A concise first total synthesis of narceine imide

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A concise and efficient total synthesis of alkaloid narceine imide is disclosed. The key steps are based upon the sequential construction of the isoindolinone template followed by metalation and coupling with an isoquinolinium salt. Subsequent E1cb elimination enables the creation of the arylmethylene unit with the concomitant formation of the dimethylaminoethyl chain and ultimate deprotection completes the synthesis of the natural product.

Introduction

Narceine imide **1a** is undoubtedly the most architecturally sophisticated embodiment of the aromatic enelactams that have been extracted from vegetable sources to date, along with fumaramidine **1b**, fumaramine **1c** and fumaridine **1d** (Fig. 1).[1]

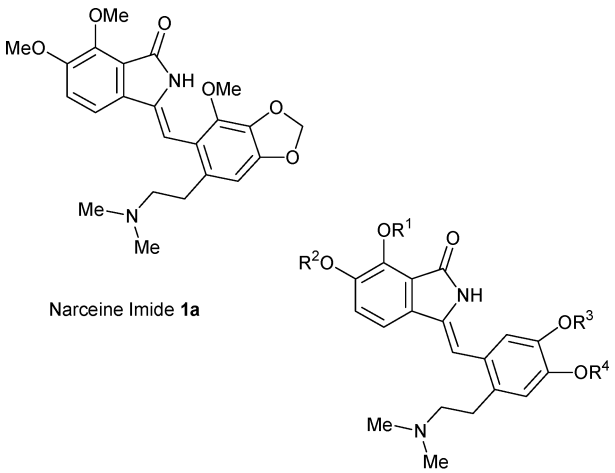

Fig. 1 Aromatic enelactams isolated from vegetable sources.

This secophthalide isoquinoline alkaloid has been isolated from the morphine fraction of poppy capsules from the plant family *Papaver somniferum*.[2] However, its presence in the natural source is not guaranteed and this enelactam is not generally considered to be a true alkaloid but is regarded conceivably as an artefact of the isolation of poppy alkaloid. Despite the fact that compounds **1a–d** incorporate an isoindolinone ring system, which has gained considerable attention due to the profound physiological and chemotherapeutic activities of many of their derivatives,[3] notably the 3-aryl and alkylmethylene derivatives,[4] studies on the pharmacological potential of these enelactamic compounds are rather scanty. However, narceine imide has recently been shown to possess a strong inhibitory action on aldehyde reductase (ALR) and on liver alcohol dehydrogenase (LADH)[5] and also to be a very potent cytotoxic agent in inhibiting P388 murine leukemia cell lines.[6] It has also served as a key intermediate for the elaboration of a variety of biologically active substances.[7] As far as we are aware, the first synthesis of narceine imide **1a** based upon an esterification/annulation sequence applied to narceine **2** (Fig. 2) was incidentally reported a long time ago,[8] but curiously, the report of this hemisynthetic route predated the isolation and structural elucidation of the natural product.[2]

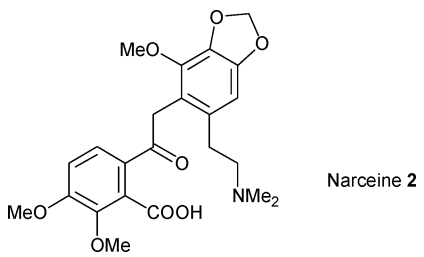

Fig. 2 Precursor in the hemisynthetic route to **1a**.

In the course of our ongoing project dealing with the synthesis and subsequent biological evaluation of a variety of opened and fused arylmethyleneisoindolinone-centred natural products[9] we herein wish to disclose an efficient and tactically new synthetic approach to opium alkaloid narceine imide that relies upon our long-standing experience in the field of isoindolinone chemistry.[10]

Results and discussion

For the elaboration of compound **1a** we opted for the synthetic route depicted in the retrosynthetic analysis (Scheme 1). We assumed that narceine imide **1a**, containing a *Z* configured stilbenoid system fused with a lactam ring, would be obtained by ultimate deprotection of the aromatic enelactam **3** with the exquisite arrangement of diverse and dense functionalities within the compact framework of the target alkaloid. We also conjectured that a Hoffmann elimination process applied to the di-heterocyclic compound **4** would provide the potential for direct access to this protected version of the target **1a** with the concomitant connection of the dialkylaminoalkyl chain to the southern aromatic nucleus of the model. We also reasoned that the requisite precursor **4**

