Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5725–5735
Tetrahedron

The palladium(0) Suzuki cross-coupling reaction as the key step in the synthesis of aporphinoids

R. Suau,[a,*] R. Rico,[a] F. Nájera,[a] F. J. Ortiz-López,[a] J. M. López-Romero,[a] M. Moreno-Mañas[b] and A. Roglans[b]

[a]*Dep. Química Orgánica, Facultad de Ciencias, Universidad de Málaga, 29071 Málaga, Spain*
[b]*Dep. Química, Universidad Autónoma de Barcelona, Cerdanyola, 08193 Barcelona, Spain*

Received 2 March 2004; revised 14 April 2004; accepted 7 May 2004

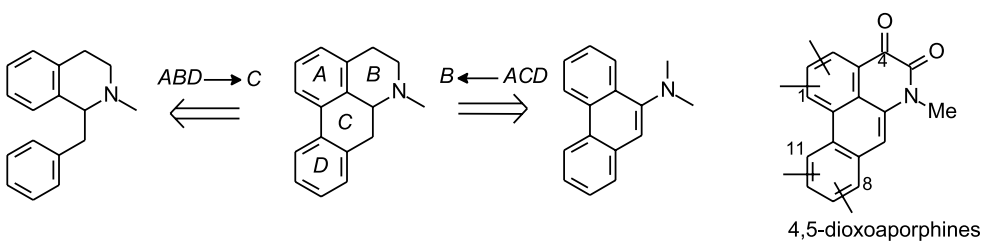
Abstract—We report a flexible approach to the total synthesis of 4,5-dioxoaporphines based on the palladium(0) catalyzed Suzuki cross-coupling of phenylboronic acids with sterically hindered 2-bromo phenyl acetates or bromo phenyl acetamides, followed by sequential bicyclization of biarylacetamides promoted by oxalyl chloride/Lewis acid. The reduction of 4,5-dioxoaporphines provides a chemoselective entry to aporphines, dehydroaporphines and 4-hydroxy-dehydroaporphines. A three-steps total synthesis for (±)-*O*,*O*′-dimethylapomorphine from readily accessible precursors is also reported.

1. Introduction

A number of approaches to the synthesis of 4*H*-dibenzo-[*de*,*g*]quinoline as the basic skeleton of the large group of aporphinoid alkaloids have been reported.[1] Most follow a biogenetic pathway the last step in which involves the cyclization of a suitably functionalized 1-benzylisoquinoline (*ABD*→*C* approach in Scheme 1). Methods used to obtain the aryl–aryl bond include the classical Pschorr reaction;[2] phenolic, monophenolic and non-phenolic oxidative coupling;[3] enamide photocyclization;[4] benzyne cyloaddition,[5] radical cyclization[6] and *ortho*-arylation.[7]

A non-biogenetic approach involving the construction of ring *B* at the final stage of the synthesis has been employed in the synthesis of aporphines and aporphine analogs[8] (particularly the highly oxidized aporphines, 4,5-dioxoaporphines,[9] which are believed to act as post-infectional phytoalexins in plants, and to exhibit significant cytotoxicity against various tumoral cell lines and DNA modifying bioactivity.[10]) This synthesis requires a suitably functionalized phenanthrene **I** as the key intermediate (*ACD*→*B* approach). These type of compounds (**I**) have been prepared following two different pathways; one starts from an accessible substrate with the preformed biaryl bond included in its structure (e.g., a functionalized fluorenone or dibenzopyrane[10a]) and the other from the radical cyclization of a functionalized stilbene prepared using the Horner protocol (Scheme 2).[10e]

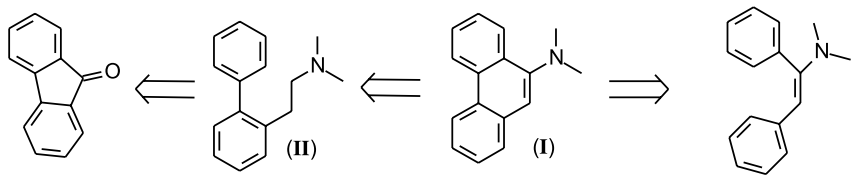
In the former case, oxidation of the fluorenone followed by homologation and Bischler–Napieralsky cyclization to the amino-phenanthrene **I** involved several steps (22% overall yield from 1-methoxyfluorenone). The latter approach



Scheme 1.

Keywords: Aporphinoids; Apomorphine; 4,5-Dioxoaporphine; 4-Hydroxy-dehydroaporphine; Aporphine; Palladium; Suzuki cross-coupling; Oxalyl chloride; Cascade cyclization; Reduction.
* Corresponding author. Tel.: +34-95213-1934; fax: +34-95213-2000; e-mail address: suau@uma.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.014



Scheme 2.

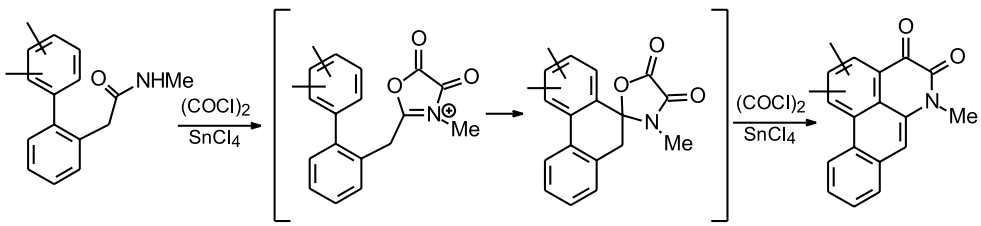
involves four steps, namely: formation of the phosphorylated benzamide, Horner reaction, radical cyclization and deprotection at nitrogen (48% average yield). In previous work we developed two different approaches to the formation of ring *B*; one involved photocyclization of α-chloroacetamides followed by oxidation or oxalyl chloride/Lewis acid reaction.[10a] Subsequently, we developed a much more direct approach based on the double cyclization of biphenyl acetamides promoted by oxalyl chloride/Lewis acid with sequential formation of rings *C* and *B* in a single step (Scheme 3).[11]

In this bicyclization, the oxalyl chloride activates the biphenylacetamide to give an electrophilic acyliminium ion which is the acylating agent that promotes the construction of ring *C*, gives the α-dicarbonyl system needed for the formation of ring *B*, and activates the Friedel–Crafts reaction in the final ring *B* closure.

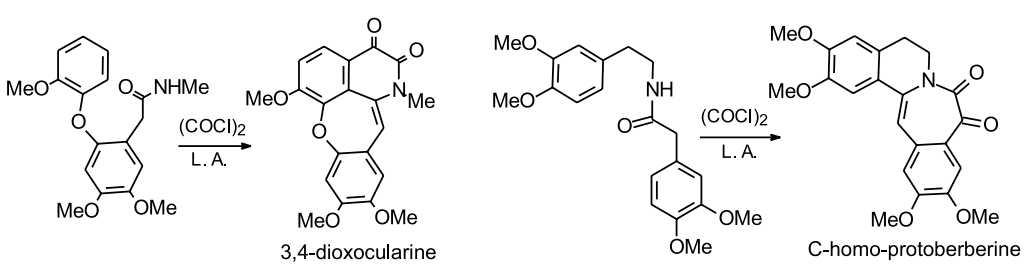
This double cyclization has also been successfully applied to the total synthesis of 3,4-dioxocularine alkaloids from aryloxy-phenylacetamides, and to the synthesis of C-homo-protoberberines that can be easily decarbonylated to the corresponding 8-oxo-berbines (Scheme 4).[12]

Although this double cyclization considerably shortens the synthesis of 4,5-dioxoaporphines, its use is limited by the availability of suitably substituted fluorenones or dibenzopyranes to match the oxygenated substitution pattern of naturally occurring 4,5-dioxoaporphines on the one hand, and by the long sequence required for homologation (reduction, halogenation, cyanation, hydrolysis and amidation) on the other. We thus focused on the synthesis of functionalized biphenyls as key intermediates (**II**, Scheme 2), using a more direct approach in order to circumvent the intermediate steps that decrease the overall yield and chose the Suzuki cross-coupling variant among the synthetic methods for biaryls.[13] This palladium-catalyzed cross-coupling of phenyl derivatives is a flexible, advantageous synthetic method for constructing C–C biaryl bonds under mild reaction conditions. It tolerates aqueous media; also, the inorganic products of the reaction can be easily eliminated, the boron compounds are stable, none of the products is toxic, and many of the aryl boronic acids are commercially available with an appropriate oxygenation aromatic pattern. However, the Suzuki biaryl cross-coupling reaction still requires some improvement, especially when sterically hindered substrates are involved. In addition, *ortho*-di and tri-substituted biaryls are also interesting because they are key structural elements of many pharmacologically active natural and synthetic products.[14]

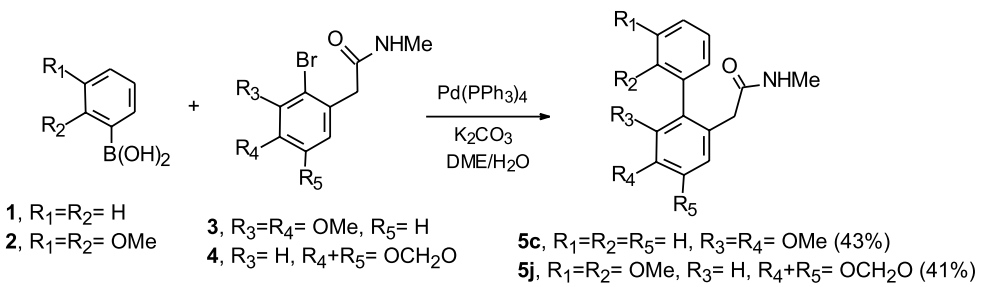
This paper reports our findings in using the Suzuki cross-coupling reaction for the synthesis of biaryl acetamides and esters, and its application to the synthesis of 4,5-dioxoaporphines, including the improvement in the cyclization of biarylacetamides promoted by oxalyl chloride/Lewis acid. This approach, which provides a convergent construction method for the aporphine skeleton in two steps, prompted us to explore the reduction of 4,5-dioxoaporphines to other aporphinoids. The results were applied to the total synthesis of (±)-*O*,*O*′-dimethylapomorphine in only three synthetic steps. The Suzuki coupling method and Meyers' protocol for the preparation of its key biphenylacetamide intermediate are compared.



