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A concise benzotriazolyl-mediated synthesis of 9-methoxycepharanone A

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Abstract—A concise synthesis of 9-methoxycepharanone A is described. The key step is the benzotriazolyl-assisted assemblage of an arylmethyleneisoindolinone ring system comprising the enol ether unit. Radical cyclization followed by deprotections and ultimate formation of the methylenedioxy group complete the total synthesis of the title compound.

1. Introduction

Aristolactams **1** are a minor group of alkaloids biogenetically derived from isoquinolines and structurally related to aporphines.[1] The richest source of this family of alkaloids which are characterized by a tetracyclic skeleton with a phenanthrene core is undoubtedly plants of the family *Aristolochiaceae*.[2] The leaves and roots of *Aristolochia* species have been used since antiquity in obstetrics and still find some applications in folk medicine in Taiwan and Southern China.[3] They are also considered to be the principal detoxification metabolites of aristolochic acids which have been implicated in an endemic renalyse known as CHN (Chinese Herbs Nephropathy).[4] Several alternative routes have been developed for the elaboration of these highly fused phenanthrene lactams. The main general synthetic approaches involve (i) the contraction of the lactone ring of dibenzochromanone derivatives[5] (route a), (ii) the photoinduced electrocyclic ring closure of iodostilbenic precursors[6] (route b), (iii) the inter[7] and intra[8] benzyne cycloaddition of (di)enamides (routes c and d) and (iv) the tributyltin-mediated radical cyclization of bromoarylmethyleneisoindolinones[9] (route e) (retrosynthetic Scheme 1).[10]

However, most of these methods are inadequate for the synthesis of models with diverse and dense functionalities on their compact framework particularly with alkoxy and/or hydroxy phenolic functions in specific positions on the basic phenanthrene nucleus. In particular, a certain number of methoxylated models **1** ($R^1 = OCH_3$) which can be regarded in one sense as having an enol ether moiety embedded in a phenanthrene unit still remain inaccessible by these conceptually different synthetic tactics. This is notably the case of 9-methoxycepharanone A (**1a**) (Fig. 1) which has been extracted from the roots of *Aristolochia auricularia* and which has been found to contain the highest reported amount of total aristolochic acids of any species.[11] We wish therefore to delineate in this paper a tactically new synthetic approach to these methoxylated aristolactams illustrated by the first total synthesis of 9-methoxycepharanone A (**1a**) isolated from *Annonaceae* species.

2. Results and discussion

We initially envisaged taking advantage of the transient formation of adducts equipped with a metalated hydroxybenzyl appendage from the two complementary procedures developed in our group for the building up of the arylmethylene isoindolinones **3**[9] (retrosynthetic Scheme 1).

These conceptually different procedures hinge upon a Horner olefination process involving a phosphorylated isoindolinone **4** (path a)[9a] and/or a hydroxylalkylation/E_1cb *anti* elimination sequence applied to an isoindolinone precursor **5** (path b).[9b] For this purpose the unsubstituted models **4a**[12] or **5a**[13] were initially synthesized by earlier techniques developed in our laboratory (Scheme 2). They were subsequently exposed to potassium bis(trimethylsilyl)-amide (KHMDS, 1 equiv, THF, −78 °C) and the corresponding metallated isoindolinones were then allowed to

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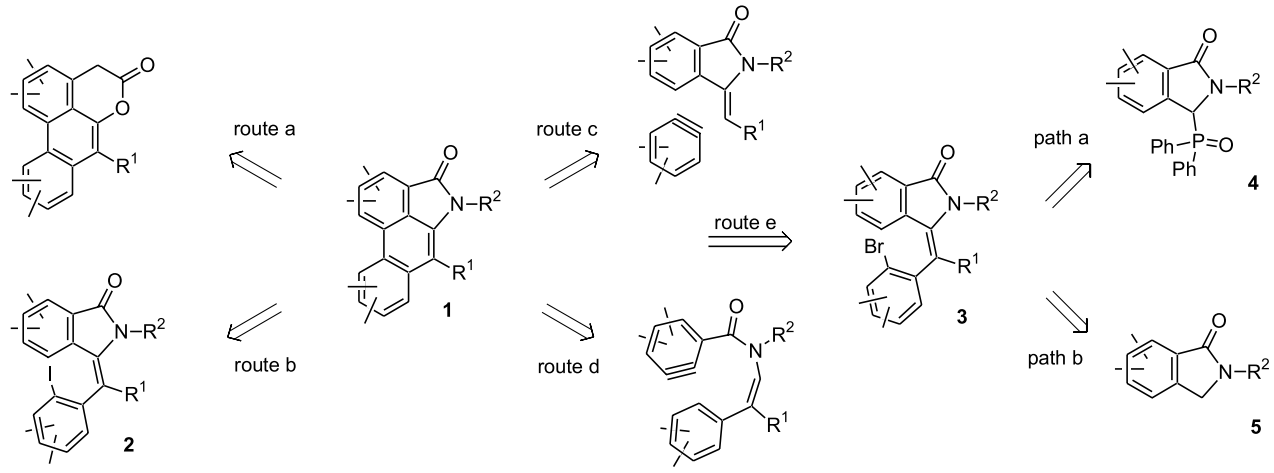


Scheme 1.