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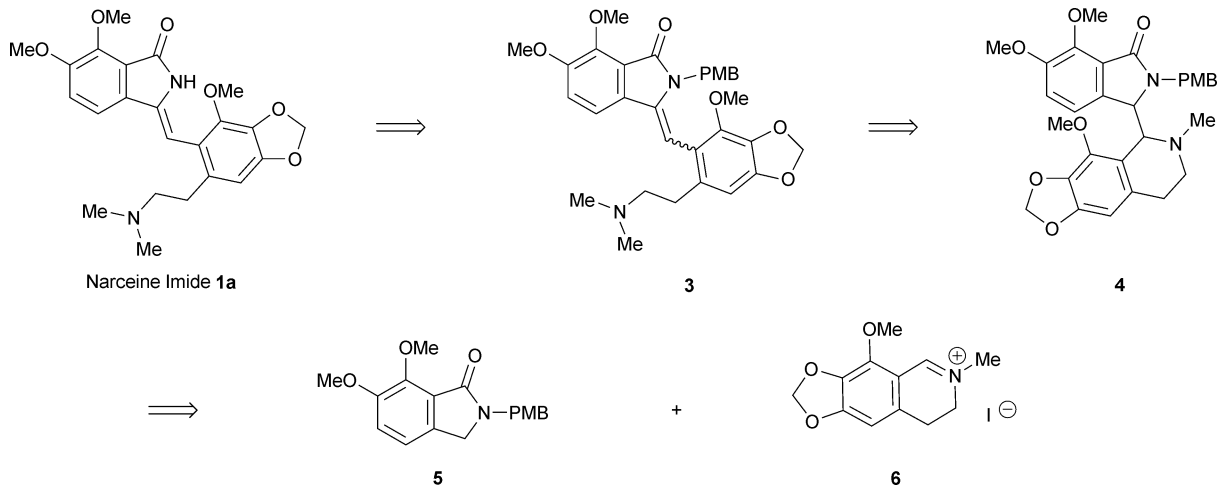


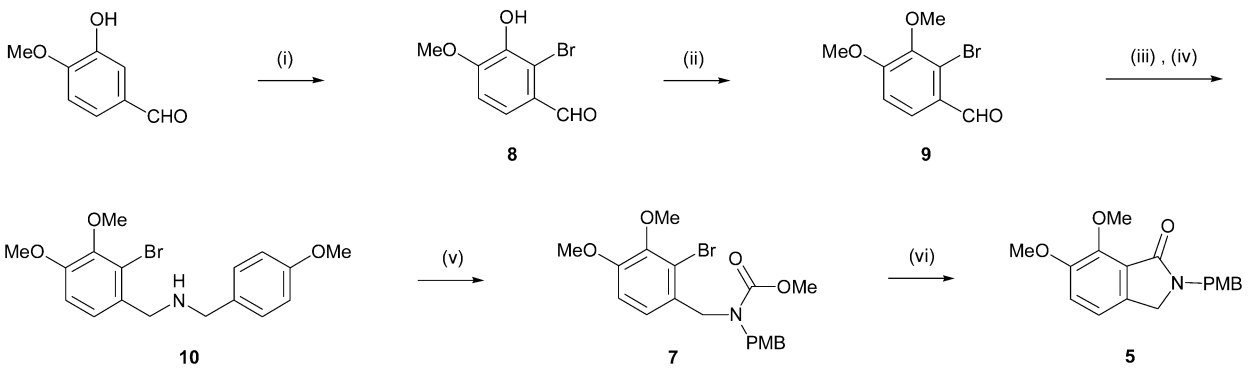
Scheme 1 Retrosynthetic analysis for the synthesis of the narceine imide **1a**.

could conceivably be assembled by sequential basic treatment of the appropriate isoindolinone **5** followed by interception with the suitably substituted isoquinolinium salt **6**. The latter, conceptually new synthetic approach, which might ensure the creation of the C–C bond linking the two different aromatic units, originated from the following premises: (i) Isoindolinones have been successfully metalated at the benzylic position of the hetero-ring system thus allowing the connection of a range of electrophiles at the 3-position of the lactam ring;[11] (ii) isoquinolinium salts are very sensitive to nucleophilic attack,[12] a property that has been skilfully exploited in alkaloid synthesis.[13]

