Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 6615–6619

TETRAHEDRON

First total synthesis of fumaridine

Véronique Rys, Axel Couture,* Eric Deniau and Pierre Grandclaudon

Laboratoire de Chimie Organique Physique, UMR 8009 Chimie Organique et Macromoléculaire, Université des Sciences et Technologies de Lille, Bâtiment C3(2), 59655 Villeneuve d'Ascq Cédex, France

Received 6 March 2003; revised 12 May 2003; accepted 24 June 2003

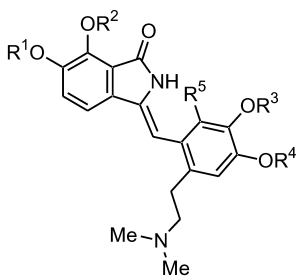
Abstract—The first total synthesis of the alkaloid fumaridine **1a** is reported. The key step is the assemblage of the arylmethylene isoindolinone **2a** (*E*) by Horner reaction between the phosphorylated isoindolinone **3a** and the suitably substituted benzaldehyde **4**. *N*-Lactam deprotection and concomitant *E*→*Z* isomerization complete the synthesis of the title compound.

1. Introduction

Fumaridine **1a** is one of the four secophthalideisoquinoline ene lactams known to date along with fumaramine **1b**, fumaramidine **1c** and narceine imide **1d** (Fig. 1).

Their occurrence is limited to the plant families *Fumariaceae*[1] and *Papaveraceae* and in particular fumaridine (hydrastinimide) has been isolated from *Fumaria densiflora*,[2] *schleicheri*,[3] *vaillanti*[4] and *parviflora*[5] plants and more recently from the stem bark of *Dactylicapnos torulosa*.[6]

These ene lactams are not generally considered to be true alkaloids but are regarded conceivably as artifacts formed during their basic extraction since their biogenetic precursors have been reported to be present in all the previously quoted *Fumaria* species.[7] All these alkaloids share the same structural feature and can be regarded in one sense as having a (*Z*)-configured stilbenoid double bond embedded in a phthalimidine skeleton. Curiously, structural assignments of fumaridine have been a subject of controversy but it has been unambiguously demonstrated that its chemical behavior and structural requirement are only compatible with structure **1a**.[8] Paradoxically, despite the fact that these structures incorporate an isoindolinone ring system, which is interesting due to the real and promising biological properties of many of their derivatives[9] notably the 3-aryl- and alkylmethylene analogues,[10] studies on their pharmacological potential, with the exception of their effects on the cardiovascular system,[11] are scanty.



1a	Fumaridine	$R^1 = R^2 = Me$; $R^3,R^4 = -CH_2-$; $R^5 = H$
1b	Fumaramine	$R^1,R^2 = R^3,R^4 = -CH_2-$; $R^5 = H$
1c	Fumaramidine	$R^1,R^2 = -CH_2-$; $R^3 = R^4 = Me$; $R^5 = H$
1d	Narceine imide	$R^1 = R^2 = Me$; $R^3,R^4 = -CH_2-$; $R^5 = OMe$

Figure 1.

2. Results and discussion

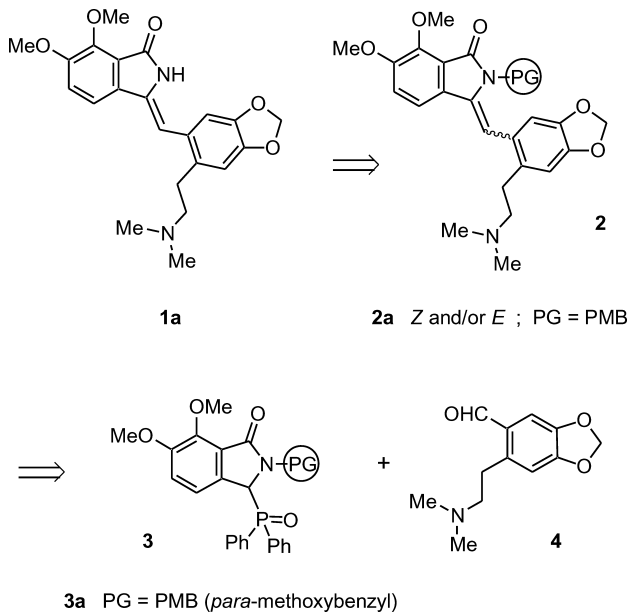
In the course of our ongoing project dealing with the synthesis and subsequent biological evaluation of a variety of compounds comprising an arylmethylene isoindolinone unit either in open systems[12] or embedded in fused models, e.g. aristolactams,[13] we became recently interested in the synthesis of these secophthalideisoquinoline ene lactams.

