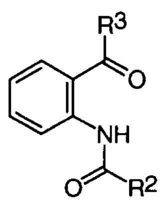


Scheme 1. Low-valent titanium induced reductive heterocycle synthesis, X = O, NR^1.

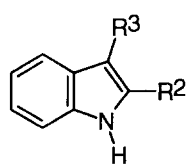
Coupling reactions of this type can be performed under quite different experimental conditions. Originally based on the use of highly activated titanium on graphite prepared from $TiCl_3$ and the potassium-graphite laminate C_8K,[5] the procedure was considerably simplified later on. In particular, an "instant method" for performing carbonyl coupling reactions has emerged, which essentially consists of mixing the substrate with $TiCl_3$ and Zn dust in an inert solvent and heating the suspension until TLC shows complete conversion.[3] Complexation of the Lewis-acidic $TiCl_3$ by the carbonyl groups thereby ensures a site-selective formation of [Ti], which can be used in only catalytic amounts if the reaction is performed in the presence of a chlorosilane.[4] Moreover, we were able to show that chlorosilanes also serve for activating commercial titanium dust, which then becomes a genuine McMurry coupling agent.[4] Although extensive comparative studies have clearly proved the versatility of these latter methods, they may be inadequate in cases where the substrates do not resist to an exposure to the Lewis-acidic $TiCl_3$ and/or TMSCl. The syntheses reported in the following illustrate *i.a.* how the experimental conditions for reductive indole formation can be adapted to the peculiarities of the starting material.

RESULTS AND DISCUSSION

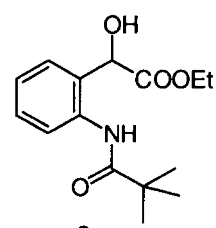
Model compounds: Variation of the C-3 Substituent. The titanium-induced indole synthesis is highly flexible with respect to the substitution pattern in the enamine region of the heterocycle formed. In particular, the R^2 group can be readily varied by acylation of a parent amino-ketone with different acyl halides or anhydrides followed by reductive coupling of the oxo-amides thus obtained. This has been amply demonstrated by our previous work.[2-4] We now report that the same flexibility accounts for the substituent at the C-3 position. The examples gathered in Table 1 show that oxo-amides **1a-f** bearing different R^3-groups at their ketone function all react properly to the corresponding substituted indole derivatives **2a-f**.



1a-f



2a-f



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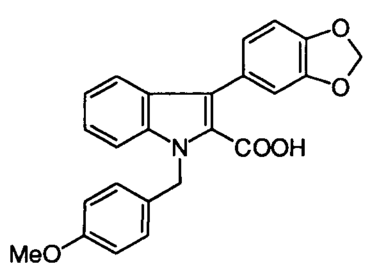
R^3 may be an aryl-, heteroaryl-, alkyl-, cyclopropyl- and even a -COOR group. These relatively robust starting materials give good yields of the respective indoles with pre-formed Ti-graphite as the reagent as well as under "instant conditions". Only in the case of the α-oxoester **1f** some reduction of the ketone without concomittant C-C-bond formation was noticed, leading to alcohol **3** as a by-product.[6] Consistent with the proposed ketone-triggered mechanism for reductive heterocycle syntheses,[3a] however, we observed that the *rate* of cyclization strongly depends on the electronic properties of the parent oxo-amide. As a rule of thumb, substrates with R^3 = aryl react more rapidly than those with R^3 = alkyl.

Table 1. Reductive Cyclization of Oxo-Amides **1** to Indoles **2** by Low-Valent Titanium.

Substrate	R^2	R^3	Conditions[a]	Time (h)	Product (Yield %)
1a	-C≡CPh	Ph	**A**	0.8	**2a** (77%)
1b	Ph	2-pyrrolyl	**A**	4	**2b** (58%)
			B	1	**2b** (92%)
1c	Ph	2-pyridylmethyl	**A**	15	**2c** (57%)
1d	Ph	$(CH_2)_8CH_3$	**A**	72	**2d** (73%)
1e	Ph	cyclopropyl	**A**	96	**2e** (78%)
			B	48	**2e** (70%)
1f	*tert*-butyl	-COOEt	**A**	2	**2f** (58%), **3** (21%)

[a] Method **A**: "instant method", $TiCl_3$, Zn dust, DME, reflux; Method **B**: Ti-graphite, DME, reflux.

Synthesis of an Endothelin-Receptor-Antagonist. The endothelin family of peptides, in particular endothelin-1, is known to exert a potent vasoconstrictor activity resulting in extremely long-lasting effects on blood pressure.[7] Moreover, the endothelins are claimed to be involved in the pathophysiology of many other diseases ranging from renal failure, pulmonary hypertension, myocardial ischemia, gastrointestinal disorders and cerebral vasospasms.[7] Therefore much effort has been put into the search for efficient endothelin converting enzyme inhibitors and, more importantly, for low-molecular weight non-peptidic endothelin-receptor-antagonists, which are a likely new class of therapeutic agents.



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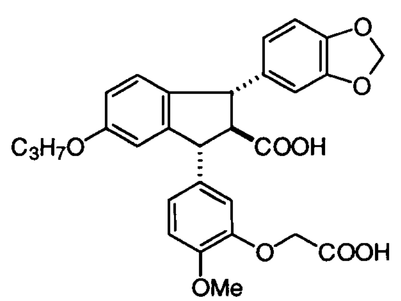

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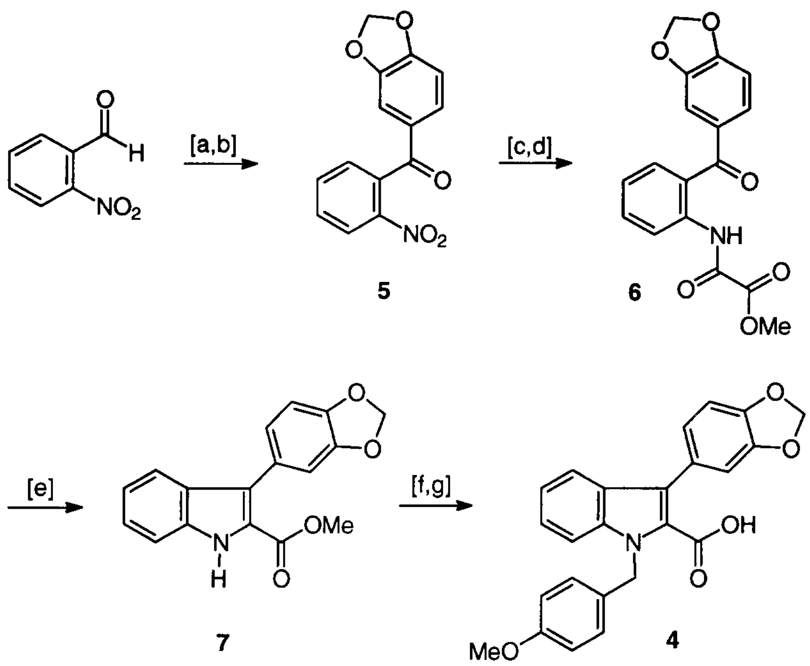
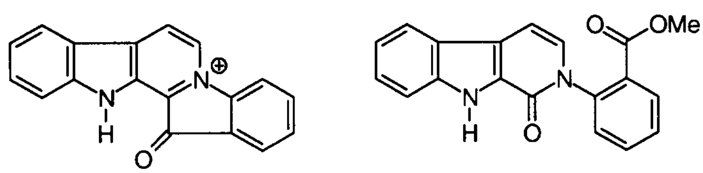


Scheme 2. Synthesis of an entothelin-receptor-antagonist: [a] 3,4-methylenedioxyphenylmagnesium bromide, THF, -78°C → r.t.; [b] PDC, CH_2Cl_2, reflux, 83% over both steps; [c] H_2 (1 atm), Pd/C (5%), ethyl acetate, quant.; [d] methyl oxalylchloride, CH_2Cl_2/pyridine, r.t., 77%; [e] $TiCl_3$, Zn, DME, reflux, 73-85%; [f] 4-$MeOC_6H_4CH_2Cl$, NaH, DMF, r.t., 93%; [g] 2N NaOH, H_2O/EtOH, reflux, 85%.

