Construction of the Six- and Five-Membered Aza-Heterocyclic Units of the Isoindoloisoquinolone Nucleus by Parham-Type Cyclization Sequences – Total Synthesis of Nuevamine

Anne Moreau,[a] Axel Couture,*[a] Eric Deniau,[a] and Pierre Grandclaudon[a]

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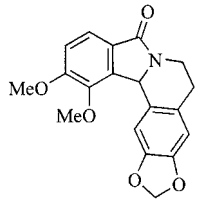
An efficient methodology for the synthesis of isoindolo[1,2-*a*]isoquinolones based on two Parham-type cyclizations allowing the formation of the five- and six-membered nitrogenated rings from carbamate or diacylamine precursors is described. The synthetic potential of this method has been further illustrated by the total synthesis of the alkaloid nuevamine.

Introduction

Nuevamine (**1a**) is the first isoindolo[1,2-*a*]isoquinolinone known to occur in nature and can still be considered the lone representative of this class of isoquinoline alkaloids. Initially, the structure of this natural product which has been isolated from *Berberis darwinii Hook*, gathered in southern Chile, in the vicinity of Cuidad Osorno,[1] was erroneously assigned but later revision led unambiguously to structure **1a** (Figure 1).[2]



Nuevamine (**1a**)

Figure 1. Structure of nuevamine (**1a**).

This alkaloid occupies a rather peculiar place since it is an eminent member of the isoindoloisoquinolone family but all of the synthetic methods developed for the construction of this class of tetracyclic lactams **1** are inadequate for the synthesis of this unique natural product. Several general approaches to the synthesis of isoindolo[1,2-*a*]isoquinolones, which are interesting due to the real and potential biological activities of many of their derivatives[3] have appeared in print. They can be broadly classified into two main categories, which differ in the nature of the carbon–carbon bond formed in the ultimate step. Thus, generation of the carbon–carbon bond (a) has been achieved by an intramolecular amidoarylation reaction involving a transient *N*-acyliminium species obtained by treatment with Lewis acid catalysts of α-hydroxy (X^1 = OH),[4] α-alkoxy (X^1 = OMe)[5] or α-benzotriazolyl (X^1 = Bt)[6] lactamic precursors **2** (retrosynthesis: Scheme 1). Formation of the carbon–carbon bond (a) has also been secured by an anionic cyclization mechanism (Parham cyclization) applied to *N*-[(iodoaryl)ethyl]-imides **3**[7] and by a base-induced aryne-mediated cyclization of a *N*-[(fluoroaryl)ethyl]isoindolinone derivative **4**.[8] The isoindolinone nucleus has also been accessed by formation of carbon–carbon bond (b) through intramolecular Heck cyclization of aromatic enamides **5** performed in the presence of a hydride source which favors the regiocontrolled formation of the five-membered product.[9] Other procedures involving the cyclization of β-phenylethylaminophthalide[10] or the palladium-catalyzed carbonylation processes[11] have been used occasionally for the assembling of the isoindoloisoquinolinone framework. However, most of these methods are rather limited in scope and have been claimed to give access only to the isoindoloisoquinoline skeleton of nuevamine-type alkaloids.

Thus, the α-substituted precursors **2** are generally obtained from the corresponding imides (X^1 = O) but the lack of regioselectivity of this chemical transformation requires the absolute necessity of having bare models or symmetrically substituted isoindolinone parent compounds.[4–6] The Parham cyclization process is also fraught with difficulties associated with the regioselectivity of the aromatic metallation/cyclization sequence applied to unsymmetrically substituted imides **3**.[7] At last, all models structurally related to **1** which have been elaborated by intramolecular Heck cyclizations are invariably alkylated at the C-12b position

[a] UMR 8009 "Chimie Organique et Macromoléculaire", Laboratoire de Chimie Organique Physique, Bâtiment C3(2), Université des Sciences et Technologies de Lille 1,
59655 Villeneuve d'Ascq Cedex, France
Fax: +33-3-20336309
E-mail: axel.couture@univ-lille1.fr