In this study we were mainly concerned with the exemplary representative fumaridine **1a** whose elaboration requires taking up a number of synthetic challenges namely (i) the construction of an unsymmetrically disubstituted isoindolinone ring system, (ii) the connection of a pendant arylmethylene unit with the mandatory *Z* geometry, (iii) the presence of an unsubstituted nitrogen lactam in a highly conjugated system which imposes a supplementary protection-deprotection sequence, a precedented issue in this series,[14] and (iv) the presence of diverse and dense

Keywords: *N*-acyliminium; alkaloids; ene lactams; Horner reaction; isoindolinones.

* Corresponding author. Tel.: +33-0-3-20-43-44-32; fax: +33-0-3-20-33-63-09; e-mail: axel.couture@univ-lille1.fr

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)01067-6



Scheme 1.

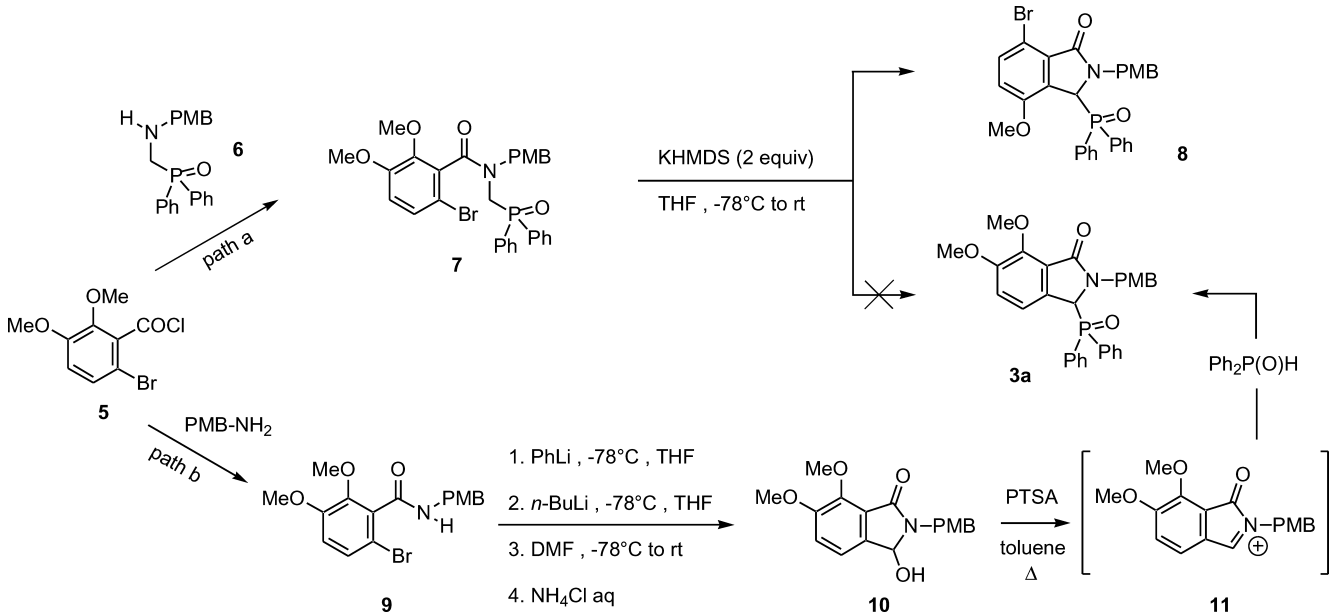
functionalities on the environmentally different aromatic moieties. As far as we are aware no total synthesis of natural product **1a** has appeared in print and solely a semisynthetic route to **1a** based upon the basic treatment of β-hydrastine methiodide has been reported.[7]