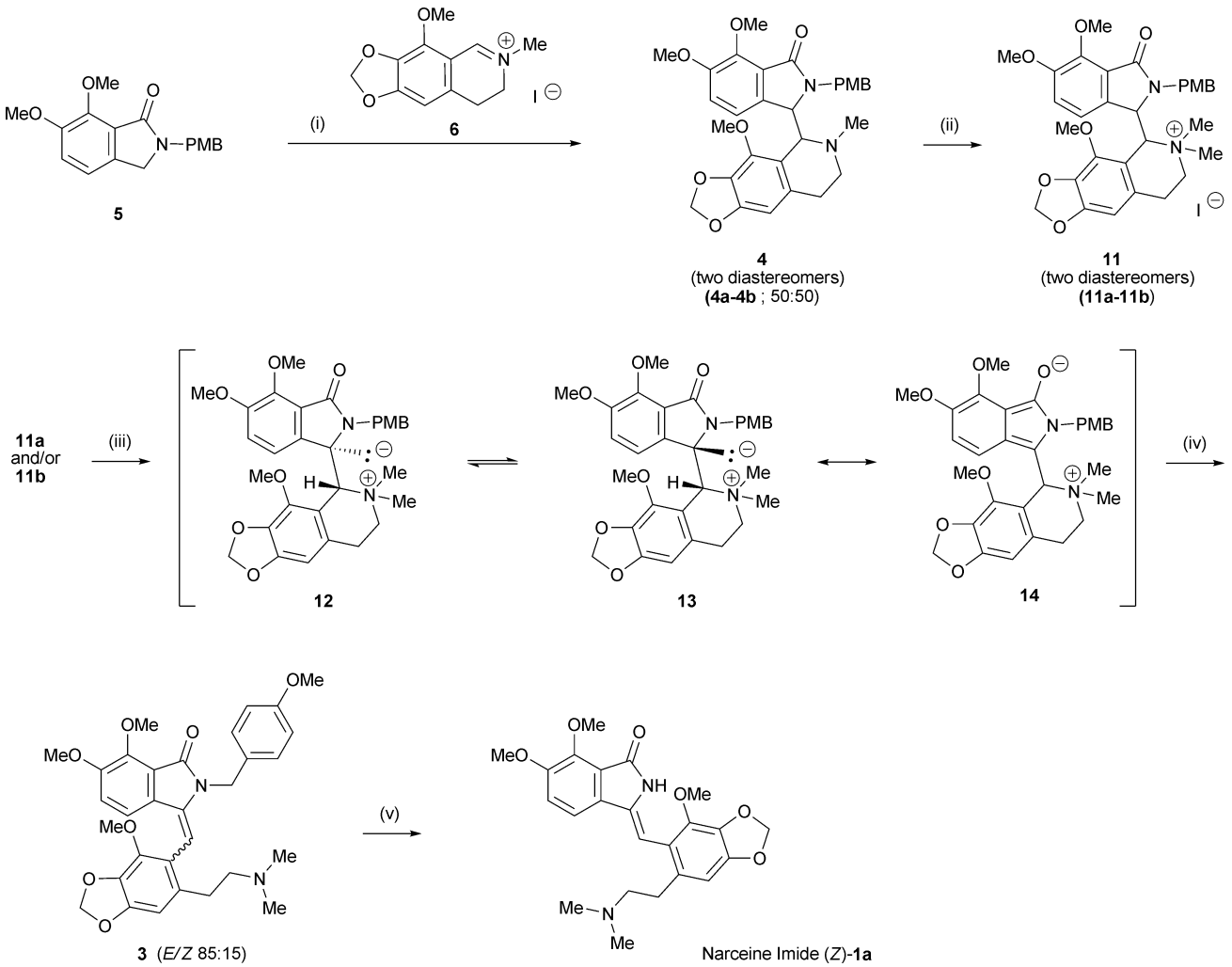
The first facet of the synthesis then started with the elaboration of the unsymmetrically substituted dimethoxyisoindolinone **5**. This was readily accomplished using the Parham cyclization process,[14] *i.e.* aromatic lithiation and subsequent trapping with an internal electrophile, and for this purpose we set out to prepare the bromoarylcarbamate **7** equipped with the appropriate functionalities to secure the creation of the lactam unit. This compound was readily synthesized by the five step sequence depicted in Scheme 2. Sequential bromination and *O*-methylation of isovanillin provided the tetrasubstituted bromobenzaldehyde derivative **9**. The subsequent synthesis of the secondary amine **10** incorporating the nitrogen protecting group PMB (*para*-methoxybenzyl) was achieved by a reductive amination process, and finally treatment of **10** with methyl chloroformate delivered the carbamate **7** almost quantitatively, thereby providing the candidate for the planned Parham cyclization process. Exposure of the bromoarylcarbamate **7** to *n*BuLi at −90 °C ensured the mandatory bromine/lithium interconversion and led to the complete consumption of the starting material and to the isolation of solely the required isoindolinone **5** in a fairly good yield.

The subsequent installation of the pendant isoquinoline unit on the isoindolinone framework was performed as a single one pot reaction (Scheme 3). In this regard, compound **5** was smoothly deprotonated with KHMDS (potassium hexamethyldisilylazide) in THF at −78 °C and subsequently allowed to react with the adequately substituted isoquinolinium iodide **6**.[13] Gratifyingly this operation straightforwardly delivered the requisite adduct **4** which was obtained as an equimolar mixture of separable diastereomers, **4a** and **4b**.