Scheme 3.



Scheme 4.



Scheme 5.

2. Results and discussion

2.1. Suzuki cross-coupling

We first examined the coupling of arylboronic acid **1** or **2** with phenyl acetamides **3** and **4**, using the standard conditions for the Suzuki coupling, namely $Pd(PPh_3)_4$ as catalyst, K_2CO_3 as base and DME–H_2O as solvent. Under these conditions, total conversion was found by ^1H NMR of the reaction crude, and high yields of the cross-coupling compounds **5c** and **5j** (87 and 83%, respectively) were determined by GC–MS (Scheme 5). However, the presence of triphenylphosphine oxide, the R_f for which is very close to those of amides **5c**,**j**, hindered the purification of the amide derivatives by column chromatography, and resulted in significantly diminished yields for the isolated compounds (43% for **5c** and 41% for **5j**).

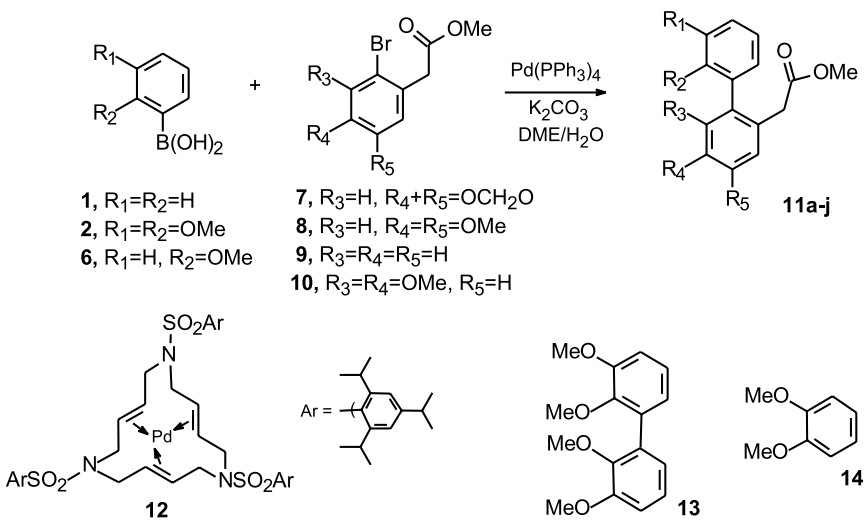
Table 1. Palladium catalyzed Suzuki cross-coupling of esters **7**–**10** with boronic acids **1**, **2** and **6** ($Pd(PPh_3)_4/K_2CO_3$/DME–H_2O)

Entry	R_1	R_2	R_3	R_4	R_5	Ester, **11**, yield, %[a]
1	H	OMe	H	H	H	**11a**, 64 (76)
2	OMe	OMe	H	H	H	**11b**, 56 (62)
3	H	H	OMe	OMe	H	**11c**, 83 (100)
4	H	OMe	OMe	OMe	H	**11d**, 58 (70)
5	OMe	OMe	OMe	OMe	H	**11e**, 31[b] (41)
6	H	OMe	H	OMe	OMe	**11f**, 67 (80)
7	OMe	OMe	H	OMe	OMe	**11g**, 45 (56)
8	H	H		OCH_2O		**11h**, 86 (100)
9	H	OMe	H	OCH_2O		**11i**, 76 (95)
10	OMe	OMe	H	OCH_2O		**11j**, 59 (69)

[a] (%) Yield by GC.
[b] 40% yield with DMF, K_3PO_4, and 10 mol% $Pd(PPh_3)_4$ as catalytic system.

Then, our attention was turned to the coupling of the ester derivatives instead of the amides in order to circumvent the purification difficulties. We first explored the coupling of 2-bromo-4,5-methylendioxy-phenylacetic methyl ester (**7**) with phenylboronic acid (**1**) (Table 1, entry 8). Under the above-described conditions, $Pd(PPh_3)_4/K_2CO_3$/DME–H_2O, refluxing compounds **1** and **7** for 18 h led to 100% conversion and, after purification, **11h** was obtained in a 86% yield. The coupling of boronic acids **1**, **2** and **6** with the bromide derivatives **7**–**10** under the same conditions afforded the biphenyl esters **11a**–**j** (Scheme 6, Table 1). Increasing the steric hindrance in the boronic acid (**6** and **2**) decreased the yield in the coupled products (entries 9 and 10, 76 and 59%, for **11i** and **11j**, respectively). The influence of the methoxy group *ortho* to the coupling position was also apparent in the reactions of bromide **10** with boronic acids **1**, **2** and **6** (entries 3–5).

The formation of the biaryl bond in highly sterically hindered biphenyls proved more difficult, as also observed in the preparation of the 1,2,1′,2′-tetramethoxylated biphenyl (**11e**), with three *ortho* substituents, and the yield dropping to 31% (Table 1, entry 5). It has been shown that improving the conditions for sterically hindered Suzuki coupling entails using of anhydrous conditions and phosphate. Using them in the coupling of **2** and **10** [DMF,



Scheme 6.

K_3PO_4, 10 mol% $Pd(PPh_3)_4$, 100 °C] raised the yield of **11e** to 40%.

Alternative catalysts and catalytic conditions were also tested. When the cross-coupling was conducted with the phosphine-free catalytic system $Pd_2(dba)_3$ in the presence of K_2CO_3, the coupling products **11h** and **11j** were obtained in lower yields (63 and 45%, respectively). The catalytic potential of the 15-membered macrocyclic triolefin palladium(0) complex (**12**), which can be recovered from reaction medium and reused with no loss of catalytic activity, was also examined.[15] The reaction of the bromide **7** with the phenylboronic acids **1** and **2**, revealed that catalyst **12** promotes the cross coupling, and biphenyls **11h** and **11j** were isolated, albeit with maximum yields around only 20%; as expected, the catalyst was quantitatively recovered in both cases after column chromatography on silica gel.

Differences in yield among biaryls exhibiting similar steric interactions can be ascribed to electronic effects.[16] Thus the decreased yield observed in the coupling of the *meta*-methoxy substituted boronic acid (**2**) (entries 2, 5, 7, 10, Table 1) can be ascribed to induction from this group of a lower electron density at position 1 of the boronic acid (**2**) compared to the unsubstituted acid (**6**), as suggested by electron density ab initio calculations (Fig. 1).[17] This effect on the yields is observed for the compound series. In fact, the dimerization product, 2,2′,3,3′-tetramethoxybiphenyl (**13**), and the deboronation product, veratrol (**14**), were always isolated from the reaction medium in the preparation of **11a**,**b**, **11d**,**e**, **11f**,**g** and **11i**,**j** (Scheme 6).

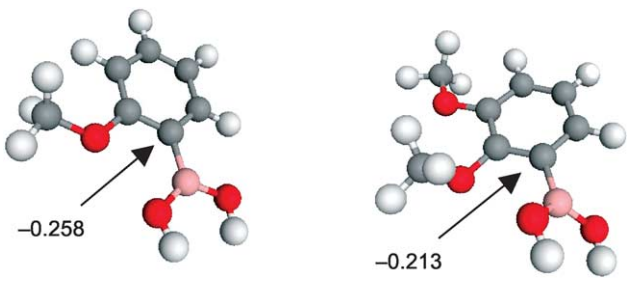


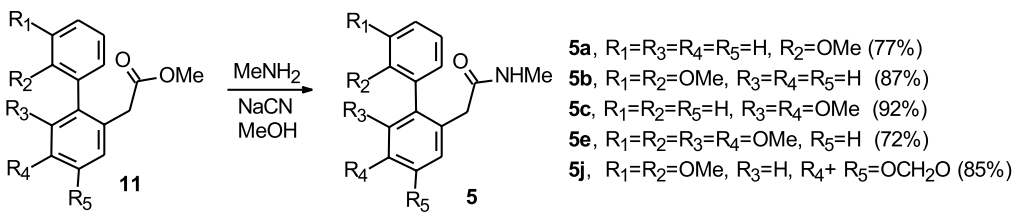
Figure 1. Electron density ab initio calculations for compounds **6** (left) and **2** (right).

Also, the presence of two methoxy groups in the molecule induces some deboronation due to an out-of-plane conformation of the boronic acid group in the more strained compound **2** which makes it more labile.

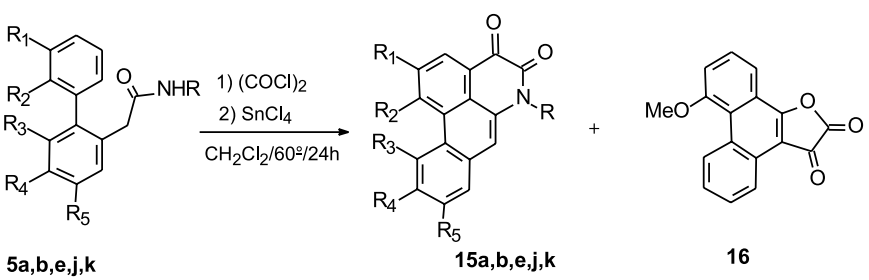
The biaryl esters **11a**–**c**, **11e** and **11j** were readily converted (yield 72–92%) to the biarylacetamides **5a**–**c**, **5e** and **5j** by aminolysis with 45% aqueous methylamine in the presence of sodium cyanide as catalyst (Scheme 7).[18]

2.2. Sequential bicyclization of biarylacetamides

The cyclization of amide **5a**, conducted under the previously described conditions[11] and using an excess of reagents [viz. 3 equiv. $(COCl)_2$ and 2.5 equiv. $SnCl_4$ in dichloromethane at 5 °C for 3 days] gave **15a** (80% yield) together with **16** (2%) and the uncyclized oxalylamidophenanthrene derivative (8%). We then standardized the reaction conditions with a larger excess of reagents (10 equiv. each), and heating at 60 °C, which shortened the reaction time (12–24 h) and raised the yield in **15a** (96%) (Scheme 8). Cepharadione-B (**15b**), which was previously obtained in 5% yield in a multistep sequence from 1-methoxyfluorenone, with formation of ring *B* by photocyclization of the corresponding phenanthryl-α-chloroacetamide, was now obtained in a 29% yield in three steps (52% biaryl coupling, 87% amidation and 65%

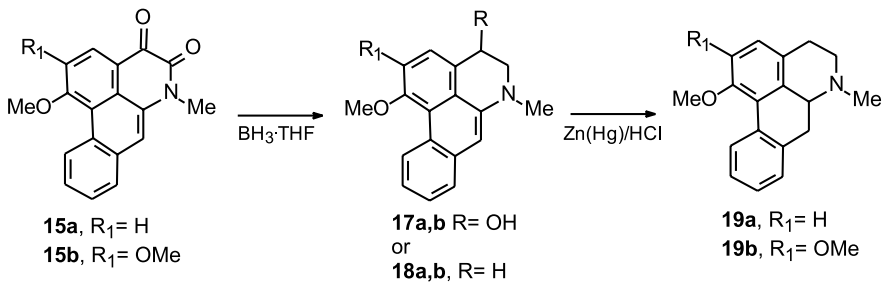


Scheme 7.