While embarking on the synthesis of this alkaloid, one of our major concerns was to develop a general and conceptually new approach that would tolerate a variety of substitution patterns liable to have some implication on the biological profile of these models. For the elaboration of compound **1a** we opted for the synthetic route depicted in the retrosynthetic Scheme 1 that relies upon our long-standing experience in the field of *N*-acylenamine chemistry.[15]

The target compound **1a** would be obtained by *N*-lactam deprotection of the parent arylmethylene isoindolinone **2**. This highly conjugated compound would be readily assembled by Horner reaction between the phosphorylated isoindolinone **3** and the suitably substituted benzaldehyde derivative **4**. Critical to the success of this strategy was then to determine a nitrogen lactam protecting group that would either influence the stereochemical outcome of the Horner process or that would force its direct precursor **2** to adopt the required *Z* geometry of the natural product upon removal. Literature precedent, although scarce, gave support to the resort of the *para*-methoxybenzyl group.[16] We indeed conjectured that the deprotection reaction, which is usually carried out at relatively high temperatures and under strong acidic conditions thus facilitating *E*→*Z* conversion,[17] would be highly stereoselective and yield the thermodynamically more stable (*Z*)-ene lactam **1a**.

We thus set out to prepare the phosphorylated *N*-*para*-methoxybenzyl isoindolinone **3a** and, for the first facet of the synthesis, we initially envisaged to take advantage of our newly developed aryne-mediated cyclization applied to halogeno-*N*-[(diphenylphosphinoyl)methyl]benzamide derivatives (Scheme 2, path a). For this purpose the required parent phosphorylated benzamide **7** was initially synthesized by coupling *N*-[(diphenyphosphinoyl)methyl]-*N*-4-methoxybenzylamine **6** with the benzoyl chloride derivative **5**. Somewhat disappointingly, compound **7** was totally recalcitrant to the aryne-mediated cyclization reaction liable to give access to the required phosphorylated isoindolinone **3a**. Indeed exposure of **7** to potassium bis(trimethylsilyl)-amide (KHMDS, 2 equiv.) at −78°C in THF led to a complex mixture of products among which the undesired, demethoxylated isoindolinone **8** was slightly predominant.

We then decided to switch our plans and to adopt an alternative strategy for the installation of the phosphoryl appendage at the benzylic position of the heteroring unit. This new synthetic route relies upon the sensitivity of *N*-acyliminium ions to nucleophilic attack with carbon or



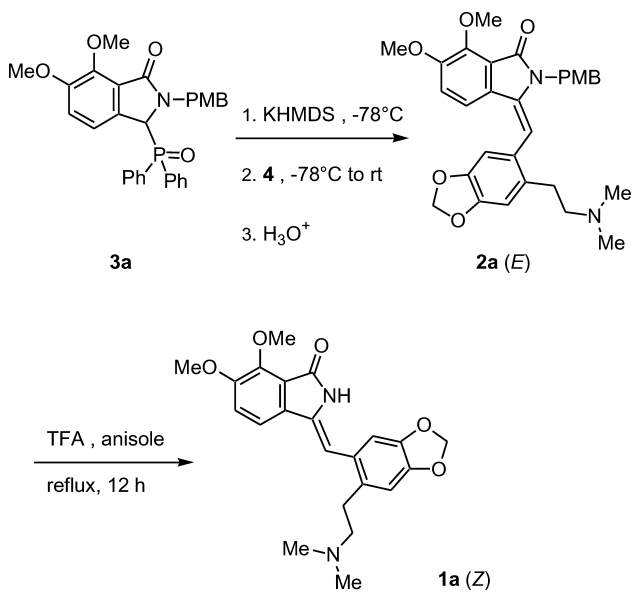
Scheme 2.