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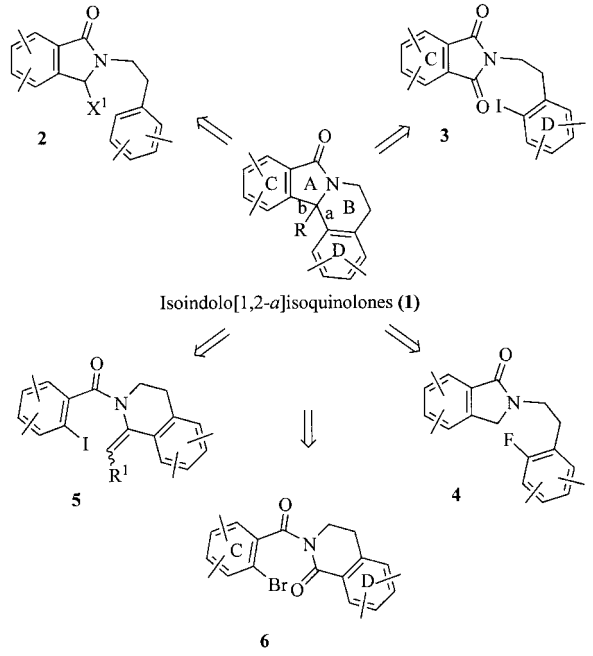


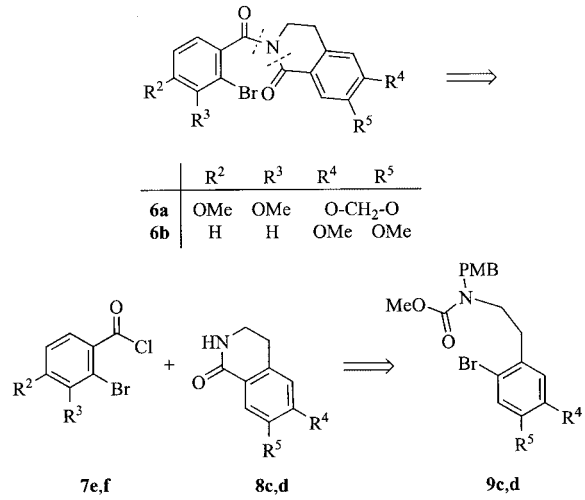
Scheme 1. Retrosynthetic disconnections of the (a) and (b) carbon–carbon bonds of the isoindoloisoquinolinone framework.

(**1**, R ≠ H).[9] Consequently, all these structural requirements and synthetic limitations preclude the synthesis of the poly-, differentially and unsymmetrically substituted alkaloid nuevamine (**1a**), so that the elegant synthetic method reported by Castedo et al.[2] from pseudomeconine and the synthetic approach recently developed in our group[8] are the sole total syntheses to date of this natural product.

Results and Discussion

We wish to delineate in this paper a concise and strategically new synthetic approach to isoindoloisoquinolones illustrated by the total synthesis of the alkaloid nuevamine. Our strategy relies on two Parham cyclization reactions for the construction of the isoquinoline unit, i.e. ring B in **1**, and of the lactam ring A embedded in the alkaloid framework in the sequel. Our synthetic plan then enriches the repertoire of the few synthetic methods relying on carbon–carbon bond formation of (b) in the ultimate step.[9] The protocol developed by Parham hinges upon aromatic lithiation usually carried out by lithium/halogen exchange, and subsequent reaction with an internal electrophile, thus allowing the construction of carbo- and heterocyclic systems.[12] We then anticipated that the assemblage of the fused isoindolinones could be obtained by using this annulation protocol and that problems of regioselectivity previously encountered with imides **3** for the creation of the lactam nucleus A in **1** could be circumvented by the tailored generation of the aryllithium species on the environmentally different aromatic unit, i.e. C in **6** instead of D in **3** (Scheme 1).

To test the feasibility of this tactically different approach we set out to prepare the two representative models **6a**,**b**. We assumed that the assemblage of these (haloaryl)isoquinolones would be achieved by acylation with **7e**,**f** of the appropriate isoquinolones **8c**,**d** which could be in turn obtained by anionic cyclization of the *N*-[(bromoaryl)ethyl]-carbamates **9c**,**d** (retrosynthesis: Scheme 2).