15a, **2-Demethoxy-cepharadione-B,** $R_1=R_3=R_4=R_5=H$, $R_2=OMe$, R=Me (96%)
15b, **Cepharadione B**, $R_3=R_4=R_5=H$, $R_1=R_2=OMe$, R=Me (65%)
15e, **4,5-Dioxodehydrocorydine**, $R_1=R_2=R_3=OMe$, $R_3=OH$, $R_5=H$, R=Me (73%)
15j, Corydione, $R_1=R_2=OMe$, $R_4+R_5=OCH_2O$, $R_3=H$, R=Me (39%)
15k, $R_1=R_3=R_4=R_5=H$, $R_2=OMe$, R=*p*-MeO-Ph (61%)

Scheme 8.



Scheme 9.

double cyclization). Cyclization of **5j** afforded the bioactive alkaloid corydione (**15j**) in a 20% overall yield from boronic acid **2**. The lower yield obtained in the cyclization of **5j** was probably due to the sensitivity of the methylenedioxo group to the reaction conditions.

Next, we attempted to expand the usefulness of this synthetic approach to the secondary amides, which could provide an entry to *N-nor*-dioxoaporphines and extend it to the synthesis of *nor*-aporphines. Direct access to these types of compounds following this synthetic pathway is limited because the reaction of oxalyl chloride with primary amides gives acyl isocyanates.[19] Protection of the nitrogen with a *p*-methoxy phenyl group, and cyclization of the secondary amide **5k**, afforded the *N-p*-methoxyphenyl substituted aporphinoid **15k** (together with the furandione **16**, Scheme 8). However, all attempts at N-deprotection using reagents such as CAN or silver nitrate, or anodic oxidation following described procedures were unsuccessful,[20] probably due to the low basicity of the nitrogen atom.

2.3. Reduction of 4,5-dioxoaporphines

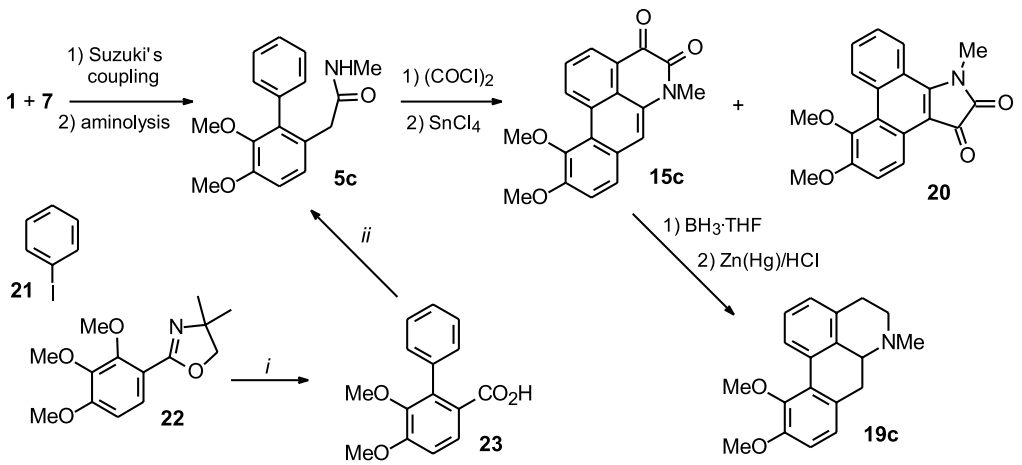
4,5-Dioxoaporphines **15a**,**b** were used as models to study the reduction to other aporphinoids (Scheme 9). Treatment with either LAH or $NaBH_4$ under variable conditions gave complex reaction mixtures. Treating **15a**,**b** with BH_3·THF at room temperature[21] provided in good yields the 4-hydroxy-dehydro aporphines **17a**,**b** (72 and 79%, respectively), which are in an oxidation state not found among naturally occurring aporphines. The same BH_3·THF procedure but heating at 60 °C instead led to the corresponding dehydroaporphines (**18a**,**b**). The completely reduced aporphine skeleton (**19a**,**b**) can be easily achieved by standard Clemmensen reduction of the 7–7a double bond (76% for **19a** and 83% for **19b**).

The attempted direct reduction of **15a** to the aporphine **19a** under Clemmensen conditions failed, probably because of the insolubility of these 4,5-dioxoaporphines under the reaction conditions used.

2.4. Synthesis of (±)-*O*,*O*′-dimethylapomorphine (19c)

Apomorphines are non-natural aporphines that result from the acid rearrangement of morphinanes. They have been widely investigated ever since the structural relationship between apomorphine and the neurotransmitter dopamine was realized.[22] Recently, it has been reported that apomorphines may play an important role in the prevention of Alzheimer's disease.[23]

Usually, apomorphine and its derivatives are obtained by semi-synthesis from morphine-related structures. Most of the reported total syntheses for apomorphine involve cathodic cyclization of 1-(*o*-iodobenzyl)isoquinolinum methiodide[24] followed by H_2/PtO_2 reduction, or start from a benzylisolquinoline diazonium salt prepared following a Bischler–Napieralski or Reissert procedure,[25] and having the *O*,*O*′-dimethyl derivative as intermediate.



Scheme 10.

Following the proposed approach, we accomplished the total synthesis of (±)-*O*,*O*′-dimethylapomorphine (**19c**). The process involved three steps, namely: coupling of the ester **7** with the boronic acid **1**, and aminolysis to the biphenylacetamide **5c** (76% total yield) and cyclization, promoted by oxalyl chloride and Lewis acid, to 4,5-dioxo-*O*,*O*′-dimethylapomorphine (**15c**), which was reduced with BH_3·THF and subjected to Clemmensen reaction with Zn(Hg)/HCl to afford (±)-**19c** in a 26% overall yield from the boronic acid **1** (Scheme 10). From the cyclization of **5c** the indanodione **20** was also isolated.[11b] Partial[26] or complete demethylation of methoxy groups in **19c** to obtain apomorphine can be readily accomplished by using various reported methods (e.g., refluxing with 57% HI in Ac_2O).

Meyers' coupling[27] is a widely used choice for biaryl coupling, so it was of interest to compare this methodology with the Suzuki coupling to prepare the biphenyl amide **5c** as the key intermediate in the synthesis of **19c**. The reaction of iodobenzene (**21**) with the oxazoline **22** gave the biphenylcarboxylic acid **23** in 61% yield; homologation of this acid led to the amide **5c** in a 55% overall yield from the oxazoline (Scheme 10). The Suzuki coupling approach therefore results in better yield (83 versus 61% in the biaryl bond formation) and is more expeditious as it avoids the need to homologate the side alkyl chain.

3. Conclusions

We prepared biphenyl acetamides and esters by palladium(0) catalyzed Suzuki cross-coupling of phenylboronic acids and phenyl bromides under very mild reaction conditions, all in moderate to good yields, even when the parent compounds were sterically hindered.

We developed a general approach to the total synthesis of aporphinoids in only three steps, namely: (i) Suzuki biaryl cross-coupling as the key step, (ii) sequential bicyclization promoted by oxalyl chloride/Lewis acid, and (iii) reduction of the α-dicarbonyl system. Compared to previously reported methods for the synthesis of aporphine alkaloids, the proposed method is expeditious, convergent on building the oxidized aporphinoids and divergent in its reduction, and cost-saving. Following this pathway, we successfully prepared *O*,*O*′-dimethylapomorphine in 29% yield from the commercial phenylboronic acid **1**.

4. Experimental

4.1. General procedures

Mps. were determined on a Gallenkamp instrument and are given uncorrected. UV spectra were recorded on a Hewlett–Packard 8452A spectrophotometer, and IR spectra on a Perkin–Elmer 883 spectrophotometer. Low resolution MS and GC/MS analyses were carried out on an HP 5988A mass spectrometer coupled to an HP 5980 gas chromatograph furnished with a fused silica capillary column (HP-1, 12 m×0.2 mm i.d., 0.33 mm film thickness). Helium, at a flow-rate of 1 mL min^{-1}, was used as the carrier gas. The column temperature was increased from 200 °C (hold 4 min) to 250 °C at 10 °C min^{-1} and then held at 250 °C for 15 min. High resolution mass spectra (EI and FAB) were recorded on a Kratos MS 50 spectrometer. NMR spectra were obtained on a Bruker WP-200 SY instrument, at 200 MHz for ^1H and 50.3 MHz for ^{13}C, or a Bruker ARX 400 model operating at 400 MHz for ^1H and 100 MHz for ^{13}C. ^1H Chemical shifts (δ_H) are given relative to residual $CHCl_3$ (δ_H 7.24 ppm) in deuteriochloroform, or to residual DMSO in DMSO-d_6. *J* values are in Hz. ^{13}C Chemical shifts (δ_C) are given relative to $CDCl_3$ (δ_C 77.0 ppm) in deuteriochloroform. TLC analyses were performed on silica gel 60 F 256 plates, and column chromatography (cc) on silica gel 60 (70–230 mesh).