In this context, a recent patent has attracted our attention, disclosing that indole-2-carboxylic acid derivatives bearing electron rich aryl substituents such as **4** are efficient endothelin-receptor-antagonists.[8] Although their biological properties have not been reported in detail, the obvious structural analogy to similarly substituted indancarboxylic acids (*e.g.* SB 209670) may suffice to stimulate research, as the latter show K_i values in the nano-molar range.[9] Herein we describe a new, titanium-mediated synthesis of one member of this series of potential drugs. Our approach to the target compound **4** turned out to be efficient and is flexible enough to allow the formation of series of analogues as necessary for screening purposes.

Reaction of 2-nitrobenzaldehyde with 3,4-methylenedioxyphenylmagnesium bromide in THF at low temperature, followed by oxidation of the crude alcohol with PDC afforded ketone **5** in 83% yield. Hydrogenolysis of the nitro group and subsequent acylation of the resulting amine with methyl oxalylchloride under standard conditions gave oxoamide **6**. This substrate was cyclized on a multigram scale to indole **7** under "instant" conditions, simply by refluxing it together with $TiCl_3$ and zinc dust in DME under Ar until complete conversion was reached. Remarkably, the methylenedioxy-acetal function was perfectly stable under these Lewis-acidic conditions. Furthermore, the reductive coupling reaction of this trifunctional substrate took place in a completely regio- and chemoselective way exclusively along the oxo-amide path without any oxo-ester cyclization interfering. Finally, N-benzylation of **7** with 4-methoxybenzylchloride followed by saponification of the methyl ester afforded compound **4** without incident. This physiologically active target was thus prepared in 7 steps from commercially available substrates in 37-43% overall yield.

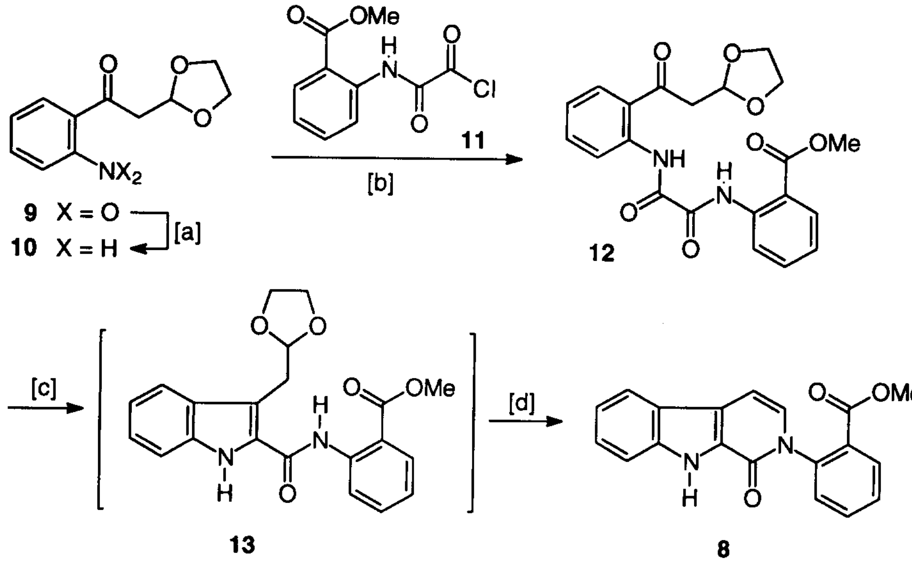
Synthesis of Secofascaplysin. Sponges of the genus *Fascaplysinopsis* have turned out to be rich sources of alkaloids and terpenes, some of which show promising antimicrobial, cytotoxic and antiviral activities.[10,11] One of these metabolites is secofascaplysin **8**, isolated from *F. reticulata* collected at the Benga lagoon of the Fiji islands.[11] **8** constitutes the first naturally occuring ß-carbolinone reported in the literature and is biogenetically derived from the pentacyclic fascaplysin, which was found to inhibit *i.a.* the reverse transcriptase of the HIV virus and has therefore been the target of several total syntheses.[12] No approach to secofascaplysin, however, has been reported in the literature so far.



Fascaplysin Secofascaplysin (**8**)

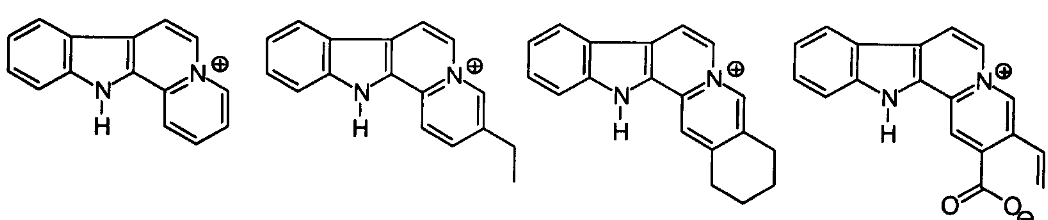
Our synthesis of this alkaloid is depicted in Scheme 3. *ortho*-Nitroacetophenone can be converted on a multigram scale in two steps into compound **9** according to a literature procedure.[13] Catalytic hydrogenation of its nitro group followed by acylation of the resulting amine **10** with the oxalic acid monochloride derivative **11** gave the unsymmetrical diamide **12** in 66% isolated yield. Acid chloride **11** is best obtained by slowly adding a solution of methyl 2-aminobenzoate in CH_2Cl_2 to a large excess of oxalyl chloride, followed by evaporation of all volatiles.

The reductive cyclization of compound **12** shows that the low-valent titanium reagent must be properly chosen according to the peculiarities of a given polyfunctional substrate. Treatment of **12** with $TiCl_3$ and Zn dust according to the "instant method"[3] leads to the spontaneous formation of secofascaplysin **8** by reductive indole formation (**12** $\rightarrow$ **13**), followed by Lewis-acid catalyzed attack of the distal amide on the 1,3-dioxolane which results in the observed closure of the C-ring (**13** $\rightarrow$ **8**). The isolated yields, however, were inacceptably low (20-30%) and could not be improved by variation of the solvent, temperature and concentration of the reactants. On the other hand, reaction of **12** with the pre-formed and hence less Lewis-acidic Ti-graphite reagent[5] gave indole **13** as the major product, but still admixed with varying amounts of tetracyclic **8** which are difficult to separate. Therefore the crude mixture consisting of **13** and **8** was treated with aqueous HCl (5%) in THF, thus affording secofascaplysin **8** in 60% isolated yield. The analytical data obtained perfectly match those reported in the literature,[11] except that our product was isolated in form of yellow crystals rather than as a "red oil". This one-pot cyclization of a substrate bearing five different reducible carbonyl groups nicely illustrates the performance of titanium-based methodology for heterocycle syntheses.



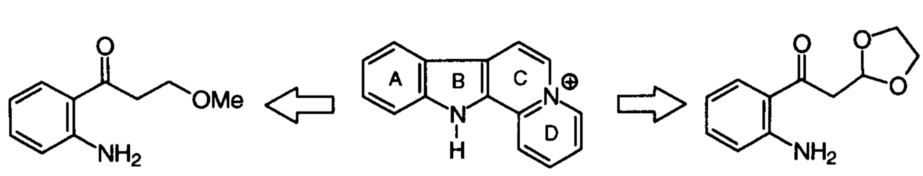
Scheme 3. Synthesis of Secofascaplysin **8**: [a] H_2 (1 atm), Pd/C (5%), EtOH, 5h, 92%; [b] CH_2Cl_2, pyridine, 20h, 66%; [c] Ti-graphite ($TiCl_3$: C_8K = 1 : 2), THF, 0°C (21h), then reflux (5h); [d] aq. HCl (5%), THF, 60°C, 5h, 60% over both steps.

Synthesis of Indolopyridocoline. Indolopyridocoline **14**, isolated from the bark of *Gonioma kamassi* E. Mey,[14] may be regarded as the parent compound of a series of indolo[2,3-a]quinolizine alkaloids comprising physiologically active compounds such as flavopereirine, sempervirine, vincarpine and others. Although we have already presented a titanium-based synthesis of **14** and the closely related flavopereirine,[3c] we would like to describe an alternative, short-cut route to alkaloids of this type.