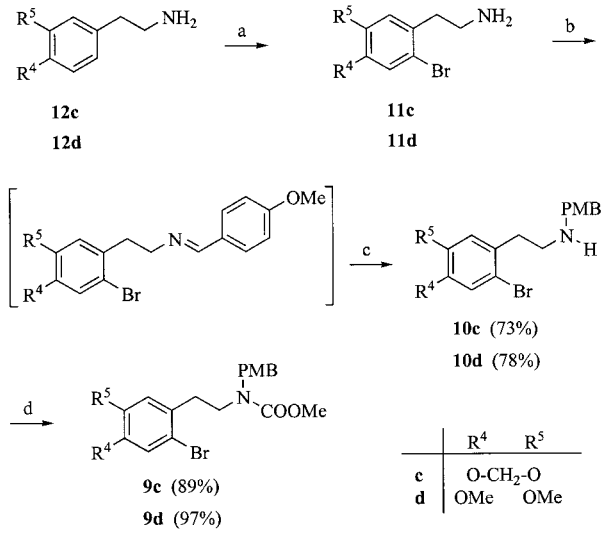


Scheme 2. Retrosynthetic disconnection of models **6a**,**b** to give the carbamates **9c**,**d**.

The first facet of the synthesis was then the formation of the halogenated (arylalkyl)amines **10c**,**d**. These compounds were easily synthesized as depicted in Scheme 3 by a reductive amination process involving the *N*-[2-(bromoaryl) ethyl]amines **11c**,**d** and 4-methoxybenzaldehyde. These brominated aromatic amines were initially obtained by bromination of the commercially available *N*-[2-(3,4-dimethoxyphenyl)ethyl]amine (**12d**) and of the methylenedioxy derivative **12c**. Subsequent treatment of amines **10c**,**d** with methyl chloroformate delivered almost quantitatively the carbamates **9c**,**d** equipped with the appropriate functionalities liable to secure the generation of the isoquinoline unit by an anionic cyclization mechanism. The literature gave sound support for the feasibility of such an approach.[4d,13]

Exposure of compounds **9c**,**d** to 1.1 equiv. of *t*BuLi at –100 °C in THF ensured bromine/lithium exchange and subsequent intramolecular aromatic acylation with the carbamate acting as the internal electrophile then provided the annulated compounds **13c**,**d** with good yields (Scheme 4). Removal of the *N*-(4-methoxybenzyl) protection by treatment of **13c**,**d** with trifluoroacetic acid (TFA) in the presence of the cation scavenger anisole proceeded uneventfully to afford the *N*-unsubstituted models **8c** and **8d**. The synthesis of the parent compounds **6a**,**b** – candidates for the ultimate annulation step – was readily achieved by coupling the appropriate carboxylic chlorides **7e**,**f** with the anion of the secondary aromatic amides **8c**,**d**. This operation delivered the *N*-[(haloaryl)carbonyl]-amides **6a**,**b** required for the anionic cyclization in fairly good yields (Scheme 4).

Applications of the Parham cyclization protocol for the formation of five-membered lactams are quite scanty and to the best of our knowledge only a few examples dealing with the synthesis of dibenzoindolones,[14] chromeno-[13a]