To trigger off the E1cb elimination process liable to give access to enelactam **3**, the di-heterocyclic precursor **4** was initially quaternized with methyl iodide in acetonitrile and the resulting isoquinolinium salt **11** was subsequently exposed to KHMDS at −78 °C followed by slow warming to room temperature. We were pleased to observe that conducting this reaction according to this procedure brought about the intramolecular elimination reaction leading to the expected dimethylaminoethyl chain tethered



Scheme 2 Synthesis of the parent isoindolinone **5**. *Reagents and conditions*: (i) Br_2, AcONa, Fe, AcOH, 5 h, 92%; (ii) MeI, KOH, MeOH, reflux, 16 h, 66%; (iii) 4-$MeOC_6H_4CH_2NH_2$ (PMB-NH_2), toluene, reflux, 3 h; (iv) $NaBH_4$, MeOH, rt, 96% over two steps; (v) ClCOOMe, NaOH, Et_2O–H_2O, 0 °C, 30 min, 89%; (vi) *n*BuLi, −90 °C, 20 min, −90 °C to −40 °C, 30 min, 61%.



Scheme 3 Total synthesis of narceine imide **1a**. *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 15 min, then **6**, −78 °C, 15 min, 65%; (ii) MeI, CH_3CN, 4 h; (iii) KHMDS, THF, −78 °C; (iv) −78 °C to rt, 87% over three steps; (v) TFA, anisole, reflux, 24 h, 77%.

arylmethylene isoindolinone **3** in a fully satisfactory yield. The efficiency of this process was probably imparted by the driving force arising from the high degree of conjugation of the final compound. Compound **3** was obtained as a mixture of *E* and *Z* isomers with the *E* isomer predominating by a large margin (E/Z = 85 : 15), the configuration of the double bond being established from the ^{1}H NMR spectrum with the use of NOE experiments. The *E* stereochemistry of the exocyclic double bond is conceivably ordained by the presence of the bulky PMB group in conjunction with the congested 2,2′-disubstituted benzene nucleus tailed with the long, highly flexible dimethylaminoethyl chain. Interestingly stereochemical considerations regarding the central C–C bond linking the two heterocyclic units in **4** and/or **11** were not crucial for the creation of the pendant arylmethylene unit. Indeed when the reaction sequence portrayed in Scheme 3 was applied to diastereochemically pure adducts **4a** or **4b**, the same geometrical isomer ratio was obtained. It is, therefore, likely that deprotonation of **11a** and/or **11b** leads to the metalated species **12** (and/or **13**), which can adopt the isomeric form **13** (and/or **12**) through the semiquinonic mesomeric form **14** owing to electronic delocalization. Consequently, once formed, **12** or **13** can collapse to (*E*)-stereospecifically enriched **3** through the E1cb mechanism.[15]

With this highly congested benzylideneisoindolinone **3** in hand, we were only a deprotection away from the target natural product. The adoption of the bulky PMB group was rewarded here. Indeed removal of this selected PMB protection is usually achieved by treatment in boiling TFA in the presence of anisole as cation scavenger.[16] These conditions are prone to favour the formation of the thermodynamically more stable stereomer with the mandatory *Z* configuration and the target product (*Z*)-**1a** was obtained exclusively and in an excellent yield by this technique. The constitution of this synthetic aromatic enelactam **1a** was secured by matching the physical and spectral data with those published for the product extracted from vegetable sources.[2]

Conclusions

In conclusion we have completed a new, concise and efficient total synthesis of alkaloid narceine imide. This new route hinges upon the initial construction of the isoindolinone template by the Parham procedure. Subsequent metalation of the lactam unit, interception with an isoquinolinium salt followed by elimination through the E1cb mechanism and ultimate deprotection complete the total synthesis of the target natural product. The advantages

of this synthesis, which lie mainly in the procedural simplicity, high efficiency and mildness of the reaction conditions, provide a strong incentive for the elaboration of a variety of biogenetically related congeners.

Experimental

General methods

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer. Coupling constants (J) are given in Hz and rounded to the nearest 0.1 Hz. Elemental analyses were determined by the CNRS microanalysis centre. The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Hexanes, ethyl acetate (AcOEt), acetone and triethylamine (Et_3N) were used as eluents. Dry glassware was obtained by oven-drying and assembly under N_2. N_2 was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use. Methanol (MeOH) was distilled from magnesium turnings and dichloromethane (CH_2Cl_2) from CaH_2, before storage on 4 Å molecular sieves.