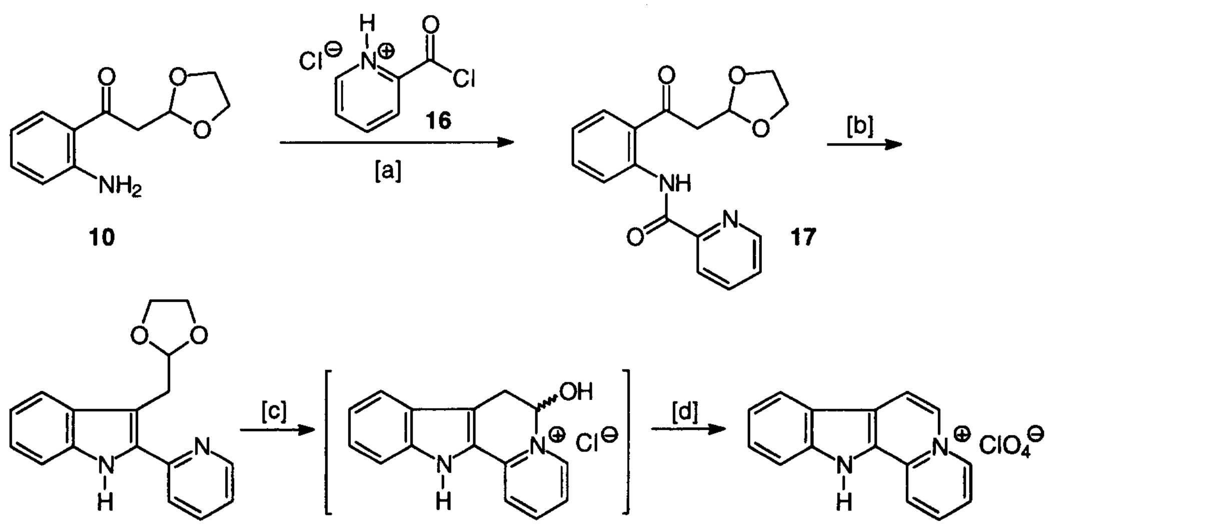
Indolopyridocoline (**14**) Flavopereirine Sempervirine Vincarpine

Our first approach was based on the use of amino ketone **15** as the starting material, which is rather sensitive because it combines a basic nitrogen atom and an aldol substructure.[3c] Moreover, a final oxidation by DDQ was necessary to afford the fully aromatic skeleton of these alkaloids. We therefore reasoned that the use of compound **10** as substrate might be advantageous: its good accessibility and successful application to the synthesis of secofascaplysin described above, together with the prospect that the formation of the aromatic C-ring may simply consist of a hydrolytic cleavage of the acetal followed by an intramolecular attack of the pyridine nitrogen atom on the liberated aldehyde function prompted us to reinvestigate the synthesis of this class of target molecules.



15 14 10

In fact, the use of **10** as the starting material resulted in a short and convergent synthesis of indolopyridocoline **14** summarized in Scheme 4. Standard acylation of **10** with the hydrochloride of pyridine-2-carboxylic acid chloride **16** gave oxo-amide **17** in 89% isolated yield. Its reaction with titanium-graphite as described above afforded indole **18** in 57% yield without noticeable cleavage of the acetal moiety interfering. Subsequent treatment of **18** with HCl in THF lead to the precipitation of the hemi-aminal **19**, which may either be isolated by filtration, or - more conveniently - can be dehydrated *in situ* to indolopyridocoline **14** on addition of Ac_2O. Thus, the target molecule was prepared in only 3 steps starting from a well accessible precursor. Since other members of the family of indolo[2,3-a]quinolizine alkaloids essentially differ from indolopyridocoline in the substitution pattern of the D-ring, this approach can be easily adapted to their synthesis just by acylating the parent amino ketone **10** with an appropriately substituted pyridine-2-carboxylic acid derivative.



18 19 14

Scheme 4. Synthesis of indolopyridocoline **14**: [a] CH_2Cl_2, pyridine, DMAP cat., 0 °C → r. t., 4h, 89%; [b] (i) Ti-graphite ($TiCl_3$: C_8K = 1 : 2), THF, reflux, 6.5h; (ii) EDTA disodium salt, H_2O, 57%; [c] HCl, THF, reflux, 8h; [d] (i) Ac_2O, reflux, overnight; (ii) $NaClO_4$, H_2O, 77% for steps [c] and [d].

EXPERIMENTAL

General. All reactions were carried out under Ar using Schlenk techniques. Melting points: Gallenkamp apparatus, corrected. NMR: Spectra were recorded on a Bruker WH 400, AMX 300 or AC 200 spectrometer at 400.1, 300.1 or 200.1 MHz (^{1}H) and 100.6, 75.5 or 50.3 MHz (^{13}C), respectively, in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The multiplicity in the ^{13}C NMR spectra refers to the geminal protons (DEPT). IR: Nicolet FT-7199, KBr, wavenumbers in cm^{-1}. MS: Varian CH-5 (70 eV). Mass spectra of the perchlorate salt of indolopyridocoline could not be obtained. In this case the zwitterion was analyzed, which had to be liberated by treatment with aqueous KOH and extraction with $CHCl_3$. UV: Varian Cary 2300, wavelength (λ) in nm, c = 10^{-3} M. Elemental analyses: Dornis and Kolbe, Mülheim. Flash chromatography: Merck silica gel 60 (230-400 mesh) with hexane/ethyl acetate as eluent in the proportions indicated. The solvents were dried by distillation over the following drying agents and were transferred under Ar: THF (Mg-anthracene), CH_2Cl_2 (CaH_2), pyridine (KOH), DME (sodium-potassium alloy).

Starting materials. The following compounds have been purchased and were used as received: 2-nitrobenzaldehyde, 2-nitroacetophenone, 2-aminobenzophenone, 1-bromo-3,4-methylenedioxybenzene, oxalyl chloride, methyl oxalyl chloride, methyl 2-aminobenzoate (Aldrich), $TiCl_3$ (99%, Aldrich), graphite (KS 5-44, Lonza AG, Switzerland). Other substrates have been prepared according to literature procedures: **1a** (ref.[3a]), **1b** (ref.[15a]), **1d** (ref.[15b]), **1e** (ref.[15b]), **9** (ref.[13]), pyridine-2-carboxylic acid chloride·hydrochloride (ref.[3c]). The synthesis of substrates **1c** and **1f** is described below.

N-[2-(2'-Pyridylacetyl)phenyl]benzamide (1c). 2-Methylpyridine (3.30 g, 35.4 mmol) dissolved in THF (10 mL) was slowly added to a solution of LDA (3.79 g, 35.4 mmol) in THF (35 mL) at 10 °C. A red suspension was formed to which N-(2-methoxycarbonylphenyl)benzamide (3.0 g, 11.8 mmol) in THF (25 mL) was added. The mixture was stirred at room temperature for 15 min and then quenched with aqueous acetic acid (10% v/v, 100 mL). The aqueous phase was extracted with CH_2Cl_2 (150 mL in three portions), the combined organic layers were dried (Na_2SO_4), evaporated and the residue was purified by flash chromatography with hexane/ethyl acetate (2/1) as eluent affording the title compound as yellow crystals (2.36 g, 63%). mp = 135-136 °C. IR: 3255, 3062, 1671, 1651, 1609, 1585, 1530, 1494, 1449, 1437, 1330, 1305, 1197, 985, 763, 752, 706, 664. ^{1}H NMR (200 MHz, keto-enol tautomer ≈ 3 : 1): δ 12.58 (br s, 0.75H), 12.20 (br s, 0.25H), 8.97 (dd, J = 1.0, 8.5, 0.75H), 8.74 (dd, J = 1.0, 8.5, 0.25H), 8.57 (d, J = 4.9, 0.75H), 8.16 (dd, J = 0.7, 8.1, 0.75H), 8.05 (dt, J = 1.8, 8.1, 2.25H), 7.86 (d, J = 5.9, 0.25H), 7.09-7.60 (m, 7.5H), 6.95 (d, J = 8.6, 0.25H), 6.77 (dt, J = 1.1, 6.5, 0.25H), 4.56 (br s, 2H). ^{13}C NMR (50 MHz, keto-enol tautomer ≈ 3 : 1, [resolved signals of minor isomer]) δ 201.7, 166.0, [154.9], 149.6, 141.7, [138.5], [138.0], [137.2], 136.7, 135.4, [134.7], 132.0, 131.9, [131.4], [130.6], 128.7, [128.5], [127.9], 127.4, [127.3], 124.0, [122.9], 122.5, 122.0, [121.5], [121.1], 120.9, 115.4, 92.3, 49.7. MS (70 eV): *m/z* (rel. intensity): 316 (10, [M^+]), 288 (10), 224 (30), 211 (16), 196 (17), 183 (12), 168 (11), 146 (13), 105 (100), 93 (20), 77 (61).- $C_{20}H_{16}N_2O_2$: *calcd.* C 75.93, H 5.10, N 8.85; *found* C 75.79, H 5.15, N 8.88.