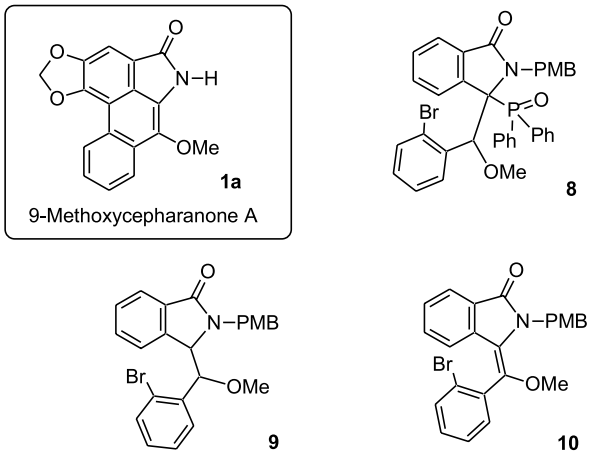
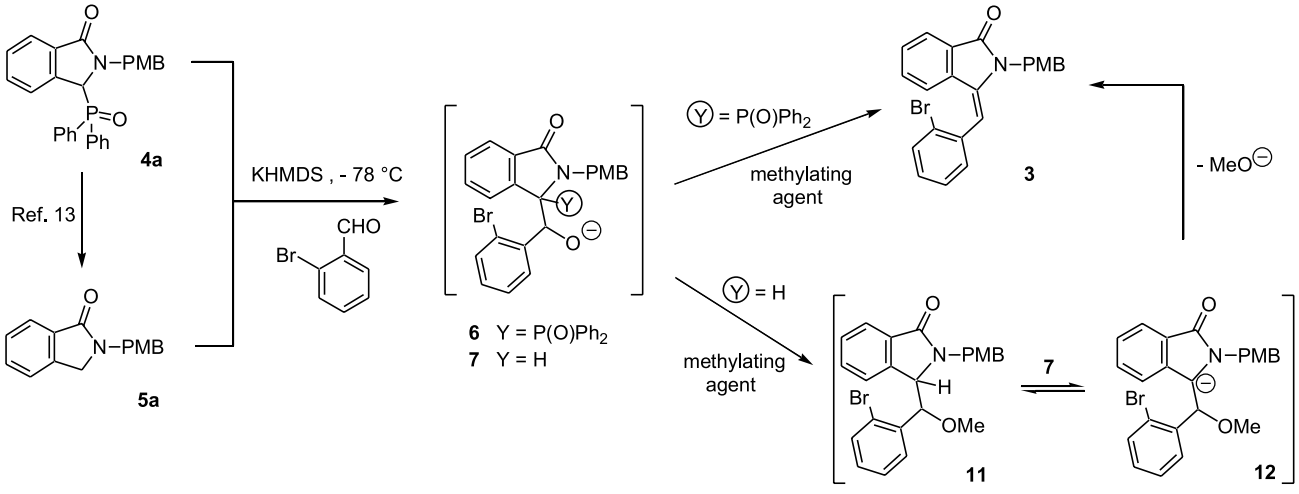


Figure 1.