Starting material

The aldehydes **8**[17] and **9**[18] were prepared according to reported procedures.

4-Methoxy-6-methyl-7,8-dihydro-1,3-dioxolo[4,5-*g*]isoquinolin-6-ium iodide (6)

The isoquinolinium iodide **6** was synthesized following a previously described procedure.[13]

^{1}H NMR δ_H (DMSO-*d6*, 300 MHz): 3.09 (2H, m, CH_2), 3.69 (3H, s, NCH_3), 3.86 (2H, m, CH_2), 4.10 (3H, s, OCH_3), 6.20 (2H, s, OCH_2O), 6.84 (1H, s, H_{ar}), 9.02 (1H, s, CH=N); ^{13}C NMR ^{13}C NMR δ_C (DMSO-*d6*, 75 MHz): 25.0 (CH_2), 46.8 (NCH_3), 48.6 (CH_2), 60.4 (OCH_3), 103.5 (OCH_2O), 103.9 (CH_{ar}), 110.8 (C), 134.3 (C), 134.9 (C), 143.6 (C), 157.1 (C), 159.5 (CH=N).

(2-Bromo-3,4-dimethoxybenzyl)-(4-methoxybenzyl)amine (10)

A solution of 2-bromo-3,4-dimethoxybenzaldehyde **9** (2.2 g, 9 mmol) and 4-methoxybenzylamine (1.36 g, 9.9 mmol) in toluene (50 mL) was refluxed for 3 h in a Dean–Stark apparatus. The solvent was removed *in vacuo* to give the crude imine which was used in the next step without further purification. $NaBH_4$ (375 mg, 9.9 mmol) was added portionwise to a solution of the crude imine in MeOH (100 mL). The mixture was then stirred at rt for 30 min. The solution was concentrated *in vacuo* and diluted with Et_2O (100 mL). The solution was washed with water (3 × 30 mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated. The crude solid residue was recrystallized from hexanes–toluene to give the pure amine **10** as a white solid (3.16 g, 96%), mp 73–74 °C.

^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 1.82 (1H, br s, NH), 3.73 (2H, s, CH_2), 3.81 (3H, s, OCH_3), 3.83 (2H, s, CH_2), 3.88 (6H, s, 2 × OCH_3), 6.83–6.90 (3H, m, H_{ar}), 7.10 (1H, d, J = 8.0 Hz, H_{ar}), 7.28 (2H, br s, H_{ar}); ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 52.4 (CH_2), 52.9 (CH_2), 55.3 (CH_3), 56.1 (CH_3), 60.5 (CH_3), 111.0 (CH), 113.8 (2 × CH), 119.7 (C), 125.3 (CH), 129.4 (2 × CH), 132.6 (C), 132.3 (C), 146.5 (C), 152.6 (C), 158.6 (C); CHN Analysis (Found: C, 55.8; H, 5.35; N, 4.0%. $C_{17}H_{20}BrNO_3$ requires C, 55.75; H, 5.5; N, 3.8%).

(2-Bromo-3,4-dimethoxybenzyl)-(4-methoxybenzyl)carbamic acid methyl ester (7)

Methyl chloroformate (1.04 g, 11 mmol) was added dropwise under stirring to a cooled (0 °C) solution of amine **10** (3.65 g, 10 mmol) in Et_2O (50 mL) followed by a solution of NaOH (440 mg, 11 mmol) in water (5 mL). The mixture was stirred at 0 °C for 30 min and the ethereal layer was separated, washed with aq. HCl (4 M, 3 × 30 mL), water (30 mL) and dried (Na_2SO_4). After evaporation of the solvent, the crude oily residue was purified by column chromatography (AcOEt–hexanes, 40 : 60) to deliver the carbamate **7** as a white solid (3.75 g, 89%), mp 83–84 °C.

^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.37–4.51 (m, 4H, 2 × CH_2), 6.83–7.00 (4H, m, H_{ar}), 7.13–7.19 (2H, m, H_{arom}); ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 49.1 (CH_2), 49.5 (CH_2), 53.0 (CH_3), 55.3 (CH_3), 56.1 (CH_3), 60.4 (CH_3), 111.3 (CH), 113.9 (CH), 118.5 (C), 119.1 (C), 122.7 (CH), 124.0 (CH), 128.8 (CH), 129.5 (CH), 146.5 (C), 152.7 (C), 157.2 (C), 157.3 (C), 159.0 (C); CHN Analysis (Found: C, 54.0; H, 5.0; N, 3.0%. $C_{19}H_{22}BrNO_5$ requires C, 53.8; H, 5.2; N, 3.3%).