Ethyl 2-oxo-2-(N-pivaloyl-2-aminophenyl)ethanoate (1f). *tert*-BuLi (9.2 mL, 14.6 mmol, 1.6M in pentane) was added to a solution of N-(2-bromophenyl)-2,2-dimethylpropionamide (1.50 g, 5.86 mmol) in

THF (30 mL) at -78 °C. To ensure complete metallation the mixture was stirred for 2 h at -20 °C. After cooling back to -78 °C, freshly distilled diethyloxalate (1.03 g, 7.03 mmol) was slowly added via syringe and the solution was allowed to warm to ambient temperature. The reaction was quenched with sat. aqueous NH_4Cl, the organic phase was separated, washed with water and brine (10 mL each), dried over Na_2SO_4 and evaporated. Purification of the remaining crude product by flash chromatography with hexane/ethyl acetate 10/1) as eluent afforded compound **1f** as yellow syrup (878 mg, 54%).[15c] IR: 3320, 2980, 1740, 1700, 1655, 1610, 1590, 1530, 1480, 1450, 1400, 1370, 1335, 1300, 1285, 1245, 1200, 1170, 1160, 1120, 1020, 980, 750, 680. ^1H NMR (200 MHz): δ 11.28 (br s, 1H), 8.76 (d, J = 8.3, 1H), 7.54 (m, 2H), 7.01 (dt, J = 0.8, 7.4, 1H), 4.35 (q, J = 7, 2H), 1.31 (dt, J = 0.9, 7, 3H), 1.25 (s, 9H). ^{13}C NMR (50 MHz) δ 190.5 (s), 178.0 (s), 163.4 (s), 143.0 (s), 136.9 (d), 133.4 (d), 122.1 (d), 120.4 (d), 117.0 (s), 62.3 (t), 40.2 (s), 27.3 (q), 13.8 (q). MS (70 eV): *m/z* (rel. intensity): 277 (5, [M^+]), 204 (100), 146 (11), 120 (27), 57 (41), 41 (13).- $C_{15}H_{19}NO_4$: *calcd.* C 64.97, H 6.91, N 5.05; *found* C 65.11, H 6.88, N 5.13.

Representative Example for an Indole Synthesis under "Instant Conditions" (Method A): 3-Phenyl-2-(phenylethynyl)indole (2a). A suspension of oxoamide **1a** (300 mg, 0.92 mmol), $TiCl_3$ (335 mg, 2.17 mmol) and Zn dust (284 mmol, 4.34 mmol) in DME (30 mL) was refluxed for 40 min, cooled to ambient temperature, filtered through a pad of silica, the inorganic residues were thoroughly washed with ethyl acetate, the combined filtrates were evaporated and the residue was purified by flash chromatography with hexane/ethyl acetate (10/1). Indole **2a** was thus obtained as yellow syrup (207 mg, 77%). IR: 3410, 3057, 2207, 1600, 1483, 1355, 1251, 1162, 1075, 1017, 911, 749, 701. ^1H NMR (200 MHz): δ 8.22 (br s, 1H), 7.83-7.89 (m, 3H), 7.12-7.55 (m, 11H). ^{13}C NMR (50 MHz) δ 136.1 (s), 134.3 (s), 131.3 (d), 128.9 (d), 128.5 (d), 128.4 (d), 126.6 (d), 126.1 (s), 124.0 (d), 122.7 (s), 120.8 (d), 120.1 (d), 116.0 (s), 111.0 (d), 94.4 (s), 82.2 (s). MS (70 eV): *m/z* (rel. intensity): 293 (100, [M^+]), 292, (41), 291 (42), 290 (12).- $C_{22}H_{15}N$: *calcd.* C 90.08, H 5.15, N 4.77; *found* 90.38, H 4.95, N 4.41.

Representative Procedure for Oxo-Amide Couplings using Ti-graphite (Method B): 2-Phenyl-3-(2-pyrrolyl)indole (2b). $TiCl_3$ (508 mg, 3.30 mmol) was added to a suspension of C_8K (890 mg, 6.59 mmol)[5] in DME (30 mL) and the mixture was refluxed for 1.5 h. Oxo-amide **1b** (200 mg, 0.69 mmol) was introduced and reflux continued for 1h. The insoluble residues were then filtered off over a pad of silica and washed with ethyl acetate, the combined filtrates were evaporated and the residue chromatographed with hexane/ethyl acetate (10/1) affording indole **2b** as yellow syrup (163 mg, 92%). This derivative slowly decomposes when kept in solution. IR: 3255, 3092, 1601, 1487, 1457, 1413, 1326, 1262, 1249, 1138, 1116, 1074, 1022, 1002, 896, 799, 746, 696, 610. ^1H NMR (200 MHz): δ 8.01 (br s, 1H), 7.80 (br s, 1H), 7.66 (d, J = 8, 1H), 7.00-7.34 (m, 8H), 6.60 (m, 1H), 6.33 (m, 1H), 6.23 (m, 1H). ^{13}C NMR (50 MHz) δ 135.9 (s), 133.4 (s), 132.5 (s), 128.8 (d), 128.3 (s), 127.9 (d), 127.8 (d), 125.1 (s), 122.8 (d), 120.4 (d), 120.0 (d), 117.2 (d), 110.9 (d), 109.0 (d), 107.7 (d), 107.1 (s). MS (70 eV): *m/z* (rel. intensity): 258 (100, [M^+]), 257 (53), 128 (17). The same product was obtained after a reaction time of 4 h according to method A using substrate **1b** (200 mg, 0.69 mmol), $TiCl_3$ (239 mg, 1.55 mmol) and Zn dust (203 mg, 3.10 mmol) in DME (20 mL), followed by a standard work-up as described.

2-Phenyl-3-(2-pyridylmethyl)indole (2c). Prepared according to method A starting with oxo-amide **1c** (300 mg, 0.95 mmol), $TiCl_3$ (472 mg, 3.10 mmol) and Zn dust (405 mg, 6.20 mmol) in DME (30 mL). For work-up the crude mixture was poured into an aqueous solution of EDTA (7 g, 100 mL, pH 11) in order to destroy titanium adducts with the pyridine nitrogen. Standard extractive work-up followed by flash chromatography afforded indole **2c** as yellow crystals (153 mg, 57%). mp = 142-144 °C. IR: 3409, 3147, 3063, 1594, 1568, 1492, 1474, 1455, 1341, 1307, 1241, 1001, 767, 740, 697. ^1H NMR (200 MHz): δ 8.70 (br s, 1H), 8.55 (d, J = 4.8, 1H), 7.02-7.57 (m, 13H), 4.47 (s, 2H). ^{13}C NMR (50 MHz) δ 161.4 (s), 149.0 (d), 136.6 (d), 136.1 (s), 135.8 (s), 132.7 (s), 129.3 (s), 128.8 (d), 127.8 (d), 127.7 (d), 122.3 (d), 121.1 (d), 119.7 (d), 119.4 (d), 110.9 (d), 109.6 (s), 33.5 (t). MS (70 eV): *m/z* (rel. intensity): 284 (80, [M^+]), 283 (13), 206 (100), 205 (11), 204 (21), 179 (10), 142 (10), 141 (17).- $C_{20}H_{16}N_2$: *calcd.* C 84.48, H 5.67, N 9.85; *found* C 84.10, H 5.68, N 9.53.