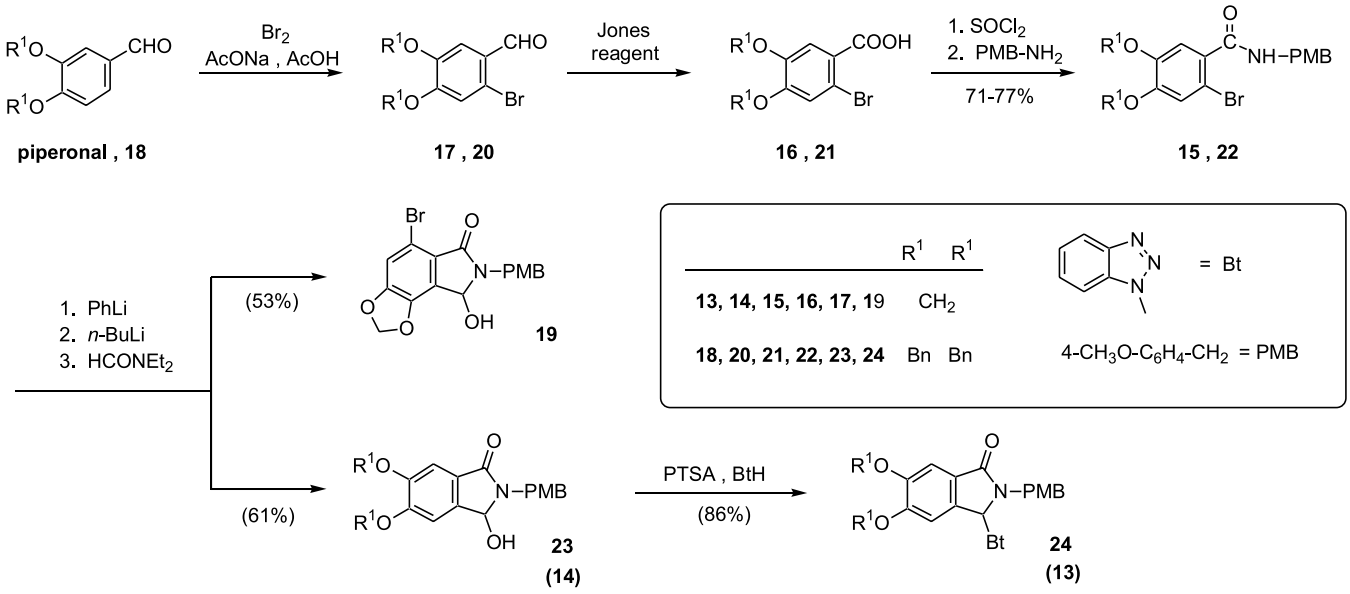
react with *ortho*-bromobenzaldehyde to provide the transient adducts **6** and **7** (Scheme 2). At this stage all attempts to methylate in situ the oxanions **6** or **7** met with no success even by varying the reaction conditions, namely by employing different bases (LHMDS, NaHMDS) or varied methylating agents (MeI, MeOTf). In both cases the elimination product **3** was invariably obtained and no trace of the expected products **8** or **9** respectively, good candidates for the elaboration of the stilbenic enol ether **10**, could be detected (Fig. 1).

One can reasonably assume that for the reaction carried out with the phosphorylated parent compound **4**, Horner olefination occurs prior to in situ *O*-alkylation. The exclusive formation of **3** upon *O*-methylation of adduct **7** still remains open to discussion. One can tentatively assume that *trans* metallation between oxanion **7** and adduct **11** occurs followed by E1cb elimination leading to enelactam **3** and that additionally the methoxylate released from **12** is of sufficient kinetic basicity to deprotonate the adduct **11** as it is formed (Scheme 2), a precedented phenomenon.[14]

We then conjectured that this problem could be circumvented by the assembly of an adduct structurally related to **6** or **7** but equipped this time with a temporary blocking group Y easily connectable to the indolinone framework, liable to allow the metallation-hydroxyalkylation-*O*-alkylation sequence and to facilitate the ultimate creation of the mandatory enol ether unit. The choice of benzotriazole was