heteroatom nucleophiles.[18] Since alkoxy and hydroxylactams[18e,f] are regarded as excellent precursors to the cationic species, we therefore planned to synthesize 6,7-dimethoxy-3-hydroxy-2-[(4-methoxyphenyl)methyl]-2,3-dihydro-1*H*-isoindol-1-one **10** (Scheme 2). The most frequently used methods to achieve the elaboration of these hydroxylactams are partial reduction of the corresponding carbonyl group of imides or anodic hydroxylation of lactams[18] but this strategy is often plagued by the problem of poor regioselectivity for unsymmetrically substituted models. This problem was circumvented by the synthetic pathway depicted in Scheme 2 (path b), which is based upon the interception of the dilithiated species derived from the bromobenzamide **9** with dimethylformamide (DMF). After experimenting a variety of reagents and conditions it was found that the best results were obtained by sequential deprotonation and bromine–lithium exchange with phenyllithium (1.12 equiv.) and *n*-butyllithium, respectively. Trapping with DMF delivered the desired hydroxylactam with a satisfactory yield (59%). The endocyclic *N*-acyliminium cation **11** was generated in boiling toluene under acidic conditions and reacted smoothly with diphenylphosphine oxide to yield the corresponding 3-diphenylphosphinoyl-6,7-dimethoxy-2-[(4-methoxyphenyl)methyl]-2,3-dihydro-1*H*-isoindol-1-one **3a** almost quantitatively.

With this phosphorylated lactam in hand, incorporation of the pendant aminoalkylarylidene unit could be envisaged by the agency of the Horner process (Scheme 3).

Thus, compound **3a** was deprotonated at −78°C using 1.1 equiv. of KHMDS in THF and the so formed carbanion was reacted with the aromatic carboxaldehyde **4**, a degradation product of cryptopleurospermin.[19,20] Warming to room temperature ensured completion of the Horner reaction and the arylmethyleneisoindolinone **2a** was quantitatively formed and isolated in high yield by this protocol.

Compound **2a** was obtained exclusively with the undesired



Scheme 3.

E geometry, the configuration of the double bond being established from its ^{1}H NMR spectrum with the use of nOe experiments. Thus the lactamic *N*-methylene H_2 of **2a** (δ 5.00 ppm) showed a strong nOe (10%) with the vinylic H (δ 6.19 ppm). The driving force arising from the high degree of conjugation of these models incorporating a central stilbenoid double bond and the presence of the bulky *para*-methoxybenzyl group on the lactam nitrogen account for the high yield and stereoselectivity of this synthesis of the ene lactam **2a**. The adoption of the *para*-methoxybenzyl protecting group for the nitrogen lactam was rewarded here: treatment of the protected arylideneisoindolinone **2a** in boiling trifluoroacetic acid in the presence of anisole as the carbocation scavenger produced selectively the thermodynamically more stable product **1a** with the *Z* geometry. The constitution and stereochemistry of the target final compound **1a** was secured by matching its ^{1}H and ^{13}C NMR, IR, UV and mass spectra with those published for the natural and hemisynthetic compound by previous investigators.[7,8]

In summary the first total synthesis of fumaridine which emphasizes the synthetic potential of phosphorylated isoindolinones has been accomplished. We also believe that this work demonstrates a general methodology, widely adaptable for the preparation of other naturally occurring *Fumariaceae* alkaloids as well as their biogenetically related congeners.

3. Experimental

3.1. General

Tetrahydrofuran (THF) and ether (Et_2O) were pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3, 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 (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, 75 and 121 MHz, for ^{1}H, ^{13}C and ^{31}P, respectively). For ^{1}H, ^{13}C NMR, $CDCl_3$ as solvent, TMS as internal standard; for ^{31}P NMR, $CDCl_3$ as solvent, H_3PO_4 as external standard. Microanalyses were performed by the CNRS microanalysis center.

The benzoyl chloride derivative **5**[21] and the dimethylaminoalkylbenzaldehyde **4**[20] were prepared according to literature methods. The phosphorylated amine **6** was also synthesized according to a reported procedure.[13a]

3.1.1. 6-Bromo-*N*-[(diphenylphosphinoyl)methyl]-2,3-dimethoxy-*N*-(4-methoxybenzyl)benzamide (7). A solution of the benzoyl chloride derivative **5** (500 mg, 1.8 mmol) in dry CH_2Cl_2 (150 mL) was added dropwise at 0°C to a solution of the phosphorylated amine **6** (630 mg, 1.80 mmol) and NEt_3 (1.82 g, 18 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 2 h. Water (50 mL) was added. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated

in vacuo to afford a solid residue which was recrystallized from hexane–toluene. Yield: 1.0 g (94%); mp 183–184°C; ^{1}H NMR (δ): 3.67 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.03 (dd, J=6.8, 15.4 Hz, 1H, NCH_2P), 4.56 (d, J=14.9 Hz, 1H, NCH_2Ar), 4.77–4.88 (m, 2H, NCH_2-P+NCH_2Ar), 6.73 (d, J=8.8 Hz, 1H, aromatic H), 6.84 (d, J=8.6 Hz, 2H, aromatic H), 7.14 (d, J=8.8 Hz, 1H, aromatic H), 7.32–7.60 (m, 8H, aromatic H), 7.78–7.90 (m, 2H, aromatic H), 7.94–8.08 (m, 2H, aromatic H) ppm; ^{13}C NMR (δ): 41.2 (d, J_{CP}=76 Hz, NCHP), 52.4, 55.2, 56.0, 61.7, 109.4, 114.0, 114.1, 126.9, 128.2, 128.6 (d, J_{CP}=11.5 Hz), 130.8, 131.0 (d, J_{CP}=10 Hz), 131.2 (d, J_{CP}=98 Hz), 131.7 (d, J_{CP}=10 Hz), 132.0 (d, J_{CP}=15 Hz), 132.9, 146.3, 152.2, 159.2, 166.1 (CO) ppm; ^{31}P NMR (δ): 30.1 ppm. Anal. calcd for $C_{30}H_{29}BrNO_5P$ (594.5): C, 60.62; H, 4.92; N, 2.36%. Found: C, 60.32; H, 5.27; N, 2.57%.

3.1.2. 7-Bromo-3-diphenylphosphinoyl-4-methoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (8). A solution of KHMDS (1.85 mL, 0.5 M in toluene, 0.92 mmol) was added dropwise over a period of 5 min to a stirred solution of compound **7** (500 mg, 0.84 mmol) and 18-crown-6 (245 mg, 0.92 mmol) in THF (50 mL) at −78°C under Ar. The solution was stirred for 30 min at this temperature and then allowed to warm to room temperature within 6 h. Aqueous NH_4Cl was added, and the mixture extracted with CH_2Cl_2 (2×50 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to a light yellow oil which was purified by flash column chromatography with acetone–hexanes (50:50) as eluent to afford **8**. Yield: 166 mg (35%); mp 104–105°C (white crystals from hexane–toluene); ^{1}H NMR (δ): 3.37 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.51–4.62 (m, 2H, NCH_2Ar+NCHP), 4.94 (d, J=14.7 Hz, 1H, NCH_2Ar), 6.81 (d, J=8.7 Hz, 2H, aromatic H), 7.15–7.29 (m, 3H, aromatic H), 7.35–7.51 (m, 6H, aromatic H), 7.61–7.75 (m, 5H, aromatic H) ppm; ^{13}C NMR (δ): 44.9, 53.8, 55.2, 61.5 (d, J_{CP}=65 Hz), 110.1, 111.8, 114.6, 128.1 (d, J_{CP}=98 Hz), 128.3 (d, J_{CP}=12 Hz), 128.6 (d, J_{CP}=11 Hz), 129.7, 130.5, 130.9, 131.4 (d, J_{CP}=9.5 Hz), 131.5 (d, J_{CP}=95 Hz), 131.6 (d, J_{CP}=10 Hz), 132.3 (d, J_{CP}=2 Hz), 133.1, 134.7, 153.6, 158.2, 166.8 (CO) ppm; ^{31}P NMR (δ): 30.3 ppm. Anal. calcd for $C_{29}H_{25}BrNO_4P$ (562.4): C, 61.93; H, 4.48; N, 2.49%. Found: C, 61.75; H, 4.76; N, 2.73%.

3.1.3. 6-Bromo-2,3-dimethoxy-*N*-(4-methoxybenzyl)benzamide (9). This secondary aromatic carboxamide was obtained by coupling 4-methoxybenzylamine (2.7 g, 19.7 mmol) with the benzoyl chloride derivative **5** (5 g, 17.9 mmol) under classical Schotten–Baumann reaction conditions as described above for benzamide **7**. Final purification by flash column chromatography with EtOAc–hexanes–NEt_3 (50:45:5) afforded **9** as white crystals. Yield: 5.24 g (77%); mp 92–93°C (hexane–toluene); ^{1}H NMR (δ): 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.57 (d, J=5.6 Hz, 2H, CH_2), 6.06 (s, 1H, NH), 6.74 (d, J=8.8 Hz, 1H, aromatic H), 6.84 (d, J=8.5 Hz, 2H, aromatic H), 7.19 (d, J=8.8 Hz, 1H, aromatic H), 7.30 (d, J=8.5 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ): 43.4, 55.3, 56.0, 62.1, 109.7, 114.0, 128.1, 129.3 (two peaks overlapping), 129.9, 133.9, 147.0, 152.1, 159.0, 165.4 (CO) ppm. Anal. calcd for $C_{17}H_{18}BrNO_4$ (380.2): C, 53.70; H, 4.77; N, 3.68%. Found: C, 53.91; H, 5.02; N, 3.61%.