3-Nonanyl-2-phenylindole (2d). Obtained upon reaction of substrate **1d** (150 mg, 0.43 mmol) with $TiCl_3$ (185 mg, 1.20 mmol) and Zn dust (157 mg, 2.40 mmol) in DME (20 mL) for 72 h according to method A. Yellow syrup (100 mg, 73%). IR: 3360, 3070, 2920, 2860, 1610, 1585, 1535, 1495, 1450, 1310, 1075, 755, 700. ^1H NMR (200 MHz): δ 7.84 (br s, 1H), 7.10-7.64 (m, 9H), 2.85 (t, J = 7.9, 2H), 1.63-1.77 (m, 2H), 1.24-1.40 (m, 12H), 0.87 (t, J = 6.2, 3H). ^{13}C NMR (50 MHz) δ 135.9 (s), 134.0 (s), 133.5 (s), 129.3 (s), 128.7 (d), 127.9 (d), 127.4 (d), 122.1 (d), 119.4 (d), 119.3 (d), 114.1 (s), 110.2 (d), 31.9 (t), 31.0 (t), 29.8 (t), 29.6 (t), 29.4 (t), 29.3 (t), 24.5 (t), 22.7 (t), 14.1 (q). MS (70 eV): *m/z* (rel. intensity): 319 (16, [M^+]), 207 (18), 206 (100).- $C_{23}H_{29}N$: *calcd.* C 86.47, H 9.15, N 4.38; *found* C 86.46, H 9.22, N 4.32.

3-Cyclopropyl-2-phenylindole (2e). Prepared via method A as described above, upon reaction of substrate **1e** (150 mg, 0.57 mmol), $TiCl_3$ (208 mg, 1.35 mmol) and Zn dust (177 mg, 2.70 mmol) in DME (20 mL) for 96 h. Yellow syrup (103 mg, 78%). IR: 3420, 3080, 3060, 3010, 1600, 1580, 1535, 1490, 1460, 1450, 1380, 1350, 1300, 1230, 1075, 1030, 1010, 880, 810, 770, 750, 700. ^1H NMR (200 MHz): δ 7.98 (br s, 1H), 7.79 (d, J = 7, 1H), 7.70 (dd, J = 1.2, 7.7, 2H), 7.09-7.51 (m, 7H), 2.00-2.07 (m, 1H), 0.90-0.95 (m, 2H), 0.51-0.60 (m, 2H). ^{13}C NMR (50 MHz) δ 135.6 (s), 132.9 (s), 129.9 (s), 128.4 (d), 127.8 (d), 127.3 (d), 122.2 (d), 119.7 (d), 119.5 (d), 119.0 (s), 114.3 (s), 110.8 (d), 6.7 (t), 6.3 (d). MS (70 eV): *m/z* (rel. intensity): 233 (100, [M^+]), 232 (81), 230 (12), 218 (43), 217 (39), 206 (45), 204 (18).- $C_{17}H_{15}N$: *calcd.* C 87.52, H 6.48, N 6.00; *found* C 87.35, H 6.72, N 5.58. The same product (62 mg, 70%) was obtained in 48 h according to method B using C_8K (378 mg, 2.80 mmol), $TiCl_3$ (216 mg, 1.40 mmol) and oxo-amide **1e** (100 mg, 0.38 mmol).

Ethyl 2-*tert*-butylindole-3-carboxylate (2f). Reaction of substrate **1f** (200 mg, 0.72 mmol) with $TiCl_3$ (262 mg, 1.70 mmol) and Zn dust (222 mg, 3.40 mmol) in DME (20 mL) for 2 h according to method A followed by a standard work-up gave indole **2f** as colorless crystals (102 mg, 58%). mp = 96-97 °C. IR: 3320, 3100, 3060, 2980, 2950, 1670, 1520, 1480, 1430, 1370, 1330, 1310, 1250, 1220, 1200, 1175, 1150, 1120, 1070, 800, 790, 720. ^1H NMR (200 MHz): δ 8.63 (br s, 1H), 8.06 (m, 1H), 7.03-7.27 (m, 3H), 4.32 (q, J = 7.1, 2H), 1.49 (s, 9H), 1.37 (t, J = 7.1, 3H). ^{13}C NMR (50 MHz) δ 165.7 (s), 154.2 (s), 133.0 (s), 128.5 (s), 122.1 (d), 121.8 (d), 121.7 (d), 110.8 (d), 103.6 (s), 59.6 (t), 33.7 (s), 28.6 (q), 14.5 (q). MS (70 eV): *m/z* (rel. intensity): 245 (64, [M^+], 202 (12), 200 (24), 185 (16), 184 (100), 158 (14), 157 (12).- $C_{15}H_{19}NO_2$ *calcd.* C 73.44, H 7.81, N 5.71; *found* C 73.31, H 7.79, N 5.74. A second, more polar fraction was isolated and identified as ethyl 2-(N-pivaloyl-2-aminophenyl)-2-hydroxyethanoate (**3**) (43 mg, 21 %) by the spectroscopic data compiled below. Yellow syrup. IR: 3480, 3400, 2980, 2920, 2910, 2880, 1740, 1630, 1600, 1500, 1480, 1470, 1460, 1400, 1370, 1280, 1220, 1190, 1140, 1100, 1045, 1030, 770, 750. ^{1}H NMR (200 MHz): δ 7.02-7.25 (m, 5H), 5.67 (br s, 1H), 4.10 (q, J = 7.2, 2H), 1.25 (s, 9H), 1.19 (t, J = 7.2, 3H). ^{13}C NMR (50 MHz) δ 169.0 (s), 165.1 (s), 138.1 (s), 129.7 (d), 126.4 (d), 125.3 (d), 125.0 (d), 119.3 (s), 74.2 (d), 61.8 (t), 37.6 (s), 27.7 (q), 14.1 (q). MS (70 eV): *m/z* (rel. intensity): 279 (29, [M^+]), 206 (14), 194 (19), 149 (15), 132 (38), 122 (47), 120 (29), 104 (11), 93 (17), 85 (23), 57 (100).

2-Nitro-3',4'-methylenedioxybenzophenone (5). A solution of 3,4-methylenedioxyphenylmagnesium bromide in THF (80 mL), prepared as usual from 1-bromo-3,4-methylenedioxybenzene (19.93 g, 99.1 mmol) and Mg turnings (2.38 g, 99.1 mmol), was slowly dropped into a stirred solution of 2-nitrobenzaldehyde (15.0 g, 99.2 mmol) at -78 °C. The mixture was allowed to warm to ambient temperature overnight and was quenched by slow addition of saturated aqueous NH_4Cl (30 mL). The organic layer was washed with water and brine (30 mL each), dried over Na_2SO_4 and evaporated. The residue was rapidly passed through silica affording the crude secondary alcohol, which was oxidized without further purification. Thus, PDC (57.6 g, 153.1 mmol) was added to a solution of the crude product in CH_2Cl_2 (300 mL) and the mixture was refluxed for 3.5 h. After filtering the mixture through a pad of silica, the remaining solids were thoroughly washed with ethyl acetate (100 mL), the combined filtrates were evaporated affording ketone **5** as pale yellow crystals, which was used in the following step without further purification (15.60 g, 83%, GC purity ≥ 94%). mp = 120-121 °C. IR: 1700, 1674, 1611, 1573, 1526, 1502, 1495, 1442, 1348, 1288, 1266, 1096, 1034, 954, 926, 855, 829, 789, 742, 713. ^{1}H NMR (200 MHz): δ 8.21 (d, J = 8, 1H), 7.77(t, J = 7, 1H), 7.65 (t, J = 7, 1H), 7.46 (d, J = 7, 1H), 7.36 (s, 1H), 7.16 (d, J = 8, 1H), 6.78 (d, J = 8, 1H), 6.05 (s, 2H). ^{13}C NMR (50 MHz): δ 191.3, 152.2, 148.1, 146.3, 135.9, 133.8, 130.5, 130.1, 128.5, 126.1, 124.1, 108.0, 107.7, 101.8. MS (70 eV): *m/z* (rel. intensity): 271 (59, [M^+]), 149 (74), 137 (100), 134 (30), 121 (25), 107 (15), 104 (34), 91 (10), 76 (14).- $C_{14}H_9NO_5$: *calcd.* C 62.00, H 3.34, N 5.16; *found* C 61.79, H 3.38, N 5.22.