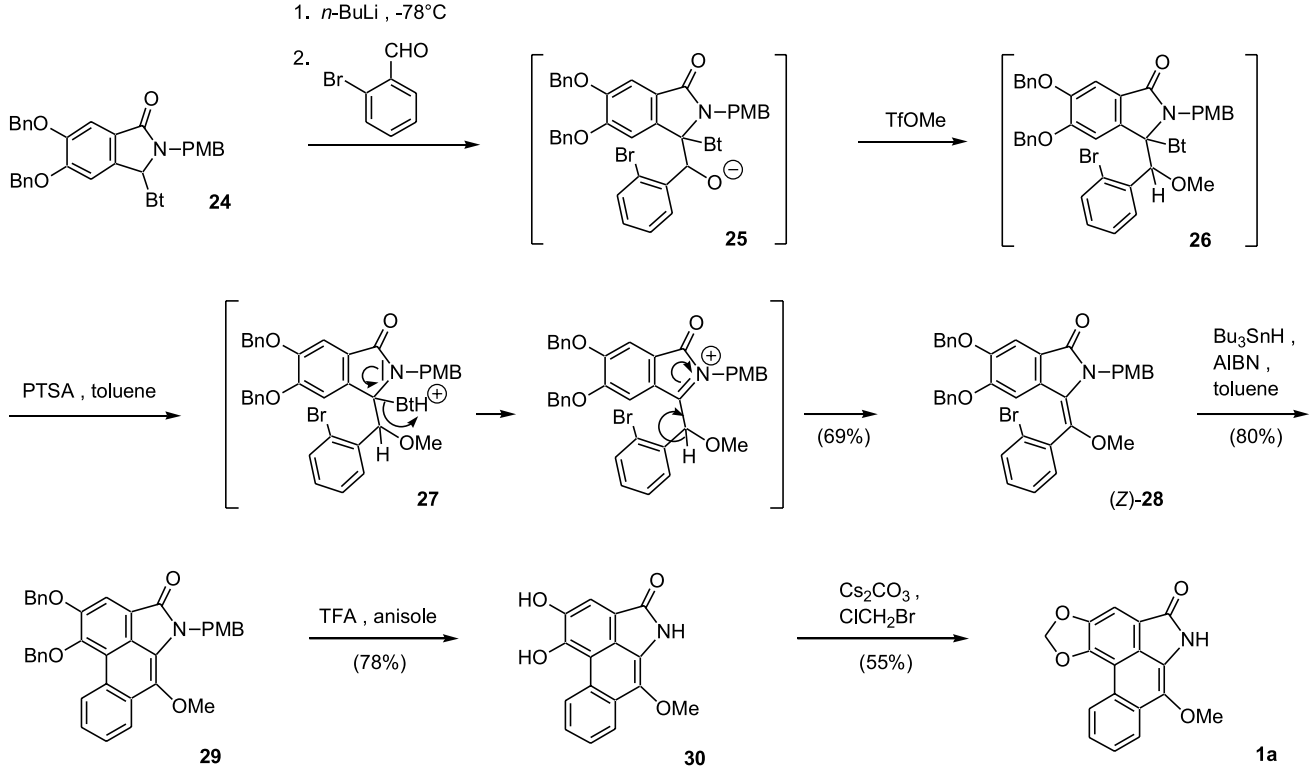


Scheme 2.



Scheme 3.

dictated by reliance on the ability of this remarkable synthetic auxiliary[15] to be involved in the generation of α-aminocarbanionic entities[16] and to generate *N*-acylenamines under basic and acidic conditions.[17] Consequently, we embarked on the synthesis of the methylenedioxyisoindolinone **13** with a pendant benzotriazolyl unit. We assumed that the construction of this compound would be achievable by using benzotriazole to trap the *N*-acyliminium species which would be derived from the appropriate hydroxylactam **14**. For the synthesis of this *N,O*-hemiacetal we initially synthesized the bromobenzamide derivative **15** from piperonal according to the synthetic route portrayed in Scheme 3. Compound **15** was then sequentially exposed to phenyllithium and *n*-butyllithium to induce the required metallation/interconversion sequence followed by quenching with DMF as the formylating agent. Unexpectedly this operation led solely to the formation of the hydroxylactam **19**. It is likely that due to the cooperative effect of the carboxamide function and of the methylenedioxy group which both rank highly in the hierarchy of *ortho*-directing metalating groups[18] metalation at their common 'in between' site is promoted thus sparing the bromine atom.



Scheme 4.

Experimenting different bases under varied conditions did not prevent the formation of this undesirable compound. We then anticipated that bromine–lithium exchange should be favored over metalation by replacement of the weakly sterically demanding methylenedioxy group by bulky dialkoxylated substitution patterns. For this purpose the sterically hindered dibenzyl derivative **22** was synthesized according to the four step sequence depicted in Scheme 3 starting from the benzyl protected isovaniline derivative **18**. Gratifyingly quenching with DMF of the dilithiated species generated by sequential treatment of **22** with PhLi and *n*-BuLi led to the desired hydroxylactam **23**. The steric congestion of the parent model **22** renders the *ortho* proton inaccessible and in the competitive process involving interconversion versus deprotonation the bromine/lithium exchange is favored.