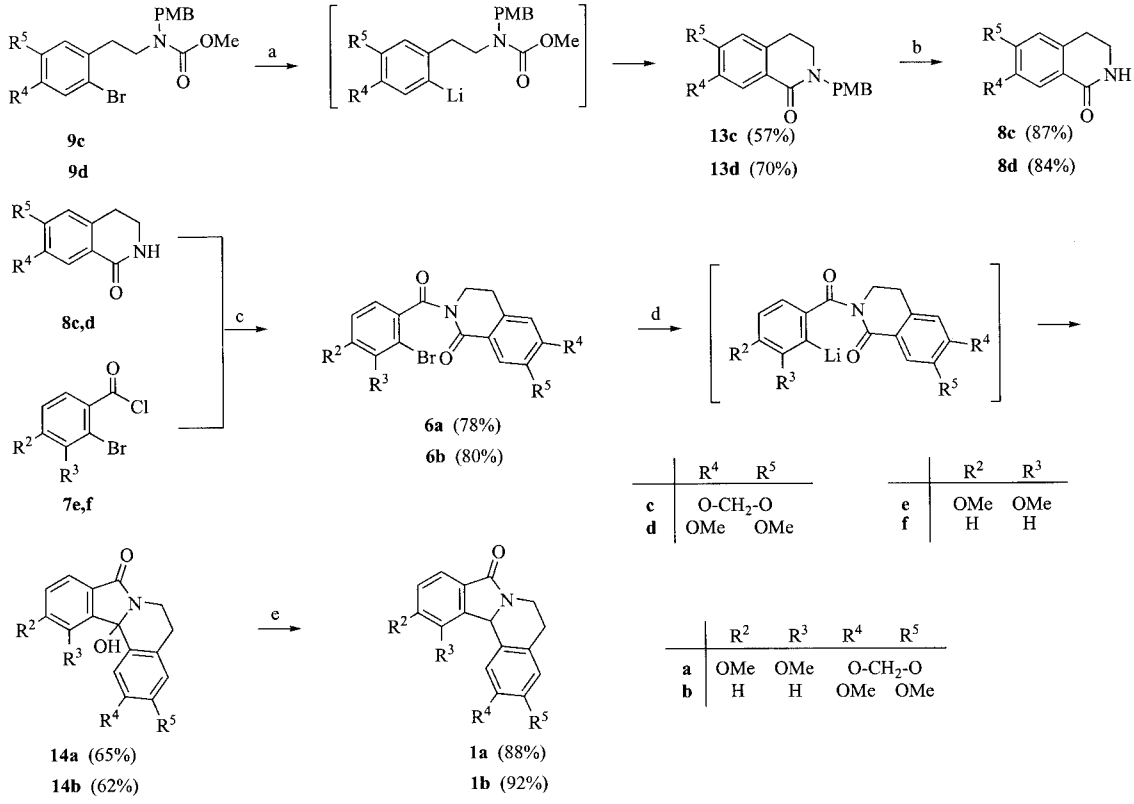
Scheme 3. Synthesis of carbamates **9c**,**d**: a) Br_2, AcOH; b) 4-Me-OC_6H_4CHO, toluene, reflux, 3 h; c) $NaBH_4$, MeOH, 20 °C, 2 h; d) ClCOOMe, Et_3N, CH_2Cl_2, 0 °C to 20 °C, 12 h. PMB = *p*-methoxybenzyl.

and (arylmethylene)isoindolinones[15] have appeared in print. Furthermore, this concept has been rarely applied to the diacylamine functionality as the internal electrophile.[16] The parent compounds **6a**,**b** were then tested as substrates for the Parham cyclization and we were pleased to observe that treatment of **6a**,**b** with *t*BuLi at –100 °C spared the imide functionality and that the initially formed aromatic anion was trapped intramolecularly by the isoquinolone carbonyl group to afford the 12b-hydroxyisoindolo[1,2-*a*]-isoquinolones **14a**,**b**.

These N,O-hemiaminals which can be regarded as immediate precursors of *N*-acyliminium species have been elegantly implicated in the formation of C12b-substituted isoindoloisoquinolone derivatives.[7] Reduction of the hydroxy group of hydroxy-lactams **14a**,**b** was readily achieved with triethylsilyl hydride (Et_3SiH)/TFA at 0 °C to afford the target natural product nuevamine (**1a**) and the structurally related congener **1b** in almost quantitative yield (Scheme 4).

Conclusions

In summary, the versatility and the regiospecificity of the synthetic protocol disclosed in this paper clearly emphasize the central position of the Parham cyclization reaction in the arsenal of annulation techniques leading to heterocyclic ring systems. Sequential application of this concept with carbamate and diacylamine precursors has allowed the construction of the isoindolinone template and of the isoquinoline nucleus embedded in the isoindolo[1,2-*a*]isoquinolone framework. The synthetic potential of this method has been further demonstrated by the third known total synthesis of the alkaloid nuevamine.



Scheme 4. Synthesis of nuevamine (**1a**) and **1b**: a) *t*BuLi, THF, –100 °C, 30 min; b) TFA, anisole, reflux, 24 h; c) **8c** or **8d**, THF, *n*BuLi, –78 °C to 20 °C, 30 min, then –78 °C, **7e** or **7f** in THF, –78 °C to 20 °C, 2 h; d) *t*BuLi, THF, –100 °C, 30 min; e) Et_3SiH (2 equiv.), TFA (1 equiv.), CH_2Cl_2, 20 °C, 2 h. PMB = *p*-methoxybenzyl.