Boronic acids **1** and **6** are commercially available and boronic acid **2** was prepared from 1,2-dimethoxy-benzene by treatment with *n*-BuLi, $B(OMe)_3$ followed by acid hydrolysis.[28] Compounds **7**, **8** and **9** were prepared from the corresponding phenylacetic acid, 3,4-dimethoxyphenylacetic acid and 3,4-methylendioxyphenylacetic acid, respectively, by bromination and esterification with $MeOH/H^+$.[29] 2-Bromo-3,4-dimethoxyphenyl acetic acid was prepared from vanillin, using the following synthetic sequence: (i) Br_2/AcOH, (ii) MeI/Na_2CO_3/DMF, (iii) $NaBH_4$/MeOH, (iv) $SOCl_2/CH_2Cl_2$, (v) NaCN/MeCN, (vi) KOH/EtOH–H_2O. From this acid, compounds **3** and **10** were prepared by amidation and esterification, respectively. Amide **4** was prepared from 3,4-methylendioxyphenylacetic acid by bromination and amidation.[30]

4.2. Suzuki cross-coupling reactions

4.2.1. Preparation of biaryl amides 5c and 5j. A mixture of $Pd(PPh_3)_4$ (0.17 mmol, 10 mol%) and bromide **3** or **4** (1.7 mmol) in DME (25 mL) was stirred for 15 min at 20 °C under argon. 2 M aqueous K_2CO_3 (5.9 mL, 11.8 mmol) was added to the mixture, followed by the corresponding boronic acid, **1** or **2** (3.5 mmol) in DME (8 mL). The mixture was refluxed for 18 h and then cooled at 20 °C. The reaction mixture was treated with water and ethyl ether. The organic extracts were washed with 1 M NaOH and water and dried over $MgSO_4$, the solvent being evaporated to dryness to give the biphenyls **5c** and **5j**, which were purified by column chromatography (silicagel, hexane–AcOEt).

(5,6-Dimethoxy)biphenyl-2′-yl N-methyl-acetamide (**5c**). 0.085 g (43%). White solid; mp 119–122 °C (AcOEt); ν (KBr) cm^{-1} 3273, 1644; λ_{max} ($CHCl_3$) nm (log ε) 284 (3.09), 244 (3.65); δ_H ($CDCl_3$) 7.4–7.3 (m, 3H, ArH), 7.2–7.1 (m, 2H, ArH), 7.05 (d, 1H, *J*=8.5 Hz, ArH), 6.91 (d, 1H, *J*=8.5 Hz, ArH), 5.1 (br s, 1H, NH), 3.89 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.26 (s, 2H, CH_2), 2.63 (d, 3H, *J*=4.8 Hz, $NHCH_3$); δ_C ($CDCl_3$) 171.7 (CO), 152.1 (C), 147.0 (C), 137.1 (C), 136.4 (C), 129.5 (2×CH), 128.2 (2×CH), 127.4 (CH), 126.3 (C), 125.9 (CH), 111.9 (CH), 60.6 (OCH_3), 55.8 (OCH_3), 40.8 (CH_2), 26.3 ($NHCH_3$); *m/z* (%) 285 (M^+, 97), 227 (76), 212 (100), 196 (57), 152 (53). Anal. calculated for $C_{17}H_{19}NO_3$: C 71.56, H 4.91, N 6.71%, found: C 71.74, H 4.72, N 6.85.

(2′,3′-Dimethoxy-4,5-methylendioxy)biphenyl-2′-yl N-methyl-acetamide (**5j**). 0.094 g (41%). White solid; mp 176–120 °C

(AcOEt); ν (KBr) cm^{-1} 3297, 1644; λ_{max} ($CHCl_3$) nm (log ε) 282 (3.25), 244 (3.88); δ_H ($CDCl_3$) 7.01 (t, 1H, J=8.0 Hz, ArH), 6.87 (dd, 1H, J=8.0, 1.5 Hz, ArH), 6.82 (s, 1H, ArH), 6.63 (m, 2H, ArH), 5.91 5.1 (br s, 1H, NH), 5.90 (d, 2H, J=2.2 Hz, OCH_2O), 3.83 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.39 (s, 2H, CH_2); 2.61 (d, 3H, J=4.7 Hz, $NHCH_3$); δ_C ($CDCl_3$) 171.9 (CO), 152.6 (C), 147.2 (C), 146.2 (C), 145.9 (C), 134.9 (C), 131.1 (C), 127.2 (C), 124.1 (CH), 122.8 (CH), 111.7 (CH), 109.9 (CH), 109.2 (CH), 101.0 (OCH_2O), 60.7 (OCH_3), 55.6 (OCH_3), 40.8 (CH_2), 26.2 ($NHCH_3$); *m/z* (%) 329 (M^+, 31), 272 (19), 240 (100). Anal. calculated for $C_{18}H_{19}NO_5$: C 65.63, H 5.82, N 4.25%, found: C 65.44, H 5.71, N 4.20.

4.2.2. Preparation of biaryl esters 11a–j. Suzuki coupling of bromo esters **7**–**10** with boronic acids **1**, **2** and **6** and work up were carried out as described above. Biaryl esters **11a**–**j** were purified by crystallization or column chromatography (silicagel, hexane–EtOAc) if necessary. An identical procedure was followed with $Pd(dba)_3$ as catalyst.

Reaction with catalyst **12**. A stirred mixture of bromide **7** (0.30 mmol), boronic acid **1** or **2** (0.32 mmol), K_2CO_3 (0.80 mmol), macrocyclic Pd(0) catalyst (**12**, 5 mol%) water (1 mL) and acetone (2 mL) was heated at 70 °C for 12 h. After cooling to room temperature, water and ether were added. The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated. Column chromatography of the residue on silica gel afforded the corresponding biphenyl esters **11h** and **11j**. Further elution (hexane–EtOAc, 10:5) provided quantitative recovery of the catalyst (**12**).

(2′-Methoxy)biphenyl-2-yl methyl acetate (**11a**). 0.28 g (64%). White solid; mp 39–42 °C (AcOEt); ν (KBr) cm^{-1} 1728 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 280 (3.45), 250 (3.51); δ_H ($CDCl_3$) 7.39–7.30 (m, 4H, ArH), 7.23–7.19 (m, 1H, ArH), 7.15 (dd, 1H, J=7.6, 1.8 Hz, ArH), 7.01 (dt, 1H, J=7.6, 1.2 Hz, ArH), 6.94 (br d, 1H, J=7.6 Hz, ArH), 3.71 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.2 (CO), 156.3 (C), 138.8 (C), 133.0 (C), 131.3 (CH), 130.4 (CH), 129.9 (CH), 129.6 (C), 129.0 (CH), 127.5 (CH), 127.0 (CH), 120.5 (CH), 110.5 (CH), 55.2 (OCH_3), 51.6 (OCH_3), 38.7 (CH_2); *m/z* (%) 256 (M^+, 83), 225 (35), 224 (97), 197 (37), 182 (57), 181 (76), 166 (32), 165 (100), 152 (53); HMRS FAB calculated for $C_{16}H_{17}O_3$ $[M+H]^+$ *m/z* 257.1178, found: 257.1170.

(2′,3′-Dimethoxy)biphenyl-2-yl methyl acetate (**11b**). 0.27 g (56%). Colorless syrup; ν (NaCl) cm^{-1} 1728 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 280 (3.15), 244 (3.60); δ_H ($CDCl_3$) 7.5–7.2 (m, 4H, ArH), 7.09 (t, 1H, J=7.6 Hz, ArH), 6.94 (dd, 1H, J=7.6, 1.5 Hz, ArH), 6.72 (dd, 1H, J=7.6, 1.5 Hz, ArH), 3.88 (2×s, 2×3H, 2×OCH_3), 3.50 (s, 3H, OCH_3), 3.37 (s, 2H, CH_2); δ_C ($CDCl_3$) 174.9 (CO), 152.7 (C), 145.7 (C), 138.0 (C), 135.3 (C), 133.7 (C), 130.1 (C), 129.4 (CH), 128.1 (CH), 126.8 (CH), 124.4 (CH), 122.7 (CH), 111.9 (CH), 60.7 (OCH_3), 60.6 (OCH_3), 55.7 (OCH_3), 40.7 (CH_2); *m/z* (%): 286 (M^+, 100), 255 (20), 227 (66); HRMS FAB calculated for $C_{17}H_{19}O_4$ $[M+H]^+$ *m/z* 287.1283, found: 287.1289.

(5,6-Dimethoxy)biphenyl-2-yl methyl acetate (**11c**). 0.40 g (83%). Yellowish syrup; ν (KBr) cm^{-1} 1726 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 282 (3.17), 246 (3.57); δ_H ($CDCl_3$) 7.40–7.31 (m, 3H, ArH), 7.25–7.17 (m, 2H, ArH), 7.03 (d, 1H, J=8.2 Hz, ArH), 6.90 (d, 1H, J=8.2 Hz, ArH), 3.87 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.35 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.4 (CO), 151.9 (C), 146.7 (C), 137.1 (C), 136.5 (C), 129.6 (2×CH), 127.9 (2×CH), 127.1 (CH), 125.6 (C), 125.4 (CH), 111.5 (CH), 60.5 (OCH_3), 55.7 (OCH_3), 51.7 (OCH_3), 38.3 (CH_2); *m/z* (%): 286 (M^+, 100), 227 (61), 212 (80), 196 (45), 180 (22), 152 (29), 141 (18), 115 (25); HRMS FAB calculated for $C_{17}H_{19}O_4$ $[M+H]^+$ *m/z* 287.1283, found: 287.1292.