Treatment of the *N,O*-hemiacetal **23** with *para*-toluenesulfonic acid (PTSA) and quenching of the transient iminium salt with benzotriazole allowed the installation of the benzotriazole unit on the isoindolinone framework. The resulting compound **24** was smoothly deprotonated with *n*-BuLi in THF at −78 °C followed by quenching with 2-bromobenzaldehyde. The transient oxanion **25** was intercepted in situ with methyl trifluoromethanesulfonate and the whole operation delivered the rather congested adduct **26** which was treated without isolation with PTSA. Gratyfyingly this operation induced elimination of the temporary synthetic auxiliary according to the mechanistic pathway depicted in Scheme 4 to provide the protected isoindolinone **28** with the required pendant enol ether unit in a fairly good yield (69%). The use of the bulky *para*-methoxybenzylgroup (PMB) on the lactam nitrogen was rewarded here: compound **28** was obtained as a mixture of *Z* and *E* isomers but with the required *Z* isomer predominating by a very large margin (*Z*/*E* 95:5). The oxidative radical cyclization of the bromostilbenic intermediate (*Z*)-**28** proceeded uneventfully to furnish the primarily annulated compound **29** with a satisfactory yield (80%). Treatment of this fused phenanthrene lactam with trifluoroacetic acid (TFA) in the presence of the cation scavenger anisole resulted in the concomitant removal of the benzyl protection of the phenolic hydroxy groups and of the lactam nitrogen to provide the methoxylated biphenolic compound **30**. The regeneration of the required methylenedioxy group was readily secured by treatment of **30** with bromochloromethane in the presence of cesium carbonate and this simple operation delivered the target natural product 9-methoxycepharanone A (**1a**) in a very satisfactory overall yield (12% over the last six steps). The spectral data of **1a** were identical to those reported for the natural product.[3a]

3. Experimental

3.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μ; 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert-Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300 (300 and 75 MHz, for ^1H, and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard. Microanalyses were performed by the CNRS microanalysis center.

3.1.1. 3-[1-(2-Bromophenyl)methyl-(*E*)-ene]-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (3). Compound **3** was obtained from **4a**[12] or **5a**[13] by following already described procedures.[9a,14] Pale yellow crystals; yield 75–82%; mp 178–179 °C; ^1H NMR (δ) 3.77 (s, 3H, OCH_3), 5.08 (s, 2H, NCH_2), 6.37 (s, 1H, CH═), 6.85 (d, J= 8.6 Hz, 2H, aromatic H), 7.12 (d, J=7.8 Hz, 1H, CH═), 7.16–7.35 (m, 5H, aromatic H), 7.44 (t, J=7.6 Hz, 2H, aromatic H), 7.64 (d, J=7.1 Hz, 1H, aromatic H), 7.89 (d, J=7.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 42.8, 55.3, 110.9, 114.1, 123.0, 123.5, 124.8, 127.3, 128.6, 128.9, 129.5, 129.6, 130.4, 131.6, 131.8, 132.9, 134.9, 135.6, 136.4, 158.9, 166.7. Anal. calcd for $C_{23}H_{18}BrNO_2$ (420.3): C, 65.73; H, 4.32; N, 3.33%. Found: C, 65.65; H, 4.15; N, 3.08%.

3.2. 2-Bromobenzoic acid derivatives

The benzaldehyde derivatives **17**,[19] **18**[20] and **20**[21] were synthesized according to literature methods.

The 2-bromobenzoic acid derivatives **16**[22] and **21** were obtained by oxidation with Jones reagent[23] of the corresponding benzaldehyde derivatives **17** and **20**.

3.2.1. 2-Bromo-4,5-dibenzyloxybenzoic acid (21). Yield 81%; mp 157–158 °C; ^1H NMR (δ) 5.17 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 7.21 (s, 1H, aromatic H), 7.32–7.45 (m, 10H, aromatic H), 7.69 (s, 1H, aromatic H); ^{13}C NMR (δ) 71.1, 71.3, 115.8, 118.2, 119.7, 121.6, 127.3, 127.4, 128.1, 128.3, 128.6, 128.7, 135.7, 136.3, 147.4, 152.8. Anal. calcd for $C_{21}H_{17}BrO_4$ (413.3): C, 61.03; H, 4.15%. Found: C, 61.35; H, 3.94%.

3.3. 2-Bromobenzamides 15 and 22

The carboxylic acids **16** and **21** were initially converted into their corresponding acid chlorides ($SOCl_2$, DMF cat., CH_2Cl_2) and then allowed to react under standard conditions with *para*-methoxybenzylamine to furnish the 2-bromobenzamides **15** and **22**.