N-[2-(3',4'-Methylenedioxybenzoyl)phenyl]oxalamide methylester (6). A mixture of nitroketone **5** (15.06 g, 55.5 mmol) and Pd on charcoal (5% w/w, 1.79 g) in ethyl acetate (450mL) was stirred under an atmosphere of H_2 (1 atm) for 20 h at ambient temperature. The hydrogen uptake was monitored by a gas-byrette. The catalyst was then filtered off and the solvent was evaporated *in vacuo*. An analytically pure sample of 2-amino-3',4'-methylenedioxybenzophenone (6.49 g, 99%) was obtained by passing 6.65 g of this crude product through a silica column with hexane/ethyl acetate (4/1) as eluent. Yellow syrup. IR: 3474, 3358, 2901, 1731, 1615, 1583, 1550, 1502, 1481, 1437, 1353, 1299, 1251, 1161, 1039, 933, 755. ^{1}H NMR (200 MHz): δ 7.43 (dd, J = 1.4, 8, 1H), 7.23 (dt, J = 1.8, 7, 1H), 7.18 (s, 2H), 6.81 (dd, J = 1.4, 7, 1H), 6.69 (dd, J = 1, 8, 1H), 6.59 (dt, J = 1.8, 8, 1H), 5.99 (s, 2H), 5.74 (bs, 1H). ^{13}C NMR (50 MHz): δ 196.8 (s), 150.2 (s), 150.1 (s), 147.2 (s), 133.6 (s), 133.5 (d), 133.4 (d), 125.0 (d), 118.3 (s), 116.6 (d), 115.1 (d), 109.3 (d), 107.3 (d), 101.3 (t). MS (70 eV): *m/z* (rel. intensity): 241 (70, [M^+]), 240 (100), 224 (14), 149 (12), 120 (14), 92 (11). To a solution of this amine (2.05 g, 8.51 mmol) in CH_2Cl_2 (50 mL) and pyridine (1.2 mL) was slowly added methyl oxalylchloride (1.20 g, 9.0 mmol). The mixture was stirred for 3h at room temperature. Standard extractive work-up followed by flash chromatography with hexane/ethyl acetate (4/1) afforded the title compound as colorless crystals (2.14 g, 77%). mp = 153-154 °C. IR: 3307, 2940-3050, 1731, 1714, 1634, 1597, 1583, 1533, 1503, 1492, 1448, 1296, 1268, 1199, 1172, 1113, 1039, 757. ^{1}H NMR (200 MHz): δ 11.86 (bs, 1H), 8.62 (dd, J = 1, 8.6, 1H), 7.60 (dt, J = 1.5, 6, 2H), 7.17-7.33 (m, 3H), 6.87 (d, J = 8.6, 1H), 6.07 (s, 2H), 3.97 (s, 3H). ^{13}C NMR (50 MHz): δ 196.3 (s), 160.5 (s), 154.1 (s), 151.5 (s), 147.5 (s), 137.6 (s), 133.3 (d), 132.4 (d), 131.9 (s), 126.7 (d), 124.7 (s), 123.3 (d), 121.2 (d), 109.6 (d), 107.4 (d), 101.7 (t), 53.6 (q). MS (70 eV): *m/z* (rel. intensity): 327 (48, [M^+]), 268 (65), 146 (100), 90 (14).- $C_{17}H_{13}NO_6$: *calcd.* C 62.39, H 4.00, N 4.28; *found* C 61.95, H 4.26, N 4.23.

Methyl 3-(3,4-methylenedioxyphenyl)indole-2-carboxylate (7). A suspension of oxoamide **6** (5.75 g, 17.56 mmol), $TiCl_3$ (10.87 g, 70.49 mmol) and Zn dust (9.22 g, 141 mmol) in DME (80 mL) was refluxed for 80 min. The insoluble residues were filtered off and washed with THF (30 mL), the combined filtrates were evaporated and the crude indole purified by flash chromatography with hexane/ethyl acetate (4/1) as eluent affording product **7** as pale yellow crystals (3.80 g, 73%). In a parallel run starting with 265 mg (0.81 mmol) of oxoamide **6**, the isolated yield of indole **7** was improved to 85% (202 mg). mp = 162-163 °C. IR: 3398, 3336, 2900-3070, 1707, 1681, 1550, 1502, 1487, 1459, 1446, 1420, 1327, 1252, 1232, 1207, 1155, 1127, 1099, 1038, 935, 808, 744, 728. ^1H NMR (200 MHz): δ 9.14 (bs, 1H), 7.62 (dd, J = 0.7, 8, 1H), 7.29-7.44 (m, 2H), 7.13 (dt, J = 1.5, 8, 1H), 7.04 (s, 1H), 7.01 (dd, J = 1.5, 7, 1H), 6.90 (d, J = 7, 1H), 6.00 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (50 MHz): δ 162.1 (s), 146.9 (s), 146.5 (s), 135.4 (s), 127.6 (s), 126.7 (s), 125.6 (d), 123.7 (d), 122.0 (s), 121.4 (d), 120.5 (d), 111.4 (d), 110.8 (d), 107.6 (d), 100.7 (t), 51.5 (q). MS (70 eV): *m/z* (rel. intensity): 295 (98, [M^+]), 263 (100), 205 (34), 177 (43). $C_{17}H_{13}NO_4$: *calcd.* C 69.15, H 4.44, N 4.74; *found* C 68.81, H 4.31, N 4.65.

3-(3,4-Methylenedioxyphenyl)-1-(4-methoxybenzyl)indole-2-carboxylic acid (4). NaH (38 mg, 1.6 mmol) was added to a solution of indole **7** (500 mg, 1.53 mmol) in DMF (40 mL) and the mixture was stirred until the evolution of gas had ceased. After addition of 4-methoxybenzylchloride (298 mg, 1.90 mmol) the reaction was stirred for 2 h at ambient temperature and was then quenched with water (40 mL). Standard extractive work-up followed by flash chromatography with hexane/ethyl acetate (4/1) gave methyl 3-(3,4-methylenedioxyphenyl)-1-(4-methoxybenzyl)indole-2-carboxylate as yellow syrup (591 mg, 93%), exhibiting the following spectroscopic properties: IR: 3000, 2960, 2940, 2900, 2840, 1705, 1610, 1540, 1510, 1490, 1480, 1460, 1445, 1350, 1330, 1275, 1250, 1170, 1125, 1105, 1070, 1040, 935, 900, 870, 810, 740. ^1H NMR (400 MHz): δ 7.59 (dd, J = 1, 7, 1H), 7.39 (d, J = 7, 1H), 7.31 (dt, J = 1, 7, 1H), 7.13 (dt, J = 1, 7, 1H), 7.05 (dd, J = 2, 7, 2H), 6.94 (s, 1H), 6.90 (d, J = 6, 2H), 6.79 (dd, J = 2, 6, 2H), 5.99 (s, 2H), 5.70 (s, 2H), 3.72 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz) δ 162.9 (s), 158.8 (s), 147.3 (s), 146.6 (s), 138.3 (s), 130.3 (s), 128.2 (s), 127.7 (d), 127.0 (s), 125.6 (d), 124.8 (s), 124.3 (s), 123.7 (d), 121.6 (d), 120.9 (d), 114.0 (d), 110.9 (d), 110.7 (d), 107.9 (d), 101.0 (t), 55.2 (q), 51.5 (q), 47.7 (t). MS (70 eV): *m/z* (rel. intensity): 415 (28, [M^+]), 121 (100). A solution of this ester (500 mg, 1.20 mmol) in EtOH (20 mL) and NaOH (2N, 6 mL) was refluxed for 6 h, diluted with water (50 mL), the aqueous phase was twice extracted with Et_2O (20 mL each), acidified with HCl to pH ≈ 1 and extracted with ethyl acetate (100 mL in several portions). The combined EtOAc layers were washed with water and brine, dried over Na_2SO_4 and evaporated. Flash chromatography of the residue with hexane/ethyl acetate (4/1) containing HOAc (2% v/v) as eluent afforded indole **4** as pale yellow crystals (409 mg, 85%). mp = 155-156 °C (ref.[8]: 155-157 °C). IR: 3200-2400, 1675, 1610, 1515, 1490, 1480, 1460, 1450, 1350, 1280, 1250, 1240, 1180, 1130, 1110, 1040, 940, 820, 810, 740. ^1H NMR (200 MHz, DMSO-d_6): δ 12.94 (br s, 1H), 7.61 (d, J = 8.4, 1H), 7.46 (d, J = 8, 1H), 7.34 (dt, J = 0.7, 7.1, 1H), 6.82-7.14 (m, 8H), 6.06 (s, 2H), 5.74 (s, 2H), 3.68 (s, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 193.3 (s), 163.6 (s), 158.6 (s), 147.1 (s), 146.4 (s), 137.5 (s), 130.6 (d), 128.1 (d), 126.4 (s), 125.1 (s), 123.6 (s), 121.0 (d), 120.9 (d), 114.1 (d), 111.5 (d), 110.8 (d), 108.1 (d), 101.1 (t), 55.2 (t), 46.8 (q). MS (70 eV):

m/z (rel. intensity): 401 (18, [M$^+$]), 121 (100).- $C_{24}H_{19}NO_5$: *calcd.* C 71.81, H 4.77, N 3.49; *found* C 71.65, H 4.85, N 3.50.