Experimental Section

General: Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled from sodium benzophenone ketyl under Ar before use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N) and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly was done under Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (230–400 mesh ASTM) was used. The melting points were performed with a Reichert–Thermopan apparatus and are not corrected. NMR: Bruker AM 300 (300 MHz and 75 MHz, for ^1H and ^{13}C); for ^1H and ^{13}C NMR, $CDCl_3$ was used as solvent and TMS as internal standard. The CNRS microanalysis centre performed the microanalyses. *N*-[(Bromoaryl)ethyl]amine derivatives **11c**[17] and **11d**[18] were prepared according to literature methods. The bromobenzoyl chloride **7e** was obtained from 2-bromo-3,4-dimethoxybenzoic acid synthesized according to a reported procedure.[19]

General Procedure for the Synthesis of the Brominated (Arylalkyl)-amine Derivatives 10c,d: A solution of *para*-anisaldehyde (18 mmol, 2.45 g) and amine **11c** or **11d** (18 mmol) in toluene (60 mL) was refluxed in a Dean–Starck apparatus for 3 h. After removal of toluene in vacuo, the *N*-[2-(bromoaryl)ethyl]-*N*-(4-methoxybenzylidene)amine derivative was used directly in the next step without further purification. $NaBH_4$ (35 mmol, 1.33 g) was added portionwise to a solution of the previously obtained Schiff base in MeOH (70 mL) at room temperature. The mixture was stirred at room temperature for 2 h and then saturated aqueous NH_4Cl solution (30 mL) was added. After stirring for 30 min, the solvent was removed under vacuo. The crude mixture was dissolved in CH_2Cl_2 (50 mL), washed with water (20 mL) and brine (30 mL). The organic solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude oily amines **10c**,**d** were purified by flash column chromatography with ethyl acetate (AcOEt)/hexanes/Et_3N (80:10:10) as eluent.

***N*-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-*N*-(4-methoxybenzyl)-amine (10c):** 4.68 g (73%), yellow-orange oil. ^1H NMR: δ = 1.45 (br. s, 1 H, NH), 2.84 (s, 4 H, CH_2), 3.75 (s, 2 H, CH_2), 3.79 (s, 3 H, CH_3), 5.93 (s, 2 H, OCH_2O), 6.72 (s, 1 H, aromatic H), 6.85 (d, J = 8.3 Hz, 2 H, aromatic H), 6.98 (s, 1 H, aromatic H), 7.23 (d, J = 8.3 Hz, 2 H, aromatic H) ppm. ^{13}C NMR: δ = 36.5, 49.0, 53.2, 55.3, 101.6, 110.2, 112.7, 113.8, 114.5, 129.3, 132.4, 146.8, 147.3, 158.6 ppm. $C_{17}H_{18}BrNO_3$ (364.2): calcd. C 56.06, H 4.98, N 3.85; found C 56.35, H 4.85, N 4.09.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-*N*-(4-methoxybenzyl)-amine (10d):** 5.22 g (78%), yellow-orange oil. ^1H NMR: δ = 1.41 (br. s, 1 H, NH), 2.87 (s, 4 H, CH_2), 3.76 (s, 2 H, CH_2), 3.78 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 6.73 (s, 1 H, aromatic H), 6.84 (d, J = 8.7 Hz, 2 H, aromatic H), 6.99 (s, 1 H, aromatic H), 7.22 (d, J = 8.7 Hz, 2 H, aromatic H) ppm. ^{13}C NMR: δ = 36.3, 49.1, 53.2, 55.3, 56.0, 56.1, 113.3, 113.8, 114.2, 115.6, 129.2, 131.4, 132.5, 148.0, 148.3, 158.6 ppm. $C_{18}H_{22}BrNO_3$ (380.3): calcd. C 56.85, H 5.83, N 3.68; found C 56.65, H 6.09, N 3.89.

General Procedure for the Synthesis of the Methyl Carbamates 9c,d: Methyl chloroformate (2.39 g, 25 mmol) was added dropwise at 0 °C to a stirred solution of the secondary amine **10c**,**d** (17 mmol) and Et_3N (2.43 g, 34 mmol) in CH_2Cl_2 (50 mL). The mixture was allowed to warm to room temperature and then stirred for an additional 3 h. The mixture was washed with water (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo and left an oily residue which was purified by flash column chromatography on silica gel with AcOEt/hexanes (40:60) as eluent.