3.1.4. 3-Hydroxy-6,7-dimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (10). A solution of PhLi (2.55 mL, 1.8 M in cyclohexane–ether 70:30, 4.5 mmol) was added dropwise to a solution of bromobenzamide **9** (1.55 g, 4.1 mmol) in THF (150 mL) at −78°C under Ar. The mixture was stirred at this temperature for 30 min and then treated dropwise with a solution of BuLi (2.85 mL, 1.6 M in hexanes, 4.5 mmol). The mixture was kept at −78°C with stirring for 5 min and a solution of dimethylformamide (DMF, 660 mg, 9 mmol) in THF (2 mL) was added dropwise by syringe. Once addition had finished, the reaction mixture was stirred for 1 h at −78°C and then allowed to warm to room temperature for an additional 1 h. Saturated aqueous NH_4Cl (50 mL) was added, and the mixture was extracted with Et_2O (3×100 mL). The organic layer was washed with water, brine, dried ($MgSO_4$) and concentrated in vacuo to a crude solid which was purified by flash column chromatography with AcOEt–hexanes (30:70) as eluent to furnish a white solid. Yield: 800 mg (59%); mp 137–138°C (hexane–toluene); ^{1}H NMR (δ): 3.72 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.21 (d, J=14.7 Hz, 1H, CH_2), 4.85 (d, J=14.7 Hz, 1H, CH_2), 5.43 (s, 1H, CHO), 6.78 (d, J=8.8 Hz, 2H, aromatic H), 6.94 (d, J=8.1 Hz, 1H, aromatic H), 7.16 (d, J=8.1 Hz, 1H, aromatic H), 7.24 (d, J=8.8 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ): 41.9, 55.2, 56.4, 62.4, 78.9, 114.0, 116.0, 118.9, 123.2, 129.3, 130.0, 137.2, 146.1, 153.3, 158.9, 165.0 (CO) ppm. Anal. calcd for $C_{18}H_{19}NO_5$ (329.4): C, 65.64; H, 5.81; N, 4.25%. Found: C, 65.52; H, 5.89; N, 4.44%.

3.1.5. 3-(Diphenyphosphinoyl)-6,7-dimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (3a). A solution of hydroxyisoindolinone **10** (700 mg, 2.13 mmol), *para*-toluenesulfonic acid (PTSA, 50 mg, 0.3 mmol) and diphenylphosphine oxide (475 mg, 2.34 mmol) in toluene (100 mL) was refluxed under Ar for 3 h in a Dean–Stark apparatus. The solvent was removed under vacuum and the oily residue was dissolved in CH_2Cl_2 (100 mL). The organic phase was then subsequently treated with aqueous $NaHCO_3$, water and brine and finally dried ($MgSO_4$). Flash column chromatography using AcOEt–hexanes (70:30) as eluent afforded the crude phosphorylated isoindolinone and final purification by recrystallization from toluene–hexane furnished **3a** as a white powder. Yield: 940 mg (86%); mp 152–153°C; ^{1}H NMR (δ): 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.20 (d, J=14.8 Hz, 1H, CH_2), 5.16 (dd, J=0.5, 9.3 Hz, 1H, NCHP), 5.28 (d, J=14.8 Hz, 1H, CH_2), 6.47 (dd, J=1.0, 7.6 Hz, 1H, aromatic H), 6.77–6.85 (m, 3H, aromatic H), 7.13 (d, J=8.5 Hz, 2H, aromatic H), 7.38–7.48 (m, 6H, aromatic H), 7.53–7.56 (m, 2H, aromatic H), 7.62–7.69 (m, 2H, aromatic H) ppm; ^{13}C NMR (δ): 44.6, 55.2, 56.6, 59.0 (d, J_{CP}=74 Hz, NCHP), 62.6, 114.0, 116.0 (d, J_{CP}=2.5 Hz), 119.3 (d, J_{CP}=3 Hz), 124.7, 127.7 (d, J_{CP}=93 Hz), 128.6 (d, J_{CP}=11.5 Hz), 128.7 (d, J_{CP}=11.5 Hz), 128.8, 129.0 (d, J_{CP}=94 Hz), 129.9, 131.7 (d, J_{CP}=9 Hz), 131.8, 132.1 (d, J_{CP}=9 Hz), 132.8 (d, J_{CP}=3 Hz), 132.9 (d, J_{CP}=2.0 Hz), 147.4, 152.7 (d, J_{CP}=2 Hz), 159.1, 166.9 (d, J_{CP}=2.0 Hz) ppm; ^{31}P NMR (δ): 31.2 ppm. Anal. calcd for $C_{30}H_{28}NO_5P$ (513.5): C,