3.3.1. 6-Bromo-1,3-benzodioxole-5-[*N*-(4-methoxybenzyl)carboxamide] (15). Yield 71%; mp 137–138 °C (from hexane–toluene); ^1H NMR (δ) 3.78 (s, 3H, OCH_3), 4.51 (d, J=5.6 Hz, 2H, NCH_2), 5.98 (s, 2H, OCH_2O), 6.34 (t, J=5.6 Hz, 1H, NH), 6.85 (d, J=8.8 Hz, 2H, aromatic H), 6.94 (s, 1H, aromatic H), 7.00 (s, 1H, aromatic H), 7.27 (d, J=8.8 Hz, 2H, aromatic H); ^{13}C NMR (δ) 47.3, 55.3, 109.6, 110.7, 113.1, 114.0, 114.1, 129.4, 129.7, 130.9, 147.4, 146.9, 166.8. Anal. calcd for $C_{16}H_{14}BrNO_4$ (364.2): C, 52.77; H, 3.87; N, 3.85%. Found: C, 52.60; H, 3.94; N, 4.05%.

3.3.2. 4,5-Dibenzyloxy-2-bromo-*N*-(4-methoxybenzyl)-carboxamide (22). Yield 77%; mp 145–146 °C (from

hexane–toluene); ^{1}H NMR (δ) 3.79 (s, 3H, OCH_3), 4.53 (d, J=5.4 Hz, 2H, NCH_2), 5.11 (s, 4H, 2×OCH_2), 6.45 (t, J=5.4 Hz, 1H, NH), 6.87 (d, J=8.6 Hz, 2H, aromatic H), 7.05 (s, 1H, aromatic H), 7.26–7.42 (m, 13H, aromatic H); ^{13}C NMR (δ) 43.8, 55.3, 71.3, 110.4, 114.1, 116.1, 118.9, 127.3, 127.4, 128.1, 128.2, 128.6, 128.7, 129.3, 129.6, 129.8, 136.1, 136.4, 148.2, 150.6, 159.1, 166.6. Anal. calcd for $C_{29}H_{26}BrNO_4$ (532.4): C, 65.42; H, 4.92; N, 2.63%. Found: C, 65.65; H, 4.94; N, 2.34%.

3.4. General procedure for the synthesis of the isoindolinones 19 and 23

A solution of PhLi (1.22 mL, 1.8 M in cyclohexane/diethyl ether, 2.2 mmol) was added dropwise at −78 °C under Ar to a stirred solution of the benzamide derivatives **15** or **22** (2.0 mmol) in THF (70 mL). After stirring for 20 min at −78 °C *n*-BuLi (1.38 mL, 1.6 M in hexanes, 2.2 mmol) was added dropwise followed by DMF (365 mg, 5.0 mmol). The reaction mixture was stirred at −78 °C for 1 h then allowed to warm to room temperature over a period of 2 h and finally quenched by addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with Et_2O (3×50 mL) and the combined organic layers were dried ($MgSO_4$). Evaporation of solvent in vacuo left a solid residue which was purified by flash column chromatography with ethyl acetate/hexanes (50:50) as eluent. Isoindolinones **19** and **23** were finally purified by recrystallization from hexane–toluene.

3.4.1. 5-Bromo-8-hydroxy-7-(4-methoxybenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-*e*]isoindol-1-one (19). Yield 416 mg (53%); mp 187–188 °C; ^{1}H NMR (δ) 3.71 (s, 3H, OCH_3), 4.22 (d, J=15.0 Hz, 1H, NCH_2), 4.77 (d, J=15.0 Hz, 1H, NCH_2), 5.62 (d, J=9.0 Hz, 1H, C*H*OH), 6.17 (s, 1H, OCH_2O), 6.24 (s, 1H, OCH_2O), 6.82 (d, J=9.0 Hz, 1H, OH), 6.88 (d, J=8.5 Hz, 2H, aromatic H), 7.23 (d, J=8.5 Hz, 2H, aromatic H), 7.28 (s, 1H, aromatic H); ^{13}C NMR (δ) 41.7, 55.1, 76.4, 103.5, 108.9, 113.6, 113.9, 122.7, 125.7, 129.2, 129.3, 142.5, 151.9, 158.5, 163.5. Anal. calcd for $C_{17}H_{14}BrNO_5$ (392.2): C, 52.06; H, 3.60; N, 3.57%. Found: C, 52.31; H, 3.38; N, 3.49%.

3.4.2. 5,6-Dibenzyloxy-3-hydroxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (23). Yield 587 mg (61%); mp 148–149 °C; ^{1}H NMR (δ) 3.74 (s, 3H, OCH_3), 4.16 (d, J=14.4 Hz, 1H, NCH_2), 4.90 (d, J=14.4 Hz, 1H, NCH_2), 5.03 (s, 2H, OCH_2), 5.08 (s, 2H, OCH_2), 5.40 (d, J=11.4 Hz, 1H, OH), 6.80 (d, J=8.6 Hz, 2H, aromatic H), 7.01 (d, J=11.4 Hz, 1H, CH), 7.03 (s, 1H, aromatic H), 7.21 (d, J=8.6 Hz, 2H, aromatic H), 7.25–7.39 (m, 11H, aromatic H); ^{13}C NMR 42.1, 55.2, 70.8, 71.0, 80.5, 107.2, 108.5, 114.1, 124.1, 127.2, 127.6, 128.0, 128.1, 128.5, 128.6, 129.2, 129.9, 136.2, 136.3, 138.0, 150.2, 152.4, 159.0, 167.5. Anal. calcd for $C_{30}H_{27}NO_5$ (481.55): C, 74.83; H, 5.65; N, 2.91%. Found: C, 75.68; H, 5.80; N, 2.72%.