Methyl [2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl](4-methoxybenzyl)-carbamate (9c): 6.39 g (89%), white crystals, m.p. 59–60 °C. ^1H NMR (mixture of two rotamers, 40:60): δ = 2.79–2.86 (m, 2 H, CH_2), 3.26–3.38 (m, 2 H, NCH_2), 3.73 (br. s, 3 H, OCH_3), 3.77 (s, 3 H, CH_3), 4.31 and 4.35 (2 × s, together 2 H, NCH_2Ar), 5.92 (s, 2 H, OCH_2O), 6.58 and 6.69 (2 × s, together 1 H, aromatic H), 6.83 (d, J = 8.3 Hz, 2 H, aromatic H), 6.95 (s, 1 H, aromatic H), 7.11–7.21 (m, 2 H, aromatic H) ppm. ^{13}C NMR (mixture of two rotamers): δ = 34.4 and 35.0, 46.0 and 47.0, 50.2 and 50.4, 52.7, 55.2, 101.6, 110.45 and 110.5, 112.7, 113.9, 114.4, 128.8 and 129.4, 129.9, 131.3, 147.0, 147.4, 156.7 and 157.2, 159.0 ppm. $C_{19}H_{20}BrNO_5$ (422.3): calcd. C 54.04, H 4.77, N 3.32; found C 54.25, H 4.49, N 3.19.

Methyl [2-(2-Bromo-4,5-dimethoxyphenyl)ethyl](4-methoxybenzyl)-carbamate (9d): 7.23 g (97%), oil. ^1H NMR (mixture of two rotamers, 45:55): δ = 2.81–2.88 (m, 2 H, CH_2), 3.32–3.37 (m, 2 H, NCH_2), 3.74 (br. s, 3 H, OCH_3), 3.75 (s, 3 H, CH_3), 3.81 (s, 6 H, 2 × CH_3), 4.29 and 4.33 (2 × br. s, together 2 H, NCH_2Ar), 6.55 and 6.70 (2 × br. s, together 1 H, aromatic H), 6.82 (d, J = 8.6 Hz, 2 H, aromatic H), 6.95 (s, 1 H, aromatic H), 7.10–7.19 (m, 2 H, aromatic H) ppm. ^{13}C NMR (mixture of two rotamers): δ = 34.0 and 34.8, 46.1 and 46.9, 50.1 and 50.3, 52.7, 55.2, 56.0, 56.1, 113.5, 113.9, 114.1, 115.5, 128.8 and 129.5, 129.9, 130.3, 148.2, 148.4, 156.7 and 157.0, 159.0 ppm. $C_{20}H_{24}BrNO_5$ (438.3): calcd. C 54.81, H 5.52, N 3.20; found C 55.12, H 5.75, N 3.01.

General Procedure for the Synthesis of the Protected Dihydroisoquinolones 13c,d: A solution of *t*BuLi (2.5 mL, 1.7 M in pentane, 4.25 mmol, 1.1 equiv.) was added dropwise by syringe at –100 °C under Ar to a solution of carbamate **9c**,**d** (3.86 mmol) in dry THF (50 mL). The reaction mixture was allowed to warm to 0 °C over a period of 30 min followed by addition of saturated aqueous NH_4Cl (5 mL). The mixture was diluted with water (30 mL), extracted with Et_2O (2 × 25 mL) and the combined organic layers were dried (Na_2SO_4). Evaporation of solvent in vacuo left a solid residue which was purified by flash column chromatography with AcOEt/hexanes (50:50) as eluent. Dihydroisoquinolones **13c**,**d** were finally purified by recrystallization from hexane/toluene.