70.17; H, 5.50; N, 2.73%. Found: C, 70.48; H, 5.67; N, 2.92%.

3.1.6. (*E*)-3-({6-[2-(dimethylamino)ethyl]-1,3-benzodioxol-5-yl}methylene)-6,7-dimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (2a). A solution of KHMDS (2.2 mL, 0.5 M in toluene, 1.1 mmol) was added dropwise over a period of 15 min to a stirred solution of the phosphorylated isoindolinone **3a** (513 mg, 1 mmol) in THF (25 mL) at −78°C under Ar. The solution was stirred for 15 min at this temperature and a solution of the benzaldehyde derivative **4** (221 mg, 1 mmol) in THF (2 mL) was added by syringe. The mixture was kept at −78°C for 15 min and then warmed to room temperature over a period of 1 h. Water was added and the mixture was extracted with Et_2O (2×50 mL). The ether extract was washed with water and brine, dried over Na_2SO_4 and evaporated in vacuo. Flash column chromatography on silica gel with AcOEt–hexanes–NEt_3 (90:5:5) as eluent allowed isolation of the ene lactam **2a** which was finally purified by recrystallization from hexane–toluene. Pale yellow crystals; yield: 400 mg (77%); mp 113–114°C; ^{1}H NMR (δ): 2.00 (s, 6H, $N(CH_3)_2$), 2.14–2.20 (m, 2H, CH_2), 2.42–2.47 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 5.00 (s, 2H, NCH_2), 5.93 (s, 2H, OCH_2O), 6.19 (s, 1H, =CHAr), 6.67–6.73 (m, 3H, aromatic H), 6.80–6.86 (m, 3H, aromatic H), 7.21–7.26 (m, 2H, aromatic H) ppm; ^{13}C NMR (δ): 31.6, 42.6, 45.2, 55.2, 56.5, 60.2, 62.5, 101.5 (OCH_2O), 107.6, 109.8, 110.3, 114.1, 116.0, 119.1, 122.2, 127.2, 128.4, 128.8, 129.2, 133.2, 135.7, 146.0 (two peaks overlapping), 147.5, 153.4, 158.9, 164.8 (CO) ppm. Anal. calcd for $C_{30}H_{32}N_2O_6$ (516.6): C, 69.75; H, 6.24; N, 5.42%. Found: C, 69.97; H, 6.50; N, 5.21%.

3.2. Alkaloid fumaridine (1a)

A solution of the arylmethylene isoindolinone **2a** (240 mg, 0.47 mmol) and anisole (510 mg, 4.7 mmol) in trifluoroacetic acid (10 mL) was refluxed under Ar for 12 h. The reaction mixture was concentrated under vacuum, the residue was dissolved in CH_2Cl_2 (20 mL) and NEt_3 (0.5 mL) was added with stirring. Water (20 mL) was then added, and the organic layer was washed with brine, dried (Na_2SO_4) and concentrated to yield a solid residue which was recrystallized from EtOH. The analytical and spectral data of synthetic **1a** (170 mg, 91%) matched those reported for the natural product.[6,8]

Acknowledgements

This research was supported by the Centre National de la Recherche Scientifique and MENESR (grant to V. R.). Also we acknowledge helpful discussions and advice from Dr T. G. C. Bird (Astra-Zeneca Pharma).