6,7-Dimethoxy-2-(4-methoxybenzyl)-2,3-dihydroisoindol-1-one (5)

A solution of *n*BuLi (3.6 mL, 1.6 M in hexane, 5.76 mmol) was added dropwise by syringe at −90 °C under N_2 to a solution of carbamate **7** (2.03 g, 4.8 mmol) in dry THF (50 mL). The reaction mixture was stirred at −90 °C for 20 min then allowed to warm to −40 °C over a period of 30 min, followed by addition of saturated aq. NH_4Cl (5 mL). The mixture was diluted with water (20 mL), extracted with Et_2O (3 × 25 ml) and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent *in vacuo* left an oily residue which was purified by flash column chromatography (AcOEt–hexanes, 60 : 40) to furnish the isoindolinone **5** as a yellow solid (915 mg, 61%), mp 72–73 °C.

^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 3.79 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 4.14 (2H, s, CH_2), 4.69 (2H, s, CH_2), 6.86 (2H, d, J = 8.5 Hz, H_{ar}), 7.00 (1H, d, J = 8.2 Hz, H_{ar}), 7.06 (1H, d, J = 8.2 Hz, H_{ar}), 7.25 (2H, d, J = 8.5, H_{ar}); ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 45.7 (CH_2), 48.4 (CH_2), 55.3 (CH_3), 56.8 (CH_3), 62.6 (CH_3), 114.1 (2 × CH), 116.4 (CH), 117.8 (CH), 125.0 (C), 129.2 (C), 129.6 (2 × CH), 134.5 (C), 147.3 (C), 152.3 (C), 159.1 (C), 166.6 (C=O); CHN Analysis (Found: C, 68.75; H, 6.1; N, 4.4%. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5%).

6,7-Dimethoxy-2-(4-methoxybenzyl)-3-(4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-2,3-dihydroisoindol-1-one (4)

A solution of KHMDS (5.4 mL, 0.5 M in toluene, 2.7 mmol) was added dropwise to a stirred solution of isoindolinone **5** (780 mg, 2.5 mmol) in dry THF (50 mL) under N_2 at −78 °C. After stirring for 15 minutes at this temperature, the iminium salt **6** (1.12 g, 3.2 mmol) was added in one go. The solution was maintained at

−78 °C for 15 minutes then allowed to warm to rt. The mixture was quenched with aq. saturated NH_4Cl solution (5 mL), and then extracted with Et_2O (2 × 30 mL), the organic layer was washed with water (15 mL) and with brine, then dried (Na_2SO_4). The solution was concentrated under reduced pressure, then the oily residue was separated by flash column chromatography on silica gel (acetone–hexanes, 50 : 50) to afford the two diastereomers **4a** and **4b** (50 : 50) as white solids. For atom numbering see Fig. 3.

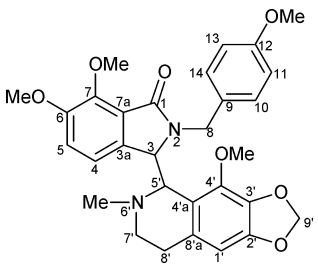


Fig. 3 Atom numbering for compound **4**.

Diastereomer 4a. White solid (440 mg, 33%) mp: thermal transformation around 190 °C. ^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 2.04 (3H, s, NCH_3), 2.44–2.61 [2H, m, (7′)-H + (8′)-H], 2.63–2.77 [1H, m, (8′)-H], 2.97–3.09 [1H, m, (7′)-H], 3.50 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.68 [1H, d, J = 14.7 Hz, (8)-H], 3.80 (3H, s, OCH_3), 4.03 [1H, d, J = 2.5 Hz, (5′-)H], 4.06 (3H, s, OCH_3), 4.52 [1H, d, J = 2.5 Hz, (3)-H], 5.23 [1H, d, J = 14.7 Hz, (8)-H], 5.80 (2H, s, OCH_2O), 6.31 [1H, s, 1H, (1′)-H_{ar}] 6.61 (2H, d, J = 8.6 Hz, H_{ar}), 6.64 (2H, d, J = 8.6 Hz, H_{ar}), 6.78 (1H, d, J = 8.1 Hz, H_{ar}), 6.92 (1H, d, J = 8.1 Hz, H_{ar}); ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 24.6 (8′-CH_2), 43.9 (NCH_3), 44.3 (8-CH_2), 47.8 (7′-CH_2), 55.2 (OCH_3), 56.7 (OCH_3), 58.5 (OCH_3), 61.3 (3- or 5′-CH), 61.4 (3- or 5′-CH), 62.6 (OCH_3), 100.5 (OCH_2O), 102.5 (CH), 113.5 (2 × CH), 115.8 (CH), 117.1 (CH), 119.2 (C), 124.5 (C), 129.3 (2 × CH), 129.6 (C), 129.8 (C), 133.9 (C), 139.5 (C), 140.8 (C), 147.0 (C), 148.2 (C), 152.0 (C), 158.7 (C), 167.6 (C=O); CHN Analysis (Found: C, 67.8; H, 6.0; N, 5.1%. $C_{30}H_{32}N_2O_7$ requires C, 67.7; H, 6.1; N, 5.3%).