(2′,5,6-Trimethoxy)biphenyl-2-yl methyl acetate (**11d**). 0.31 g (58%). Yellowish syrup; ν (KBr) cm^{-1} 1724 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 280 (3.66), 244 (3.65); δ_H ($CDCl_3$) 7.34 (ddd, 1H, J=7.9, 7.3, 1.8 Hz, ArH), 7.08 (dd, 1H, J=7.3, 1.8 Hz, ArH), 7.04 (d, 1H, J=8.2 Hz, ArH), 7.01–6.91 (m, 2H, ArH), 6.90 (d, 1H, J=8.2 Hz, ArH), 3.86 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.30 (s, 6H, 2×OCH_3), 3.30–3.29 (br s, 2H, CH_2); δ_C ($CDCl_3$) 172.3 (CO), 156.7 (C), 151.8 (C), 146.9 (C), 133.3 (C), 131.5 (CH), 129.0 (CH), 126.2 (C), 125.2 (CH), 125.1 (C), 120.3 (CH), 111.5 (CH), 110.5 (CH), 60.4 (OCH_3), 55.7 (OCH_3), 55.3 (OCH_3), 51.6 (OCH_3), 38.2 (CH_2); *m/z* (%) 316 (M^+, 100), 284 (26), 257 (31), 241 (28), 226 (77), 211 (29); HRMS FAB calculated for $C_{18}H_{21}O_5$ $[M+H]^+$ *m/z* 317.1389, found: 317.1379.

(2′,3′,5,6-Tetramethoxy)biphenyl-2-yl methyl acetate (**11e**). 0.18 g (31%). Colorless crystals; mp 63–66 °C; ν (KBr) cm^{-1} 1726 (ν_{CO}) 1726 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 280 (3.50), 244 (3.63); δ_H ($CDCl_3$) 7.05 (dd, 1H, J=8.2, 7.6 Hz, ArH), 7.03 (d, 1H, J=8.2 Hz, ArH), 6.92 (dd, 1H, J=8.2, 1.8 Hz, ArH), 6.90 (d, 1H, J=8.2 Hz, ArH), 6.68 (dd, 1H, J=7.6, 1.8 Hz, ArH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.33–3.32 (sa, 2H, CH_2); δ_C ($CDCl_3$) 172.4 (CO), 152.7 (C), 151.7 (C), 146.7 (C), 146.6 (C), 133.2 (C), 130.7 (C), 126.2 (C), 125.1 (CH), 123.4 (CH), 123.2 (CH), 111.9 (CH), 111.6 (CH), 60.6 (OCH_3), 60.3 (OCH_3), 55.7 (2×OCH_3), 51.7 (OCH_3), 38.2 (CH_2); *m/z* (%) 346 (M^+, 41), 287 (11), 255 (100), 241 (22), 225 (18). Anal. calculated for $C_{19}H_{22}O_6$: C 65.88, H 6.40%, found: C 66.07, H 6.52.

From this reaction, the following compounds were also isolated: veratrol (**14**, 0.69 g) and 2,2′,3,3′-tetramethoxybiphenyl (**13**, 0.22 g), mp 96–99 °C (CH_2Cl_2).[31]

When the reaction was conducted as above, but using K_3PO_4 as base and anhydrous DMF as solvent, **11e** was isolated in a 40% yield.

(2′,4,5-Trimethoxy)biphenyl-2-yl methyl acetate (**11f**). 0.36 g (67%). Syrup that solidified on standing; mp 54–57 °C; ν (KBr) cm^{-1} 1726 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 278 (3.70), 252 (3.71); δ_H ($CDCl_3$) 7.33 (ddd, 1H, J=8.2, 7.3, 1.8 Hz, ArH), 7.16 (dd, 1H, J=7.3, 1.8 Hz, ArH), 6.99 (dt, 1H, J=7.3, 1.8 Hz, ArH), 6.93 (br d, 1H, J=8.2 Hz, ArH), 6.87 (s, 1H, ArH), 6.72 (s, 1H, ArH), 3.90 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.4 (CO), 156.4

(C), 148.0 (C), 147.6 (C), 131.5 (CH), 130.8 (C), 129.4 (C), 128.8 (CH), 124.9 (C), 120.4 (CH), 113.4 (CH), 112.8 (CH), 110.5 (CH), 55.8 (2×OCH_3), 55.2 (OCH_3), 51.6 (OCH_3), 38.2 (CH_2); *m/z* (%) 316 (M^+, 79), 257 (35), 226 (100), 211 (24), 181 (10); HRMS FAB calculated for $C_{18}H_{21}O_5$ $[M+H]^+$ *m/z* 317.1389, found: 317.1399.

(2′,3′,4,5-Tetramethoxy)biphenyl-2-yl methyl acetate (**11g**). 0.26 g (45%). Colorless crystals. Mp 63–65 °C; ν (KBr) cm^{-1} 1739 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 282 (3.72), 248 (3.85); δ_H ($CDCl_3$) 7.05 (dd, 1H, *J*=8.2, 7.3 Hz, ArH), 6.89 (dd, 1H, *J*=8.2, 1.8 Hz, ArH), 6.84 (s, 1H, ArH), 6.76 (dd, 1H, *J*=7.3, 1.8 Hz, ArH), 6.75 (s,1H, ArH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.47–3.46 (br s, 2H, CH_2), 3.46 (s, 3H, OCH_3); δ_C ($CDCl_3$) 172.4 (CO), 152.7 (C), 148.1 (C), 147.4 (C), 146.5 (C), 134.8 (C), 130.5 (C), 124.7 (C), 123.6 (CH), 123.3 (CH), 113.3 (CH), 112.6 (CH), 111.5 (CH), 60.4 (OCH_3), 55.8 (OCH_3), 55.8 (2×OCH_3), 51.6 (OCH_3), 38.2 (CH_2); *m/z* (%) 346 (M^+, 100), 314 (25), 299 (25), 256 (75), 241 (32), 225 (20); HRMS FAB calculated for $C_{19}H_{23}O_6$ $[M+H]^+$ *m/z* 347.1495, found: 347.1498.

From this reaction, **13** (0.20 g) and **14** (0.10 g) were also isolated.

(4,5-Methylenedioxy)biphenyl-2-yl methyl acetate (**11h**). 0.39 g (86%). Yellowish syrup; ν (NaCl) cm^{-1} 1727; λ_{max} ($CHCl_3$) nm (log ε) 294 (3.91), 256 (3.89); δ_H ($CDCl_3$) 7.5–7.2 (m, 5H, ArH), 6.82 (s, 1H, ArH), 6.74 (s, 1H, ArH), 5.98 (s, 2H, OCH_2O), 3.63 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.2 (CO), 146.8 (C), 146.4 (C), 140.7 (C), 135.8 (C), 129.1 (2×CH), 128.0 (2×CH), 126.8 (CH),124.7 (C), 109.9 (CH), 109.8 (CH), 101.0 (OCH_2O), 51.6 (OCH_3), 38.2 (CH_2); *m/z* (%) 270 (M^+, 61), 211 (22), 181 (100), 152 (29), 153 (28). Anal. calculated for $C_{16}H_{14}O_4$: C 71.09, H 5.22%, found: C 71.00, H 5.29.

(2′-Methoxy-4,5-methylenedioxy)biphenyl-2-yl methyl acetate (**11i**). 0.39 g (76%). White solid; mp 70–72 °C; ν (KBr) cm^{-1} 1736 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 284 (3.79), 248 (3.68); δ_H ($CDCl_3$) 7.32 (ddd, 1H, *J*=8.2, 7.3, 1.8 Hz, ArH), 7.11 (dd, 1H, *J*=7.3, 1.8 Hz, ArH), 6.97 (dt, 1H, *J*=7.3, 1.1 Hz, ArH), 6.92 (br d, 1H, *J*=8.2 Hz, ArH), 6.84 (s, 1H, ArH), 6.68 (s, 1H, ArH), 5.96–5.95 (br d, 2H, OCH_2O), 3.71 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.36 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.3 (CO), 156.5 (C), 147.0 (C), 146.5 (C), 132.0 (C), 131.5 (CH), 129.3 (C), 128.9 (CH), 126.2 (C), 120.5 (CH), 110.6 (CH), 110.5 (CH), 110.1 (CH), 101.1 (OCH_2O), 55.3 (OCH_3), 51.7 (OCH_3), 38.4 (CH_2); *m/z* (%) 300 (M^+, 51), 268 (25), 211 (100), 183 (23), 152 (20), 139 (27); HRMS FAB calculated for $C_{17}H_{17}O_5$ $[M+H]^+$ *m/z* 301.1076, found: 301.1063.

(2′,3′-Dimethoxy-4,5-methylenedioxy)biphenyl-2-yl methyl acetate (**11j**). 0.14 g (59%). White solid; mp 122–125 °C (AcOEt); ν (KBr) cm^{-1} 1730; λ_{max} ($CHCl_3$) nm (log ε) 288 (3.89), 252 (3.93); δ_H ($CDCl_3$) 7.07 (t, 1H, *J*=8.0 Hz, ArH), 6.91 (d, 1H, *J*=8.0 Hz, ArH), 6.84 (s, 1H, ArH), 6.74 (d, 1H, *J*=8.0 Hz, ArH), 6.73 (s, 1H, ArH), 5.99 (d, 2H, *J*=2.2 Hz, OCH_2O), 3.90 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.3 (CO), 152.8 (C), 147.0 (C), 146.5 (C), 146.3 (C), 134.9 (C), 131.7 (C), 126.1 (C), 123.8 (CH), 123.4 (CH), 111.8 (CH), 110.2 (CH), 109.9 (CH), 101.1 (OCH_2O), 60.5 (OCH_3), 55.8 (OCH_3), 51.7 (OCH_3), 38.4 (CH_2); *m/z* (%) 330 (M^+, 50), 315 (70), 271 (18), 241 (100). Anal. calculated for $C_{18}H_{18}O_6$: C 65.43, H 5.50%, found: C 65.42, H 5.51.

4.3. Preparation of amides 5a–c, 5e and 5j

A solution of esters **11a–c**, **11e** and **11j** (1.2 mmol), sodium cyanide (5.8 mg, 0.12 mmol) and methylamine (5 mL, 58 mmol) in methanol (10 mL) held in a sealed round-bottom flask was stirred at 60 °C (bath temperature). After 2 h, the methanol was removed in vacuo, and the residue was dissolved in CH_2Cl_2. This solution was washed with water, dried and evaporated to dryness to obtain the corresponding amides (**5a–c**, **5e** and **5j**).