3.4.3. 3-(Benzotriazol-1-yl)-5,6-dibenzyloxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (24). A solution of isoindolinone **23** (578 mg, 1.2 mmol), benzotriazole (155 mg, 1.3 mmol) and PTSA (5 mg, cat) in 30 mL of toluene was refluxed for 3 h. After evaporation of the toluene under vacuum the crude reaction mixture was dissolved in CH_2Cl_2 (30 mL), washed twice with aq Na_2CO_3 (5%) then water and dried (Na_2SO_4). The solvent was evaporated and the product was triturated with Et_2O to afford a white solid which was recrystallized from hexane–toluene. Yield 601 mg (86%); mp 163–164 °C; ^{1}H NMR (δ) 3.71 (s, 3H, OCH_3), 3.79 (d, J=14.7 Hz, 1H, NCH_2), 4.90 (d, J=14.7 Hz, 1H, NCH_2), 5.00 (s, 2H, OCH_2), 5.28 (s, 2H, OCH_2), 6.41 (d, J=8.3 Hz, aromatic H), 6.69 (d, J=8.1 Hz, 2H, aromatic H), 6.75 (s, 1H, CH), 7.09–7.13 (m, 3H, aromatic H), 7.17–7.49 (m, 12H, aromatic H), 7.57 (s, 1H, aromatic H), 8.02 (d, J=8.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 43.4, 55.2, 71.0, 71.2, 71.7, 108.3, 108.4, 110.3, 114.0, 120.1, 124.5 (two peaks overlapping), 127.0, 127.3, 127.9, 128.0, 128.1, 128.2, 128.5, 128.7, 129.9, 130.6, 132.7, 135.6, 136.2, 147.0, 151.2, 153.1, 159.1, 167.0. Anal. calcd for $C_{36}H_{30}N_4O_4$ (582.7): C, 74.21; H, 5.19; N, 9.62%. Found: C, 73.98; H, 5.35; N, 9.57%.

3.4.4. 5,6-Dibenzyloxy-3-[1-(2-bromophenyl)-1-methoxymethyl-(*Z*)-ene]-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (28). A solution of *n*-BuLi (0.7 mL, 1.6 M in hexanes, 1.1 mmol) was added dropwise with stirring under Ar at −78 °C to a solution of **24** (583 mg, 1.0 mmol) in THF (20 mL). The red solution was stirred at −78 °C for 15 min then a solution of *ortho*-bromobenzaldehyde (202 mg, 1.1 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was allowed to warm to −40 °C over 5 min then recooled to −78 °C. A solution of methyl trifluoromethanesulfonate (181 mg, 1.1 mmol) in THF (1 mL) was added at once and the reaction mixture was allowed to warm at room temperature. Water (20 mL) was added and the resulting mixture was extracted with Et_2O (3×15 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated in vacuo to left a solid residue which was dissolved in toluene (20 mL). After addition of a catalytic amount of PTSA, the solution was stirred at room temperature for 1 h. The toluene was evaporated in vacuo and the residue dissolved in CH_2Cl_2 (30 mL). The solution was washed with aq. sat. $NaHCO_3$, brine and finally water and dried ($MgSO_4$). After removal of CH_2Cl_2 the crude product was purified by flash column chromatography with ethyl acetate/hexanes (30:70) as eluent. Yield 457 mg (69%); mp 170–171 °C; ^{1}H NMR (δ) 3.10 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.66 (s, 2H, OCH_2), 5.18 (s, 2H, NCH_2), 5.36 (s, 2H, OCH_2), 5.46 (s, 1H, aromatic H), 6.84 (d, J=8.5 Hz, 2H, aromatic H), 7.17–7.21 (m, 4H, aromatic H),), 7.29–7.44 (m, 12H, aromatic H), 7.63 (d, J=7.6 Hz, 1H, aromatic H); ^{13}C NMR (δ) 45.4, 55.3, 55.9, 70.2, 70.9, 106.1, 107.5, 113.6, 119.6, 122.0, 125.9, 126.8, 127.2, 127.8, 127.9, 128.2, 128.4, 128.5, 130.0, 131.3, 131.4, 133.3, 133.5, 133.9, 136.4, 136.7, 138.6, 149.1, 151.7, 158.3, 167.0. Anal. calcd for $C_{28}H_{32}BrNO_5$ (662.6): C, 68.89; H, 4.87; N, 2.11%. Found: C, 69.03; H, 4.79; 2.40%.