References

1. Blasko, G.; Gula, D. J.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 105–122.
2. Aboudi, A. F.; Al-Eisawi, D. M.; Sabri, S. S.; Zarga, M. H. A. *J. Nat. Prod.* **1986**, *49*, 369.
3. Kiriakov, K.; Mardirosyan, Z.; Panov, P. *Doklady Bolgarskoi Akademii Nauk* **1980**, *33*, 1377–1379, *Chem. Abstr.* **1981**, *94* 188644.
4. Ibragimova, M. U.; Israilov, I. A.; Yunusov, M. S.; Yunusov, S. Y. *Khimiya Prirodnykh Soedinenii* **1974**, *4*, 476–478, *Chem. Abstr.* **1975**, *82* 28586.
5. Hussain, S. F.; Minard, R. D.; Freyer, A. J.; Shamma, M. *J. Nat. Prod.* **1981**, *44*, 169–178.
6. Ruecker, G.; Breitmaier, E.; Zhang, G. L.; Mayer, R. *Phytochemistry* **1994**, *36*, 519–523.
7. Blasko, G.; Elando, V.; Sener, B.; Freyer, A. J.; Shamma, M. *J. Org. Chem.* **1982**, *47*, 880–885.
8. Shamma, M.; Moniot, J.-L. *J. Chem. Soc., Chem. Commun.* **1975**, 89–90.
9. (a) Allin, S. M.; Vaidya, D. G.; Page, M. I.; Slawin, A. M. Z.; Smith, T. *Tetrahedron Lett.* **2000**, *41*, 2219–2222. (b) Cho, C. S.; Shim, H. S.; Choi, H.-J.; Kim, T.-J.; Shim, S. C.; Kim, M. C. *Tetrahedron Lett.* **2000**, *41*, 3891–3893. (c) Mamouni, A.; Daich, A.; Decroix, B. *Synth. Commun.* **1997**, *27*, 2241–2249. (d) Campbell, J. B.; Dedinas, R. F.; Trumbower-Walsh, S. A. *J. Org. Chem.* **1996**, *61*, 6205–6211. (e) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491–2517.
10. (a) Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 2003–2006. (b) Deniau, E.; Enders, D. *Tetrahedron Lett.* **2002**, *43*, 8055–8058.
11. Aliev, K. U. *Meditsinskii Zhurnal Uzbekistana* **1973**, 33–35, *Chem. Abstr.* **1974**, *80* 103986.
12. (a) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C.; Rys, V. *Tetrahedron Lett.* **2002**, *43*, 2207–2210. (b) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313–10330.
13. (a) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128–3132. (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Rybalko-Rosen, H.; Léonce, S.; Pfeiffer, B.; Renard, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557–3559.
14. Gramain, J.-C.; Troin, Y.; Mavel, S.; Vallée-Goyet, D. *Tetrahedron* **1991**, *47*, 7287–7300.
15. (a) Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P.; Carpentier, J.-F. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1403–1408. (b) Hoarau, C.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2001**, 2559–2567. (c) Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2001**, *66*, 8064–8069.
16. Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339–2358.
17. (a) Stachel, H. D.; Poschenrieder, H.; Wiesend, B. *Z. Naturforsh., Teil B* **1983**, 988–991. (b) Effenberger, F.; Beisswenger, T. *Chem. Ber.* **1984**, *117*, 1497–1512. (c) Baccolini, G.; Gianelli, M. *Tetrahedron* **1995**, *51*, 9487–9492.
18. (a) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slavwin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905–4908. (b) El Gihani, M. T.; Heaney, H.; Suhaibar, K. F. *Synlett* **1996**, 871–872. (c) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080–2092. (d) Hucher, N.; Decroix, B.; Daïch, A. *J. Org. Chem.* **2001**, *66*, 4695–4703. (e) Hiemstra, H.; Speckamp, W. N. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1042–1082. (f) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416.
19. Johns, S. R.; Lamberton, J. A.; Sioumis, A. A.; Willing, R. I. *Aust. J. Chem.* **1970**, *23*, 353–361.
20. Dunmore, G. C.; Manske, R. H.; Rodrigo, R. *Heterocycles* **1977**, *8*, 391–395.
21. Nimgirawath, S.; Ponghusabun, O. *Aust. J. Chem.* **1994**, *47*, 951–955.