Diastereomer 4b. White solid (429 mg, 32%) mp: thermal transformation around 190 °C. ^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 1.86–1.96 [1H, m, (8′)-H], 2.00–2.10 [1H, m, (7′)-H], 2.15–2.25 [1H, m, (7′)-H], 2.30 (3H, s, NCH_3), 2.45–2.60 [1H, m, (8′)-H], 3.67 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.91 [1H, d, J = 14.9 Hz, (8)-H], 4.03 (3H, s, OCH_3), 4.24 [1H, s, (5′-)H], 4.55 [1H, s, (3)-H], 5.40 [1H, d, J = 2.5 Hz, (8)-H], 5.78 [2H, d, J = 8.2 Hz, H_{ar}], 5.81 (2H, s, OCH_2O), 6.23 [1H, s, 1H, (1′)-H_{ar}], 6.68 (2H, d, J = 8.2 Hz, H_{ar}), 6.78 (1H, d, J = 8.4 Hz, H_{ar}), 7.22 (1H, d, J = 8.4 Hz, H_{ar}); ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 23.1 (8′-CH_2), 44.1 (NCH_3), 43.4 (8-CH_2), 46.6 (7′-CH_2), 55.3 (OCH_3), 56.5 (OCH_3), 58.0 (OCH_3), 59.0 (3- or 5′-CH), 60.1 (3- or 5′-CH), 62.6 (OCH_3), 100.5 (OCH_2O), 102.6 (CH), 113.8 (2 × CH), 115.2 (CH), 118.4 (CH), 117.5 (C), 125.3 (C), 129.3 (C), 129.8 (2 × CH), 130.4 (C), 133.8 (C), 137.7 (C), 140.4 (C), 147.0 (C), 148.2 (C), 152.0 (C), 158.9 (C), 166.9 (C=O); CHN Analysis (Found: C, 67.4; H, 6.2; N, 5.2%. $C_{30}H_{32}N_2O_7$ requires C, 67.7; H, 6.1; N, 5.3%).

3-{1-[6-(2-Dimethylaminoethyl)-4-methoxybenzo[1,3]dioxol-5-yl]-methylidene}-6,7-dimethoxy-2-(4-methoxybenzyl)-2,3-dihydroisoindol-1-one (3)

A solution of **4** (530 mg, 1 mmol) in acetonitrile (10 mL) was refluxed with an excess of methyl iodide (0.5 mL, 8 mmol) for 4 h. The solvent was removed under reduced pressure to furnish **11** as a white solid. A solution of KHMDS (2.6 mL, 0.5 M in toluene, 1.3 mmol) was added to a suspension of **11** in dry THF under N_2 at −78 °C. The mixture was allowed to warm to rt and the solution was quenched with water (10 mL) and extracted with Et_2O (3 × 20 mL). The organic layers were washed with water (10 mL), brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the oily residue was separated by flash column chromatography on silica gel (AcOEt–Et_3N, 90 : 10) to afford the two isomers (*E*)-**3** and (*Z*)-**3** as yellow solids.

(*E*)-Isomer. Yellow solid (401 mg, 74%), mp 154–155 °C. ^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 1.98 (6H, s, 2 × NCH_3), 2.06–2.25 (2H, m, CH_2), 2.27–2.41 (1H, m, CH_2), 2.43–2.57 (1H, m, CH_2), 3.73 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.11 (3H, s, OCH_3), 4.89 (1H, d, J = 15.5 Hz, NCH_2Ar), 5.16 (1H, d, J = 15.5 Hz, NCH_2Ar), 5.93 (1H, d, J = 1.3 Hz, OCH_2O), 5.97 (1H, d, J = 1.3 Hz, OCH_2O), 6.00 (1H, s, CH_{vinyl}), 6.51 (1H, s, H_{ar}), 6.55 (1H, d, J = 8.3 Hz, H_{ar}), 6.81–6.88 (3H, m, H_{ar}), 7.28 (2H, d, J = 6.5 Hz, 2H, H_{ar}); ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 31.5 (CH_2), 42.5 (CH_2), 45.1 (2 × NCH_3), 55.2 (OCH_3), 56.5 (OCH_3), 59.7 (OCH_3), 62.4 (OCH_3), 60.1 (CH_2), 101.0 (OCH_2O), 102.7 (CH_{vinyl}), 104.1 (CH), 114.0 (2 × CH), 116.1 (CH), 118.5 (CH), 120.1 (C), 122.1 (C), 128.6 (2 × CH), 129.2 (C), 129.4 (C), 133.8 (C), 135.3 (C), 136.1 (C), 141.4 (C), 146.5 (C), 148.9 (C), 153.3(C), 158.8 (C), 164.9 (C=O). CHN Analysis (Found: C, 68.3; H, 6.15; N, 4.8%. $C_{31}H_{34}N_2O_7$ requires C, 68.1; H, 6.3; N, 5.1%).