6-(4-Methoxybenzyl)-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (13c): 0.68 g (57%), white crystals, m.p. 118–119 °C. ^1H NMR: δ = 2.75 (t, J = 6.6 Hz, 2 H, CH_2), 3.36 (t, J = 6.6 Hz, 2 H, NCH_2), 3.73 (s, 3 H, OCH_3), 4.64 (s, 2 H, NCH_2Ar), 5.92 (s, 2 H, OCH_2O), 6.52 (s, 1 H, aromatic H), 6.81 (d, J = 8.5 Hz, 2 H, aromatic H), 7.21 (d, J = 8.5 Hz, 2 H, aromatic H), 7.54 (s, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 28.1, 45.2, 49.7, 55.2, 101.4, 106.8, 108.3, 114.0, 123.5, 129.4, 129.6, 133.6, 146.8, 150.3, 159.0, 164.1 ppm. $C_{18}H_{17}NO_4$ (311.3): calcd. C 69.44, H 5.50, N 4.50; found C 69.22, H 5.69, N 4.41.

6,7-Dimethoxy-2-(4-methoxybenzyl)-3,4-dihydro-2*H*-isoquinolin-1-one (13d): 0.88 g (70%), white crystals, m.p. 86–87 °C. ^1H NMR: δ = 2.80 (t, J = 6.7 Hz, 2 H, CH_2), 3.40 (t, J = 6.7 Hz, 2 H, NCH_2), 3.74 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.66 (s, 2 H, NCH_2Ar), 6.57 (s, 1 H, aromatic H), 6.81 (d, J = 8.5 Hz, 2 H, aromatic H), 7.22 (d, J = 8.5 Hz, 2 H, aromatic H), 7.62 (s, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 27.7, 45.4, 49.8, 55.2, 56.0, 56.05, 109.3, 110.6, 113.9, 122.0, 129.4, 129.7, 131.7, 147.9, 151.8, 158.9, 164.5 ppm. $C_{19}H_{21}NO_4$ (311.3): calcd. C 69.71, H 6.47, N 4.50; found C 69.84, H 6.59, N 4.39.

General Procedure for the Synthesis of the Dihydroisoquinolones 8c,d: A solution of **13c**,**d** (1.73 mmol) in a mixture of anisole (2 mL) and TFA (1.5 mL) was heated under reflux under Ar for 24 h. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (20 mL). Et_3N (0.5 mL) was then added with stirring.

After addition of water (10 mL), the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated under vacuum to yield **8c**,**d** as a white solid residue which was finally recrystallized from hexane/toluene. **8c**: 288 mg (87%), white crystals, m.p. 183–184 °C (ref.[20] 185 °C); **8d**: 301 mg (84%), white crystals, m.p. 174–175 °C (ref.[21] 175 °C).

General Procedure for the Synthesis of the *N*-Acyldihydroisoquinolones 6a,b: A solution of dihydroisoquinolone **8c**,**d** (2.9 mmol) in THF (40 mL) was added to a solution of *n*BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) at –78 °C under Ar. The solution was then allowed to warm to room temperature over a period of 30 min and then recooled to –78 °C. A solution of acyl chloride **7e**,**f** (2.9 mmol) in dry THF (5 mL) wad added and the mixture was stirred at –78 °C for 10 min and then at room temperature for 2 h. Aqueous saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with AcOEt (2×25 mL). The organic layers were dried ($MgSO_4$) and concentrated under vacuum. The white solid residue was purified by flash column chromatography with acetone/hexanes (40:60) as eluent. *N*-Acyldihydroisoquinolones **6a**,**b** were finally purified by recrystallization from hexane/toluene.

6-(2-Bromo-3,4-dimethoxybenzoyl)-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (6a): 0.98 g (78%), white crystals, m.p. 149–150 °C. ^{1}H NMR: δ = 3.05 (t, J = 6.0 Hz, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.20 (t, J = 6.0 Hz, 2 H, NCH_2), 6.00 (s, 2 H, OCH_2O), 6.68 (s, 1 H, aromatic H), 6.92 (d, J = 8.5 Hz, 1 H, aromatic H), 7.11 (d, J = 8.5 Hz, 1 H, aromatic H), 7.42 (s, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 28.3, 43.2, 56.0, 60.6, 101.9, 107.2, 108.8, 111.2, 114.6, 122.1, 123.7, 132.8, 137.0, 146.3, 147.4, 152.3, 154.4, 164.0, 170.4 ppm. $C_{19}H_{16}BrNO_6$ (434.2): calcd. C 52.55, H 3.71, N 3.23; found C 52.33, H 3.79, N 3.36.