4.3.1. Compound 5a. 0.29 g (96%). White solid; mp 125–126 °C (Lit.[11] 125–126 °C). **5b**: 0.30 g (89%), white solid; mp 92–94 °C (Lit.[11] 93–96 °C). **5c**: 0.31 g (92%), white solid; mp 119–121 °C. **5e**: 0.34 g (82%), yellowish syrup.[11] **5j**: 0.33 g (85%), white solid; mp 176–180 °C.

4.3.2. Preparation of 5k. A mixture of ester **11a** (1.0 g, 3.9 mmol) and KOH (1.5 g, 26.3 mmol) in water (40 mL) was refluxed to complete dissolution of the ester (ca. 30 min). The reaction mixture was then cooled at room temperature and acidified with conc. HCl. The white solid was filtered off, dried and dissolved in benzene (60 mL). Over this solution cooled at 5 °C, pyridine (0.5 mL) and oxalyl chloride (6.11 mL, 70.2 mmol) were added, the latter dropwise. The mixture was stirred at 20 °C for 1 h. Benzene and excess reagent were removed in vacuo and the resulting acid chloride was dissolved in chloroform (3 mL). This solution was added to a cooled (0 °C) mixture of *p*-anisidine (3.1 mL, 35.1 mmol), TEA (1.3 mL) and chloroform (6 mL). The reaction mixture was stirred at 20 °C for 1/2 h and washed sequentially with 1 M NaOH, 1 M HCl and water. The organic solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the amide **5k** (1.04 g), in 85% yield, as a white solid; mp 124–126 °C (acetone); ν (KBr) cm^{-1} 3304, 2937, 1724, 1510; λ_{max} ($CHCl_3$) nm (log ε) 248 (3.84); δ_H ($CDCl_3$) 7.5–6.7 (m, 12H, ArH), 3.75 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.51 (s, 2H, CH_2); δ_C ($CDCl_3$) 169.1 (CO), 156.1 (2×C), 138.9 (C), 133.5 (C), 129.4 (C), 131.1 (CH), 130.9 (CH), 130.0 (CH), 129.2 (CH), 128.1 (CH), 127.4 (CH), 121.3 (2×CH), 120.9 (CH), 113.9 (2×CH), 111.0 (CH), 55.5 (OCH_3), 55.3 (CH_2), 42.3 (CH_2); *m/z* (%) 347 (M^+, 14), 165 (25), 181 (10), 182 (11), 123 (100). Anal. calculated for $C_{22}H_{21}NO_3$: C 76.05, H 6.10, N 4.03%, found: C 76.40, H 6.01, N 4.09.

4.3.3. Reaction of biarylacetamides 5a–c, 5e, 5j and 5k with $(COCl)_2/SnCl_4$. Over a N_2 degassed solution of the biphenyl acetamides (**5**, 4 mmol) in dichloromethane (8 mL) oxalyl chloride (0.83 mL, 10 mmol) was added. The flask was tightly sealed with a septum and heated at 60 °C, and stannyl chloride (1.2 mL, 10 mmol) was added. The reaction mixture was stirred at 60 °C (oil bath temperature) for 24 h, diluted with dichloromethane and supplied with 2 M HCl. The dichloromethane was separated and washed with water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The reaction crude was

purified by preparative tlc (SiO_2, 20:0.4 CH_2Cl_2:CH_3OH) to obtain the aporphinoids **15a**–**c**, **15e**, **15j**,**k**.

2-Demethoxy-cepharadione-B (**15a**). 1.09 g (96%). Yellow-orange solid; mp 256–258 °C (EtOH) (Lit.[10a] 255–257 °C).

Cepharadione-B(**15b**). 0.84 g (65%). Orange solid; mp 266–270 °C (EtOH) (Lit.[32] 266–268 °C).

4,5-Dioxo-O,O′-dimethylapomorphine (**15c**). 0.55 g (43%). Red solid; mp 215–217 °C ($CHCl_3$/MeOH); ν (KBr) cm^{-1} 3480, 1652; λ_{max} (EtOH) nm (log ε): 460 (3.52), 374 (3.25), 318 (3.61), 250 sh (4.13), 240 (4.19), 204 (4.13); δ_H ($CDCl_3$) 10.09 (dd, 1H, *J*=8.5, 1.0 Hz, ArH), 8.62 (dd, 1H, *J*=8.5, 1.0 Hz, ArH), 7.88 (t, 1H, *J*=8.5 Hz, ArH), 7.67 (d, 1H, *J*=8.7 Hz, ArH), 7.52 (s, 1H, H-7), 7.39 (d, 1H, *J*=8.7 Hz, ArH), 4.05 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.84 (s, 3H, NCH_3); δ_C ($CDCl_3$) 176.7 (CO), 156.5 (CO), 152.2 (C), 146.9 (C), 136.0 (CH), 130.7 (C), 130.0 (C), 129.1 (CH), 128.0 (CH), 127.4 (C), 127.3 (C), 125.6 (CH), 123.4 (C), 121.7 (C), 115.1 (CH), 114.5 (CH), 59.8 (OCH_3), 55.5 (OCH_3), 30.5 (NCH_3); *m/z* (%) 321 (M^+, 100), 293 (12), 278 (34), 250 (32), 235 (38). Anal. calculated for $C_{19}H_{15}NO_4$: C 71.01, H 4.71, N 4.36%, found: C 71.05, H 4.80, N 4.39.

From the crude of this reaction, 1-methyl-6,7-dimethoxy-dibenzo[*e*,*g*]indano-4,5-dione (**20**) was also isolated: 64 mg (19%), red solid; mp 164–169 °C; ν (KBr) cm^{-1} 1698; λ_{max} ($CHCl_3$) nm (log ε): 414 (2.67), 346 sh (3.12), 304 (3.53), 258 (4.09); δ_H ($CDCl_3$) 9.79 (m, 1H, ArH), 8.66 (d, 1H, *J*=8.8 Hz, ArH), 8.49 (m, 1H, ArH), 7.82 (dt, 1H, *J*=8.6, 1.5 Hz, ArH), 7.64 (dt, 1H, *J*=8.6, 1.2 Hz, ArH), 7.37 (d, 1H, *J*=8.8 Hz, ArH), 4.03 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.79 (s, 3H, NCH_3); δ_C ($CDCl_3$) 182.0 (CO), 160.5 (CO), 154.5 (C), 151.3 (C), 147.0 (C), 136.3 (C), 131.6 (CH), 129.6 (CH), 127.1 (CH), 124.6 (CH), 122.2 (C), 121.8 (C), 121.6 (C), 120.2 (CH), 115.8 (CH), 60.0 (OCH_3), 56.5 (OCH_3), 31.7 (NCH_3); *m/z* (%) 321 (M^+, 100), 306 (7), 293 (7), 278 (28), 250 (25); HRMS calculated for $C_{19}H_{15}NO_4$ [M^+] *m/z* 321.1001, found: 321.1000.

4,5-Dioxodehydrocorydine (**15e**). 1.07 g (73%). Orange solid; mp 258–262 °C (EtOH) (Lit.[11] 258–262 °C).

Corydione (**15j**). 0.57 g (39%). Red solid; mp 267–272 °C (MeOH) (Lit.[33] 273–275 °C).

N-p-(Methoxyphenyl)-2-demethoxy-cepharadione-B (**15k**). 0.67 g (61%). Yellow solid; mp >300 °C ($CHCl_3$); ν (KBr) cm^{-1} 1650; δ_H (DMSO-d_6) 9.50 (br d, 1H, *J*=8.7 Hz, H-11), 8.64 (d, 1H, *J*=8.8 Hz, ArH), 7.78–7.74 (m, 2H, ArH), 7.70–7.57 (m, 2H, ArH), 7.40 (d, 2H, *J*=8.8 Hz, ArH), 7.20 (d, 2H, *J*=8.8 Hz, ArH), 6.94 (s, 1H, H-7), 4.32 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3); δ_C ($CDCl_3$+TFA) 176.0 (CO), 160.6 (C), 159.0 (CO), 134.1 (C), 131.7 (C), 131.5 (CH), 131.3 (CH), 130.4 (CH), 129.5 (CH), 129.3 (2×CH), 128.3 (CH), 128.0 (CH), 124.3 (C), 122.4 (C), 120.1 (C), 116.1 (2×CH), 115.0 (C), 114.8 (C), 114.7 (C), 112.1 (CH), 57.0 (OCH_3), 55.9 (OCH_3); *m/z* (%) 383 (M^+, 59), 355 (100), 340 (53). Anal. calculated for $C_{24}H_{17}NO_4$: C 75.17, H 4.47, N 3.66%, found: C 75.27, H 4.51, N 3.88.

From this reaction, 8-methoxy-phenanthro[9,10-*b*]furano-4,5-dione (**16**) was also isolated: 0.16 g (18%), red solid; mp 196–198 °C dec. (Lit.[11] 196–197 °C)..

4.4. Synthesis of 5c by Meyers' coupling

4.4.1. Preparation of 23. Iodobenzene **21** (3 g, 14.7 mmol) was added over a mixture of magnesium (0.39 g, 1.6 mmol) in dry THF (80 mL). After refluxing for 1 h, the reaction mixture was cooled. Then, a solution of the oxazoline **22**[27] (2.1 g, 7.9 mmol) in dry THF (60 mL) was added. After 30 min at 20 °C, the reaction mixture was refluxed for 5 h. The solvent was removed and the residue dissolved in CH_2Cl_2. The organic layer was washed with 1 M HCl, water, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was treated with MeI (100 mL) at 20 °C for 12 h. The excess MeI was removed in vacuo and a 1:1 solution of methanol:20% aq. NaOH was added. The solution was refluxed for 12 h, the MeOH being removed in vacuo and the residue dissolved in 1 M NaOH. The aqueous layer was washed with TBME, acidified with concentrated HCl, diluted with water and filtered to obtain **23** as a white solid; overall yield: 1.3 g (61%); mp 190–195 °C (Et_2O); ν (KBr) cm^{-1} 3500–2300, 1685, 1673; λ_{max} ($CHCl_3$) nm (log ε): 286 sh (3.21), 252 (3.71); δ_H ($CDCl_3$+TFA) 7.94 (d, 1H, *J*=8.8 Hz, ArH), 7.4–7.3 (m, 3H, ArH), 7.25–7.15 (m, 2H, ArH), 7.01 (d, 1H, *J*=8.8 Hz, ArH), 3.97 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3); δ_C ($CDCl_3$+TFA) 172.9 (CO), 157.3 (C), 145.9 (C), 139.6 (C), 135.6 (C), 129.5 (CH), 128.8 (2×CH), 127.8 (2×CH), 127.6 (CH), 120.6 (C), 110.8 (CH), 61.0 (OCH_3), 56.0 (OCH_3); *m/z* (%) 258 (M^+, 100), 225 (36), 184 (29). Anal. calculated for $C_{45}H_{44}O_{13}$: C 68.17, H 5.59%, found: C 67.87, H 5.42.