2-(2-Aminobenzoylmethyl)-1,3-dioxolane (10). Compound **9** (4.20 g, 17.7 mmol) was dissolved in EtOH (350 mL) and hydrogenated (H_2, 1 atm) over Pd on charcoal (5% w/w, 490 mg). The course of the reaction was monitored by a gas-byrette. After 5 h, the suspension was filtered through a short pad of silica and the catalyst was washed with ethyl acetate (100 mL) in several portions. Evaporation of the solvents followed by flash chromatography with hexane/ethyl acetate (4/1) as eluent gave amine **10** as yellow crystals (3.37 g, 92%). mp = 67-68 °C. IR: 3451, 3339, 2894, 1649, 1617, 1587, 1548, 1486, 1206, 1140, 1053, 972, 756. ^{1}H NMR (200 MHz): δ 7.57 (dd, J = 1.4, 8.7, 1H), 7.13 (dt, J = 1.5, 8.5, 1H), 6.51 (m, 2H), 6.02 (br s, 2H), 5.32 (t, J = 5, 2H), 3.83 (m, 4H), 3.20 (d, J = 5, 2H). ^{13}C NMR (50 MHz) δ 198.2, 150.4, 134.2, 131.0, 117.4, 117.0, 115.3, 101.3, 64.6, 44.0. MS (70 eV): *m/z* (rel. intensity): 207 (26, [M$^+$]), 179 (12), 161 (12), 146 (16), 135 (11), 120 (63), 92 (25), 73 (100), 65 (23), 45 (27).- $C_{11}H_{13}NO_3$: *calcd.* C 63.76, H 6.32, N 6.76; *found* C 63.72, H 6.31, N 6.80.

Oxalylchloride Derivative 11. A solution of methyl 2-aminobenzoate (0.76 g, 5.0 mmol) in CH_2Cl_2 (80 mL) was added dropwise via a syringe pump over a period of 45 h to a solution of oxalyl chloride (12 g, 94.5 mmol) in CH_2Cl_2 (10 mL). The volatiles were evaporated leaving back the desired monochloride as white solid which was used without further purification. mp = 106-107 °C (dec.).

Oxo-Amide Derivative 12. A solution of the monochloride derivative **11** (1.01 g, 4.18 mmol) in CH_2Cl_2 (40 mL) was added over a period of 2 h to a solution of amine **10** (844 mg, 4.07 mmol) in CH_2Cl_2 (30 mL) and pyridine (1.4 mL). Standard extractive work-up after 18 h reaction time followed by recrystallization of the remaining solid from toluene gave the unsymmetrical diamide **12** as colorless crystals (1.10 g, 66%). mp = 177-178 °C. IR: 3217, 2955, 2891, 1694, 1664, 1602, 1578, 1509, 1449, 1299, 1271, 1221, 1140, 1087, 761. ^{1}H NMR (200 MHz): δ 13.20 (br s, 1H), 12.80 (br s, 1H), 8.85 (dt, J = 1, 6.3, 2H), 8.05 (dd, J = 1.2, 7.9, 1H), 7.94 (dd, J = 1.2, 7.9, 1H), 7.58 (tt, J = 1.7, 7.6, 2H), 7.10-7.24 (m, 2H), 5.45 (t, J = 4.9, 1H), 3.82-4.01 (m, 4H), 3.96 (s, 3H), 3.38 (d, J = 4.9, 2H). ^{13}C NMR (50 MHz) δ 200.1, 167.9, 158.8, 158.1, 139.6, 139.0, 135.0, 134.5, 131.3, 131.0, 123.8, 123.7, 123.0, 120.9, 120.4, 116.4, 101.2, 64.9, 52.6, 44.6. MS (70 eV): *m/z* (rel. intensity): 412 (4, [M$^+$]), 146 (53), 73 (100).

Secofascaplysin (8). To a suspension of C_8K (815 mg, 6.02 mmol)[5] in THF (20 mL) was added $TiCl_3$ (463 mg, 3.00 mmol) in one portion. The resulting slurry was refluxed for 1.5 h, cooled to 0 °C, oxoamide **12** (206 mg, 0.50 mmol) was added and the mixture was kept at that temperature for 21 h. In order to ensure complete conversion of the substrate, the suspension was then refluxed for another 5 h. The graphite was filtered off, washed with ethyl acetate, and the combined filtrates were evaporated. From the remaining solid an analytically pure sample of indole **13** can be obtained by flash chromatography with hexane/ethyl acetate (4/1 → 1/1), which exhibits the following analytical properties: mp = 170-171 °C. IR: 2933, 1698, 1660, 1606, 1586, 1524, 1449, 1385, 1316, 1264, 1138, 1084, 1024, 748. ^{1}H NMR (200 MHz): δ 11.31 (br s, 1H), 9.30 (br s, 1H), 8.61 (dd, J = 0.7, 8.3, 1H), 8.03 (dd, J = 1.5, 7.9, 1H), 7.76 (d, J = 8.1, 1H), 7.58 (dt, J = 1.5, 7.4, 1H), 7.11-7.41 (m, 4H), 5.34 (t, J = 4.4, 1H), 3.92 (s, 3H), 3.77-3.87 (m, 4H), 3.63 (d, J = 4.4, 2H). ^{13}C NMR (50 MHz) δ 167.9, 160.8, 140.1, 135.4, 133.8, 130.6, 128.8, 128.6, 124.6, 122.9, 122.0, 120.7, 119.9, 117.1, 112.9, 111.4, 103.8, 64.8, 52.0, 29.5. MS (70 eV): *m/z* (rel. intensity): 380 (23, [M^+]), 308 (14), 275 (12), 73 (100). HCl (5% w/w, 0.5 mL) was added to a solution of the crude product in THF (10 mL) and the mixture was refluxed for 5 h until indole **13** could not be detected any more by TLC. After neutralization with aqueous $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (40 mL in several portions), the combined organic layers were dried (Na_2SO_4), evaporated and the residue chromatographed with hexane/ethyl acetate (4/1) as eluent giving secofascaplysin **8** (94 mg, 60%) as pale yellow crystals ("red oil", ref.[11]). mp = 105-107 °C. IR: 3171, 1730, 1653, 1592, 1556, 1452, 1303, 1262, 1127, 1108, 1094, 1071, 950, 744, 716, 706, 646. ^1H NMR (200 MHz): δ 11.38 (br s, 1H), 8.17 (dd, J = 1.7, 7.6, 1H), 7.94 (d, J = 7.9, 1H), 7.72 (dt, J = 1.7, 7.6, 1H), 7.60 (dt, J = 1.5, 7.6, 1H), 7.36-7.48 (m, 3H), 7.21 (dt, J = 2.2, 7.9, 1H), 7.06 and 7.12 (AB-system, J = 6.9, 2H), 3.54 (s, 3H). ^{13}C NMR (50 MHz) δ 165.5, 156.1, 140.8, 139.9, 133.2, 131.2, 129.2, 128.9, 128.8, 127.9, 127.8, 126.7, 124.9, 122.3, 121.0, 120.0, 112.9, 101.5, 52.3. MS (70 eV): *m/z* (rel. intensity): 318 (80, [M^+]), 286 (12), 259 (100).