2-(2-Bromobenzoyl)-6,7-dimethoxy-3,4-dihydro-2*H*-isoquinolin-1-one (6b): 0.905 g (80%), white crystals, m.p. 148–179 °C. ^{1}H NMR: δ = 3.08 (t, J = 6.2 Hz, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.27 (t, J = 6.2 Hz, 2 H, NCH_2), 6.70 (s, 1 H, aromatic H), 7.23–7.29 (m, 1 H, aromatic H), 7.32–7.41 (m, 2 H, aromatic H), 7.49 (s, 1 H, aromatic H), 7.53 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 27.8, 43.0, 56.0, 56.2, 109.4, 111.1, 117.9, 120.3, 127.4, 127.8, 130.4, 132.5, 135.0, 140.0, 148.4, 153.8, 164.4, 170.6 ppm. $C_{18}H_{16}BrNO_4$ (390.2): calcd. C 55.40, H 4.13, N 3.59; found C 55.49, H 3.89, N 3.46.

General Procedure for the Synthesis of the Hydroxyisoindolo[1,2-*a*]isoquinolone Derivatives 14a,b: A solution of *t*BuLi (1.0 mL, 1.7 M in pentane, 1.69 mmol, 1.1 equiv.) was added dropwise by syringe at –100 °C under Ar to a solution of the *N*-acyl-lactames **6a**,**b** (1.55 mmol) in dry THF (30 mL). The reaction mixture was allowed to warm to room temperature over a period of 30 min followed by addition of saturated aqueous NH_4Cl (5 mL). The mixture was diluted with water (30 mL), extracted with Et_2O (2×25 mL) and the combined organic layers were dried (Na_2SO_4). Evaporation of solvent in vacuo left an oily residue which was purified by flash column chromatography with acetone/hexanes (60:40) as eluent. Compounds **14a**,**b** were finally purified by recrystallization from hexane/toluene.

12b-Hydroxy-5,12b-dihydro-6*H*-11,12-dimethoxy-1,3-dioxolo[4,5-*g*]-isoindolo[1,2-*a*]isoquinolin-8-one (14a): 358 mg (65%), white crystals, m.p. 192–193 °C. ^{1}H NMR: δ = 2.69–2.75 (m, 1 H, CH_2), 2.82–2.93 (m, 1 H, CH_2), 3.30–3.40 (m, 1 H, NCH_2), 3.95 (s, 3 H, OCH_3), 3.97–4.06 (m, 1 H, NCH_2), 4.09 (s, 3 H, OCH_3), 5.85 (s, 1 H, OCH_2O), 5.90 (s, 1 H, OCH_2O), 6.53 (s, 1 H, aromatic H), 7.00 (d, J = 8.2 Hz, 1 H, aromatic H), 7.41 (d, J = 8.2 Hz, 1 H, aromatic H), 8.03 (s, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 29.0, 34.9, 56.4, 61.7, 88.1, 101.1, 108.4, 109.0, 113.5, 119.8, 124.3, 128.8, 129.9, 139.9, 144.6, 146.5, 147.7, 157.1, 166.6 ppm. $C_{19}H_{17}NO_6$ (355.3): calcd. C 64.22, H 4.82, N 3.94; found C 63.98, H 5.01, N 4.17.

12b-Hydroxy-2,3-dimethoxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (14b): 299 mg (62%), white crystals, m.p. 159–160 °C (ref.[4d] 157–159 °C).

General Procedure for the Synthesis of the Target Products 1a,b: TFA (114 mg, 1.0 mmol) was added to a stirred solution of compounds **14a**,**b** (1.0 mmol) in dry CH_2Cl_2 (20 mL), followed by the addition of triethylsilyl hydride (233 mg, 2.0 mmol). After stirring at room temperature for 2 h, aqueous saturated $NaHCO_3$ solution (10 mL) was added and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 (2×15 mL). The combined organic layers were washed with brine (2×10 mL) and dried ($Mg SO_4$). Evaporation of the solvent under vacuum afforded a white solid which was recrystallized from hexane/toluene. The analytical data of the synthesized nuevamine (**1a**, 299 mg, 88%) match those reported for the natural product[1,2] and the data of 2,3-dimethoxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (**1b**, 272 mg, 92%) match those of the previously synthesized product.[11]

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