4.4.2. Homologation reaction. A N_2 purged solution of **23** (1 g, 3.9 mmol) in dry THF (20 mL) was supplied with LAH (0.17 g, 4 mmol) in small portions over a period of 30 min. After stirring the reaction medium for 1 h at 20 °C, excess hydride was decomposed by addition of 1 M H_2SO_4 and the resulting suspension treated with more dilute acid and extracted with TBME. The extracts were carefully dried over $MgSO_4$ and the volume reduced to 15 mL. This ether solution was ice cooled and thionyl chloride (0.44 mL, 5.9 mmol) was added dropwise. The mixture was stirred at 20 °C for 30 min. TBME and excess thionyl chloride were removed in vacuo. The crude product was dissolved in acetonitrile (40 mL), NaCN (2 g, 40 mmol) being then added and the mixture refluxed for 48 h. After evaporation of the solvent, the residue was dissolved in H_2O, extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under reduced pressure to obtain a white solid.

To an ice cooled solution of this solid (0.9 g, 3.3 mmol) and pyridine (0.3 mL) in benzene (50 mL), oxalyl chloride (5.8 mL, 66 mmol) was added dropwise. The mixture was stirred at 20 °C for 30 min. Benzene and excess reagent were removed in vacuo and the resulting acid chloride was dissolved in acetone (3 mL). This solution was added to a cooled mixture of methylamine (40% in water, 2.6 mL, 33 mmol), TEA (1.2 mL) and water (2 mL). The reaction mixture was stirred at 20 °C for 1 h and washed sequentially with 1 M NaOH, 1 M HCl, and water. The organic solution

was dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain **5c**. Overall yield: 0.84 g (90%).

4.5. Reduction of 4,5-dioxoaporphines

4.5.1. Reduction with BH_3·THF. A mixture of the 4,5-dioxoaporphines **15a**,**b** (0.2 mmol) and BH_3·THF (3 mL) under an N_2 atmosphere at 0 °C was slowly warmed to 20 °C (3 h). The reaction mixture was concentrated to dryness and the residue dissolved in chloroform. The organic layer was washed with water, dried over $MgSO_4$ and concentrated in vacuo to obtain the 4-hydroxy-dehydroaporphines **17a**,**b**.

4-Hydroxy-2-demethoxy-dehydronuciferine (**17a**). 0.040 g (72%). Syrup; ν (KBr) cm^{-1} 3349; λ_{max} ($CHCl_3$) nm (log ε): 374 sh (3.17), 330 (3.67), 266 (4.09), 250 (4.16); δ_H ($CDCl_3$) 9.49 (br dd, 1H, *J*=8.3 Hz, H-11), 7.71 (dd, 1H, *J*=8.3, 1.3 Hz, H-8), 7.53, 7.16 (2×d, 2×1H, *J*=8.0 Hz, H-2, H-3), 7.5–7.3 (m, 2H, H-9, H-10), 6.86 (s, 1H, H-7), 4.95 (br t, 1H, H-4), 4.10 (s, 3H, OCH_3), 3.42 (dd, 1H, *J*=11.5, 3.5 Hz, H-5), 3.49 (dd, 1H, *J*=11.5, 2.7 Hz, H-5), 3.14 (s, 3H, NCH_3); δ_C ($CDCl_3$) 159.1 (C-1), 142.0 (C), 133.8 (C), 128.3 (CH), 127.8 (C), 126.6 (CH), 126.4 (CH), 126.1 (CH), 125.1 (C), 124.4 (C), 123.1 (CH), 121.4 (C), 108.7 (CH), 105.4 (CH), 68.0 (C-4), 57.5 (CH_2), 55.8 (OCH_3), 40.5 (NCH_3); *m*/*z* (%) 279 (M^+, 100), 264 (14), 246 (41). Anal. calculated for $C_{18}H_{17}NO_2{\cdot}1H_2O$: C 72.71, H 6.44, N 4.71%, found: C 72.81, H 6.47, N 4.80.

4-Hydroxy-dehydronuciferine (**17b**). 0.049 g (79%). Syrup; ν (KBr) cm^{-1} 3373; λ_{max} ($CHCl_3$) nm (log ε): 376 sh (2.85), 332 (3.50), 292 sh (3.44), 256 (4.01); δ_H ($CDCl_3$) 9.46 (br dd, 1H, *J*=8.0, 1.8 Hz, H-11), 7.67 (dd, 1H, *J*=8.0, 1.4 Hz, H-8), 7.47 (dt, 1H, *J*=8.0, 1.8 Hz, H-9), 7.36 (dt, 1H, *J*=8.4, 1.0 Hz, H-10), 7.32 (s, 1H, H-3), 6.67 (s, 1H, H-7), 4.92 (br t, 1H, H-4), 4.02 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.51 (dd, 1H, *J*=11.4, 2.6 Hz, H-5), 3.41 (dd, 1H, *J*=11.4, 3.8 Hz, H-5′), 3.11 (s, 3H, NCH_3); δ_C ($CDCl_3$) 151.5 (C-1), 147.2 (C-2), 142.0 (C), 134.4 (C), 130.4 (C), 127.7 (CH), 127.0 (CH), 126.6 (CH), 125.7 (C), 124.6 (C), 123.4 (CH), 118.1 (C), 111.6 (CH), 103.1 (CH), 68.3 (C-4), 59.7 (OCH_3), 57.6 (CH_2), 56.3 (OCH_3), 40.4 (NCH_3); *m*/*z* (%) 309 (M^+, 100); HRMS calculated for $C_{19}H_{19}NO_3$ [M^+] *m*/*z* 309.1365, found: 309.1364.

4.5.2. Reaction with BH_3·THF followed by Clemmensen reduction. A mixture of **15a**–**c** (0.2 mmol) and BH_3·THF (2 mL) under N_2 was refluxed for 5 h. The reaction mixture was concentrated in vacuo to obtain the corresponding dehydroaporphinoids **18** (^{1}H NMR), which, without further purification, were dissolved in conc. HCl (5 mL) and a mixture of Zn (dust, 1 g), $HgCl_2$ (0.06 g), conc. HCl (0.1 mL) and water (2 mL) was added. The reaction mixture was refluxed for 1 h, cooled and filtered, the filter being washed with 20% HCl. The filtrates were basified with 30% NaOH and extracted with chloroform. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated to dryness to obtain the corresponding aporphinoids **19a**–**c**.

(±)-2-Demethoxy-nuciferine (**19a**). 0.040 g (76%). Syrup; ν (NaCl) cm^{-1} 1456, 1262, 1237, 1095, 1049, 799, 743; λ_{max} (EtOH) nm (log ε): 304 (3.47), 272 (3.75), 216 (4.11); δ_H ($CDCl_3$) 8.25 (m, 1H, H-11), 7.13–7.32 (m, 3H, ArH), 7.04 (d, 1H, *J*=8.4 Hz, ArH), 6.88 (d, 1H, *J*=8.4 Hz, ArH), 3.85 (s, 3H, OCH_3), 3.2–3.0 (m, 4H), 2.8–2.4 (m, 3H), 2.54 (s, 3H, NCH_3); δ_C ($CDCl_3$) 154.8 (C-1), 136.4 (C), 136.0 (C), 132.1 (C), 128.6 (CH), 128.4 (CH), 127.5 (CH), 126.7 (CH), 126.3 (CH), 125.3 (C), 121.8 (C), 110.7 (CH), 62.8 (C-6a), 55.6 (OCH_3), 53.2 (CH_2), 43.9 (NCH_3), 34.6, 28.4 (2×CH_2); *m*/*z* (%) 266 (M^+, 17), 265 (95), 264 (100), 222 (82); HRMS calculated for $C_{18}H_{19}NO$ [M^+] *m*/*z* 265.1466, found: 265.1461.

(±)-Nuciferine (**19b**). 0.037 g (83%). Yellowish syrup which crystallizes on standing; mp 133–136 °C (Lit.[4a] 134.5–135.5 °C).

(±)-O,O-Dimethylapomorphine (**19c**). 0.047 g (78%), yellowish syrup.[34]

Acknowledgements

Financial support from the Spanish Government (Project DGI BQU 2001/1890) is gratefully acknowledged. F. J. O. L. also wishes to acknowledge an award of a grant from this project.