3.4.5. 1,2-Dibenzyloxy-6-methoxy-5-(4-methoxybenzyl)-4,5-dihydrodibenzo[*cd,f*]indol-4-one (29). To a solution of **28** (430 mg, 0.65 mmol) in dry degassed benzene (300 mL) refluxing under Ar, was added a solution of *n*-Bu_3SnH (295 mg, 1.0 mmol) and AIBN (65.5 mg, 0.4 mmol) in dry degassed benzene (50 mL) by syringe over a period of 10 min. Once addition had finished, refluxing was kept up for a further 3 h. The benzene was evaporated under reduced pressure, and the residue was dissolved in CH_3CN (50 mL). The solution was washed with hexane (3×30 mL) and

concentrated in vacuo to a yellow oil which was purified by flash column chromatography with ethyl acetate/hexanes (40:60) as eluent. Recrystallization from EtOH afforded **29** as yellow crystals. Yield 303 mg (80%); mp 117–118 °C; ^{1}H NMR (δ) 3.74 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.25 (s, 2H, NCH_2), 5.30 (s, 2H, OCH_2), 5.36 (s, 2H, OCH_2), 6.83 (d, J=8.1 Hz, 2H, aromatic H), 7.37–7.61 (m, 14H, aromatic H), 7.92 (s, 1H, aromatic H), 8.12 (d, J=8.1 Hz, 1H, aromatic H), 9.33 (d, J=8.1 Hz, 1H, aromatic H); ^{13}C NMR (δ) 44.7, 55.2, 62.8, 72.2, 75.1, 111.5, 113.9, 119.4, 120.8, 124.3, 124.9, 126.1, 127.4, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 130.4, 131.0, 136.3, 136.4, 136.8, 150.4, 152.9, 158.8, 167.8. Anal. calcd for $C_{38}H_{31}NO_5$ (581.7): C, 78.47; H, 5.37; N, 2.41%. Found: C, 78.41; H, 5.13; N, 2.22%.

3.4.6. 1,2-Dihydroxy-6-methoxy-4,5-dihydrodibenzo[*cd, f*]indol-4-one (30). A solution of **29** (290 mg, 0.5 mmol) and anisole (550 mg, 5 mmol) in trifluoroacetic acid (20 mL) was refluxed under Ar for 60 h. The solvent and excess anisole were removed under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL) and NEt_3 (1 mL) was added with stirring. Water (2 mL) was then added, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated under vacuum to yield a solid residue which was recrystallized from EtOH. Yellow crystals, yield 110 mg (78%); mp 326–327 °C; ^{1}H NMR (DMSO-*d6*; δ) 4.06 (s, 3H, OCH_3), 7.53–7.59 (m, 3H, aromatic H), 8.15 (d, J=5.6 Hz, 1H aromatic H), 9.29 (s, 1H, aromatic H), 10.37 (s, 2H, 2×OH), 10.83 (s, 1H, NH); ^{13}C NMR (DMSO-*d6*; δ) 60.7, 111.1, 112.2, 115.0, 120.8, 122.1, 125.0, 125.4, 126.4, 127.6, 128.1, 129.6, 133.8, 144.9, 148.3, 168.5. Anal. calcd for $C_{16}H_{11}NO_4$ (281.3): C, 68.33; H, 3.94; N, 4.98%. Found: C, 68.49; H, 3.83; N, 5.27%.

3.5. 9-Methoxycepharanone A (1a)

A suspension of **30** (80 mg, 0.28 mmol) and Cs_2CO_3 (204 mg, 0.63 mmol) in DMF (5 mL) was stirred at room temperature for 30 min. Bromochloromethane (81 mg, 0.63 mmol) was added and the mixture was stirred at 50 °C for an additional 12 h. CH_2Cl_2 (50 mL) was then added and the resulting solution was successively washed with water, brine and dried (Na_2SO_4). After removal of the solvent under vacuum, the crude solid residue was recrystallized from EtOH. Yellow crystals; yield 45 mg (55%). The analytical data of synthetic **1a** matched those reported for the natural product.[3a]

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