N-[2-([1,3]-dioxolan-2-yl-acetyl)-phenyl]pyridine-2-carboxylic acid amide (17). To a solution of amine **10** (587 mg, 2.84 mmol) in CH_2Cl_2 (25 mL) and pyridine (5 mL) were added DMAP cat. and the hydrochloride of pyridine-2-carboxylic acid chloride **16** (1.01 g, 5.67 mmol) at 0 °C. The mixture was stirred for 1 h at that temperature and then allowed to warm to 20 °C. After another 3 h the reaction was quenched by adding saturated aqueous Na_2CO_3 (50 mL), the aqueous layer was extracted with ethyl acetate (200 mL in several portions), the combined organic phases were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatorgaphy with hexane/ethyl acetate (3/1 → 1/1) as eluent afforded the title compound as colorless crystals (790 mg, 89%). mp = 121-123 °C. IR: 3211, 2883, 1683, 1667, 1578, 1523, 1455, 1419, 1299, 1198, 1135, 1056, 975, 764. ^1H NMR (200 MHz): δ 13.31 (br s, 1H), 8.93 (dd, J = 0.9, 8.5, 1H), 8.70 (br s, 1H), 8.19 (d, J = 7.7, 1H), 7.89 (dd, J = 1.4, 8.0, 1H), 7.79 (dt, J = 1.6, 7.7, 1H), 7.53 (dt, J = 1.3, 7.9, 1H), 7.38 (m, 1H), 7.09 (dt, J = 1.1, 7.6, 1H), 5.41 (t, J = 4.9, 1H), 3.86 (m, 4H), 3.35 (d, J = 4.9, 2H). ^{13}C NMR (50 MHz) δ 199.7, 163.6, 150.0, 148.3, 140.0, 136.9, 134.5, 131.1, 126.0, 122.8, 122.4, 122.3, 120.8, 101.0, 64.6, 44.5. MS (70 eV): *m/z* (rel. intensity): 312 (7, [M^+]), 225 (17), 206 (14), 197 (100), 78 (31), 73 (24). $C_{17}H_{16}N_2O_4$: *calcd.* C 65.38, H 5.16, N 8.97; *found* C 65.48, H 5.14, N 8.89.

3-[(1,3-Dioxolan-2-yl)methyl]-2-(2-pyridyl)indole (18). Graphite (1.23 g, 102 mmol) was degassed *in vacuo* at 150-160 °C. After connecting the flask to the argon line, potassium (502 mg, 12.8 mmol) was added in pieces with vigorous stirring at that temperature leading to the formation of C_8K in 5-10 min. After cooling to ambient temperature it was suspended in THF (60 mL), $TiCl_3$ (990 mg, 6.42 mmol) was added in one portion, and the resulting slurry was refluxed for 1.5 h to ensure complete reduction. A solution of oxo-amide **17** (100 mg, 0.321 mmol) in THF (15 mL) was then dropped into the refluxing suspension of Ti-graphite over a period of 3.5 h and heating was continued for another 3 h after the addition was complete. The mixture was allowed to cool to ambient temperature and the reaction was quenched by slowly pouring the suspension into an saturated aqueous solution of Na_2CO_3 containing EDTA·2Na·$2H_2O$ (2.4 g, 6.4 mmol). Extraction with ethyl acetate (200 mL in two portions), drying of the combined organic phases (Na_2SO_4), evaporation of the solvent and flash chromatography of the residue with hexane/ethyl acetate (3/1) gave indole **18** as pale yellow syrup (51 mg, 57%). IR: 3422, 3055, 2923, 2883, 1590, 1452, 1338, 1132, 1035, 742. ^1H NMR (200 MHz): δ 9.77 (br s, 1H), 8.53 (d, J = 4.5, 1H), 8.01 (d, J = 8.1, 1H), 7.66 (m, 2H), 7.26 (d, J = 7.7, 1H), 7.00-7.20 (m, 3H), 5.22 (t, J = 4.6, 2H), 3.82 (m, 4H), 3.37 (d, J = 4.6, 2H). ^{13}C NMR (50 MHz) δ 150.3, 148.8, 136.5, 135.3, 133.2, 129.8, 123.0, 121.5, 121.3, 119.6, 119.3, 110.9, 108.9, 104.3, 64.7, 30.1. MS (70 eV): *m/z* (rel. intensity): 280 (25, [M^+]), 219 (33), 207 (100), 73 (55), 45 (15). HR-MS: $C_{17}H_{16}N_2O_2$: *calcd.* 280.12118; *found* 280.12085.

6-Hydroxy-7H-indolo[2,3-a]quinolizin-5(12H)-ium chloride (19). To a solution of indole **18** (30 mg, 0.11 mmol) in THF (10 mL) was added conc. HCl (3 drops) and the resulting solution was refluxed for 4 h. The precipitate was filtered off, washed with THF and dissolved in MeOH. Evaporation of the solvent and drying of the residue *in vacuo* afforded compound **19** as yellow crystals (29 mg, 100%). mp = 255-258 °C (dec.). IR: 3423, 3079, 1628, 1617, 1554, 1496, 1458, 1293, 1170, 1106, 1049, 745. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.78 (br s, 1H), 9.01 (d, J = 6.1, 1H), 8.81 (br s, 1H), 8.50 (t, J = 7.5, 1H), 8.42 (d, J = 7.5, 1H), 7.80 (t, J = 6.1, 1H), 7.68 (d, J = 8.1, 1H), 7.48 (d, J = 8.1, 1H), 7.29 (t, J = 7.5, 1H), 7.09 (t, J = 7.5, 1H), 6.27 (br s, 1H), 3.50 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 147.4, 143.6, 141.0, 129.4, 127.7, 126.9, 125.9, 125.0, 123.0, 122.3, 122.2, 116.4, 114.3, 91.2, 28.9. MS (70 eV): *m/z* (rel. intensity): 236 (18, [(M-HCl^+]), 219 (36), 207 (100), 103 (16), 78 (16), 51 (14), 36 (27). HR-MS for [M-HCl]$^+$: $C_{15}H_{12}N_2O$ *calcd.* 236.09496; *found* 236.09363.

Indolopyridocoline Perchlorate (14). To a solution of indole **18** (40 mg, 0.14 mmol) in THF (10 mL) was added conc. HCl (3 drops) and the solution was refluxed for 8 h. Acetic anhydride (5 mL) was then added to the resulting suspension and reflux was continued overnight. After being cooled to ambient temperature, the reaction mixture was quenched by slowly pouring it into H_2O (50 mL). The aqueous phase was made alkaline by adding NaOH, extraced with $CHCl_3$ (100 mL in two portions) and the organic layers were washed with HCl (1N, 200 ml in several portions). The aqueous layers were combined and concentrated *in vacuo*. A solution of $NaClO_4$ (1.0 g) in H_2O (10 mL) was then slowly added, the suspension formed was stirred for 60 min, the precipitated product was filtered off, washed with H_2O and dried *in vacuo*. Yellow crystals (35 mg, 77%). mp = 280-283 °C, dec. (ref.[3c] 282-285 °C, dec.). UV (MeOH) λ_{max} (log ε): 252 (3.93), 314 (4.12), 387 (4.14). UV (MeOH/KOH) λ_{max} (log ε): 263 (3.92), 411 (4.14). IR: 3300, 3060, 1650, 1630, 1470, 1380, 1100, 750, 630. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.52 (bs, 1H), 9.42 (d, J = 6.9, 1H), 9.09 (d, J = 6.9, 1H), 8.96 (d, J = 8.6, 1H), 8.84 (d, J = 6.9, 1H), 8.44 (m, 2H), 8.02 (t, J = 6.6, 1H), 7.86 (d, J = 8.3, 1H), 7.73 (t, J = 7.6, 1H), 7.47 (t, J = 7.5, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.32, 141.00, 139.88, 136.34, 134.60, 133.49, 131.47, 126.95, 126.13, 125.83, 125.63, 125.51, 124.57, 120.72, 116.78. MS (of the zwitterion, *c.f.* general): *m/z* (rel. intensity): 219 (16), 218 ([M^+], 100), 217 (10). HR-MS: $C_{15}H_{10}N_2$, *calcd.* 218.084398, *found* 218.084334.

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