(*Z*)-Isomer. Yellow solid (73 mg, 13%), mp 124–125 °C. ^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 2.01 (6H, s, 2 × NCH_3), 2.05–2.25 (3H, m, 3H, CH_2), 2.30–2.47 (1H, m, CH_2), 3.63 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 4.57 (1H, d, J = 15.6 Hz, NCH_2Ar), 4.72 (1H, d, J = 15.6 Hz, NCH_2Ar), 5.84 (1H, d, J = 1.3 Hz, OCH_2O), 5.88 (1H, d, J = 1.3 Hz, OCH_2O), 6.10 (1H, s, CH_{vinyl}), 6.32 (1H, s, H_{ar}), 6.46 (2H, d, J = 8.7 Hz, H_{ar}), 6.54 (2H, d, J = 8.7 Hz, H_{ar}), 7.07 (1H, d, J = 8.3 Hz, H_{arom}), 7.35 (1H, d, J = 8.3 Hz, H_{arom}); ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 31.5 (CH_2), 43.4 (CH_2), 45.3 (2 × NCH_3), 55.2 (OCH_3), 56.8 (OCH_3), 59.1 (OCH_3), 59.7 (CH_2), 62.5 (OCH_3), 99.3 (CH_{vinyl}), 100.8 (OCH_2O), 103.0 (CH), 113.3 (2 × CH), 114.9 (CH), 116.7 (CH), 119.0 (C), 120.3 (C), 127.7 (2 × CH), 129.8 (C), 132.0 (C), 134.0 (C), 134.5 (C), 134.9 (C), 141.5 (C), 145.7 (C), 149.0 (C), 153.0 (C), 158.5 (C), 166.7 (C=O); CHN Analysis (Found: C, 68.2; H, 6.0; N, 4.8%. $C_{31}H_{34}N_2O_7$ requires C, 68.1; H, 6.3; N, 5.1%).

Narceine imide (1a)

A solution of **3** (275 mg, 0.5 mmol) and anisole (540 mg, 5.0 mmol) in trifluoroacetic acid (10 mL) was refluxed under N_2 for 24 h. The reaction mixture was concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (20 mL) and Et_3N (0.5 mL) was added with stirring. Water (3 × 50 mL) was then added, and the separated organic layer was washed with brine, dried ($MgSO_4$) and concentrated to

yield an oily residue. Purification by flash column chromatography (AcOEt–Et_3N, 95 : 5) and recrystallization from EtOH gave **1a** as a yellow solid (163 mg, 77%), mp 149–150 °C (lit.:[2] 151–152 °C).

^1H NMR δ_H ($CDCl_3$, 300 MHz): 2.26 (6H, s, 2 × NCH_3), 2.48 (1H, d, J = 7.2 Hz, CH_2), 2.51 (1H, d, J = 5.8 Hz, CH_2), 2.76 (1H, d, J = 5.8 Hz, CH_2), 2.79 (1H, d, J = 7.2 Hz, CH_2), 3.94 (6H, s, 2 × OCH_3), 4.11 (3H, s, OCH_3), 5.96 (2H, s, OCH_2O), 6.25 (1H, s, CH_{vinyl}), 6.53 (1H, s, CH_{ar}), 7.16 (1H, d, J = 8.3 Hz, H_{ar}), 7.47 (1H, d, J = 8.3 Hz, H_{ar}), 8.37 (1H, br s, NH); ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 32.2 (CH_2), 45.6 (2 × NCH_3), 56.7 (OCH_3), 60.1 (OCH_3), 60.3 (CH_2), 62.5 (OCH_3), 97.9 (CH), 101.2 (OCH_2O), 104.8 (CH), 115.1 (CH), 116.7 (CH), 119.3 (C), 121.4 (C), 132.1 (C), 133.6 (C), 133.7 (C), 135.7 (C), 140.5 (C), 147.0 (C), 148.8 (C), 153.1 (C), 166.6 (C=O).

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