References and notes

1. (a) Kametani, T. In *Aporphine Alkaloids. The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. XXIV, pp 153–251, Chapter 4. (b) Shamma, M.; Moniot, J. L. *The Isoquinoline Alkaloids Research, 1972–1977*; Plenum: New York, 1978. (c) Shamma, M. The Isoquinoline Alkaloids. *Organic Chemistry*; Blomquist, A. T., Wasserman, H., Eds.; Academic: New York, 1972; Vol. 25. (d) Bentley, K. W. Aporphinoid Alkaloids. *The Isoquinoline Alkaloids*; Ravindranath, B., Ed.; Harwood Academic: Bangalore, 1998; Vol. 1, pp 131–181, part 8. (e) Bentley, K. W. *Nat. Prod. Rep.* **2003**, *20*, 342–365, and previous reviews on aporphinoids.
2. (a) Kametani, T.; Sugi, H.; Shibuya, S.; Fukumoto, K. *Chem. Pharm. Bull.* **1971**, *19*, 1513–1519. (b) Cava, M.; Lakshmikanthan, M. V. *J. Org. Chem.* **1970**, *35*, 1867–1869. (c) Suess, T.; Stermitz, F. R. *J. Nat. Prod.* **1981**, *44*, 688–692.
3. (a) Kametani, T.; Ihara, M.; Takemura, M.; Satoh, Y.; Terasawa, H.; Ohta, Y.; Fukumoto, K.; Takahashi, K. *J. Am. Chem. Soc.* **1977**, *99*, 3805–3808. (b) Kametani, T.; Ihara, M.; Takemura, M.; Satoh, Y.; Terasawa, H.; Ohta, Y.; Fukumoto, K.; Takahashi, K. *J. Am. Chem. Soc.* **1977**, *99*, 3805–3808. (c) Hoshino, O.; Umezawa, B. Lead tetraacetate oxidation in alkaloid synthesis. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1989; Vol. 36, p 69, Chapter 2. (d) Hoshino, O.; Ogasawara, H.; Arasawa, M. *Heterocycles* **1993**, *35*, 1005–1014. (e) Hara, H.; Komoriya, S.; Mayashita, T.; Hoshino, O. *Tetrahedron: Asymmetry* **1995**, *6*, 1683–1692. (f) Landais, Y.; Rambault, D.; Robin, J.-P. *Tetrahedron Lett.* **1987**, *28*, 543–546. (g) Landais, Y.; Robin, J.-P. *Tetrahedron* **1992**, *48*, 7185–7196. (h) Planchenault, D.; Dhal, R.; Robin, J.-P. *Tetrahedron* **1993**, *49*, 5823–5830. (i) Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *Can. J. Chem.* **1987**, *65*,

2356–2361. (j) Gottlieb, L.; Meyers, A. I. *J. Org. Chem.* **1990**, *55*, 5659–5662.
4. (a) Cava, M. P.; Mitchell, M. J.; Havlizek, S. C.; Lindert, A.; Spangler, R. J. *J. Org. Chem.* **1970**, *35*, 175–179. (b) Lenz, G. R. *Synthesis* **1978**, 489–518. (c) Yang, N. C.; Lenz, G. R.; Shani, A. *Tetrahedron Lett.* **1966**, *7*, 2941–2946. (d) Lenz, G. R. *J. Org. Chem.* **1988**, *53*, 4447–4452. (e) Atanes, N.; Castedo, L.; Guitián, E.; Saá, J. M. *Heterocycles* **1987**, *26*, 1183–1184. (f) Cava, M. P.; Libsch, S. S. *J. Org. Chem.* **1974**, *39*, 577–578.
5. (a) Castedo, L.; Guitián, E.; Saá, J. M.; Suau, R. *Tetrahedron Lett.* **1982**, *23*, 457–458. (b) Saá, C.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron Lett.* **1985**, *26*, 4559–4560. (c) Atanes, N.; Castedo, L.; Guitián, E.; Saá, C.; Saá, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984–2988. (d) Castedo, L.; Guitián, E.; Saá, C.; Suau, R.; Saá, J. M. *Tetrahedron Lett.* **1983**, *24*, 2107–2108. (e) Atanes, N.; Pérez, S.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron* **1994**, *50*, 11257–11266. (f) Atanes, N.; Castedo, L.; Cobas, A.; Guitián, E.; Saá, C.; Saá, J. M. *Tetrahedron* **1989**, *45*, 7947–7956. (g) Gómez, B.; Martín, G.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron* **1993**, *49*, 1251–1256.
6. (a) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron Lett.* **1991**, *32*, 529–530. (b) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Heterocycles* **1994**, *38*, 1–4. (c) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1994**, *50*, 2107–2114. (d) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 4075–4082. (e) Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 307–310.
7. (a) Fürstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112–2113. (b) Cuny, G. D. *Tetrahedron Lett.* **2003**, *44*, 8149–8152.
8. (a) Yasuda, M.; Hamasuna, S.; Yamano, K.; Kubo, J.-i.; Shima, K. *Heterocycles* **1992**, *34*, 965–977. (b) Lewis, F. D.; Reddy, G. D.; Cohen, B. E. *Tetrahedron Lett.* **1994**, *35*, 535–538. (c) Gerecke, M.; Brossi, A. *Helv. Chim. Acta* **1979**, *62*, 1549–1558. (d) Seijas, J. A.; de Lera, A. R.; Villaverde, M. C.; Castedo, L. *J. Chem. Soc. Chem. Commun.* **1985**, 839–840. (e) Seijas, J. A.; de Lera, A. R.; Villaverde, M. C.; Castedo, L. *Heterocycles* **1985**, *23*, 3079–3084. (f) Ramana, M. M. V.; Potnis, P. V. *Tetrahedron Lett.* **1996**, *37*, 1671–1672.
9. Guinaudeau, H.; Leboeuf, M.; Cave, A. *J. Nat. Prod.* **1994**, *57*, 1033–1135, and references therein.
10. (a) Suau, R.; López-Romero, J. M.; Rico, R.; Alonso, F. J.; Lobo, C. *Tetrahedron* **1996**, *52*, 11307–11320. (b) Wijeratne, E. M. K.; Gunatilaka, A. A. L.; Kingston, D. G. I.; Haltiwanger, R. C.; Eggleston, D. S. *Tetrahedron* **1995**, *51*, 7877–7882. (c) Stévigny, C.; Block, S.; de Pauw-Gillet, M. C.; de Hoffmann, E.; Llabrès, G.; Adjakidjé, V.; Quetin-Leclercq, J. *Planta Med.* **2002**, *68*, 1042–1044. (d) Jantan, I.; Abdul Rafi, I. A.; Jalil, J. *Planta Med.* **2001**, *67*, 466–467. (e) Hoarau, C.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2001**, 2559–2567.
11. (a) Suau, R.; López-Romero, J. M.; Rico, R. *Tetrahedron Lett.* **1996**, *37*, 9357–9360. (b) Suau, R.; López-Romero, J. M.; Rico, R. *Tetrahedron* **1997**, *53*, 14397–14410.
12. (a) Suau, R.; Rico, R.; López-Romero, J. M.; Nájera, F.; Ruiz, A.; Ortiz, F. J. *Arkivoc* **2002**, *v*, 62–72. (b) Suau, R.; López-Romero, J. M.; Rico, R.; Ruiz, A. *Tetrahedron* **2000**, *56*, 993–998.
13. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
14. (a) Nicolau, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152. (b) Shi, Q.; Chen, K.; Morris-Natschke, S. L.; Lee, K. H. *Curr. Pharm. Des.* **1998**, *4*, 219–248. (c) Gussio, R.; Zaharevitz, D. W.; McGrath, C. F.; Pattabiraman, N.; Kellogg, G.; Schultz, C.; Link, A.; Kunick, C.; Leost, M.; Meijer, L.; Sausville, E. A. *Anticancer. Drug Des.* **2000**, *15*, 53–66, and references therein. (d) Birkenhager, W. H.; de Leeuw, P. W. *J. Hypertens.* **1999**, *17*, 873–881.
15. (a) Cortés, J.; Moreno-Mañas, M.; Pleixats, R. *Eur. J. Org. Chem.* **2000**, 239–243. (b) Cerezo, S.; Cortés, J.; Galván, D.; Lago, E.; Marchi, C.; Molins, E.; Moreno-Mañas, M.; Pleixats, R.; Torrejón, J.; Vallribera, A. *Eur. J. Org. Chem.* **2001**, 329–337.
16. Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351.
17. The structures of the compounds studied were fully optimized using theoretical ab initio calculations involving the 6-31G* basis set.
18. Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. J. *J. Org. Chem.* **1987**, *52*, 2033–2036.
19. Speziale, A.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 3742–3742.
20. (a) N-Deprotection with CAN: Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765–2768. (b) With silver nitrate: Bhattarai, K.; Cainelli, G.; Panunzio, M. *Synlett* **1990**, 229–230. (c) Anodic oxidation: Corley, E. G.; Karady, S.; Abramson, N. L.; Ellison, D.; Weinstock, L. M. *Tetrahedron Lett.* **1988**, *29*, 1497–1500.
21. The BH_3·THF complex has been used for the reduction of isatin to indole, albeit in a moderate yield. Jiang, B.; Smallher, J. M.; Amaral-Ly, C.; Wuonola, M. A. *J. Org. Chem.* **1994**, *59*, 6823–6827.
22. Menon, M.; Clark, W. G.; Neumeyer, J. L. *Eur. J. Pharmacol.* **1978**, *52*, 1–9.
23. Lashuel, H.; Hartley, D. M.; Balakhaneh, D.; Aggarwal, A.; Teichberg, S.; Callaway, D. J. E. *J. Biol. Chem.* **2002**, *45*, 42881–42890.
24. Gottlieb, R.; Neumeyer, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 7108–7109.
25. (a) Neumeyer, J. L.; Neustadt, B. R.; Weinhardt, K. K. *J. Pharm. Sci.* **1970**, *59*, 1850–1852. (b) Sugasawa, S.; Tachikawa, R. *Tetrahedron* **1958**, *4*, 205–212. (c) Neumeyer, J. L.; Neustadt, B. R.; Oh, K. H.; Weinhardt, K. K.; Boyce, C. B. *J. Med. Chem.* **1973**, *16*, 1223–1228.
26. Davis, P.; Abdel-Maksoud, H.; Trainor, T. M.; Vouros, P.; Neumeyer, J. L. *Biochem. Biophys. Res. Commun.* **1985**, *127*, 407–412.
27. Meyers, A.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383–7385.
28. Prévot-Halter, I.; Smith, T.; Weiss, J. *J. Org. Chem.* **1997**, *62*, 2186–2192.
29. Kulka, M.; Manske, R. *J. Am. Chem. Soc.* **1953**, *75*, 1322–1324.
30. Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H.; et al. *J. Org. Chem.* **1999**, *64*, 6583–6596.
31. Horner, L.; Weber, K. H. *Chem. Ber.* **1963**, *96*, 1568–1571.
32. Akasu, M.; Itokawa, H.; Fujita, M. *Tetrahedron Lett.* **1974**, *15*, 3609–3612.
33. Kiryakov, H.; Iskrenova, E. S. *Planta Med.* **1980**, *39*, 210–210.
34. Kim, C.; Kim, M. S.; Yoon, U. C. *Bull. Kor. Chem. Soc.* **1985**, *6*, 172–173.