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A combined RCM-Bischler–Napieralski strategy towards the synthesis of the carbon skeleton of excentricine and related stephaoxocanes

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ABSTRACT

A convenient synthetic approach to a cyclodeca[*ij*]isoquinoline derivative, which embodies the carbon skeleton of excentricine and related stephaoxocanes, is described. The synthesis involves the combined use of ring closing metathesis and Bischler–Napieralski cyclizations for the construction of the homocyclic and nitrogen-bearing rings, respectively.

1. Introduction

Plants employed as sources of traditional herbal remedies are currently being scrutinized as part of the great worldwide effort aimed to identify novel structures, develop new bioactive compounds and turn them into powerful medicines.[1] In the past two decades, plants of the genera *Stephania* and *Cissampelos* (Menispermaceae) have gained considerable attention; their extracts[1a,2] and several alkaloids isolated from them were shown to be bioactive.[2a,3]

Phytochemical investigations carried out during the last 15 years in China, Brazil and Japan revealed the existence of the stephaoxocanes, as a small family of eight isoquinoline alkaloids, characterized by carrying the unique tetracyclic stephaoxocane skeleton (**1a**).[4a] These alkaloids were isolated from *Stephania cepharantha* Hayata, *Stephania excentrica* H. S. Lo, *Stephania longa* Lour and *Cissampelos glaberrima* A. St. Hill, and include compounds with the nitrogen-bearing heterocyclic ring at the isoquinoline level (Fig. 1), such as in stephaoxocanidine (**1b**)[4a] and eletefine (**1c**);[4b] in addition, they comprise a single example of a dihydroisoquinoline-type compound (stephaoxocanine, **2**)[4c] and also several tetrahydroisoquinolines [excentricine (**3a**)[4d] and stephalonganines A (**3b**) and B (**3c**)][4e] and their *N*-methyl derivatives [*N*-methylexcentricine (**3d**)[4f] and stephalonganine C (**3e**)].[4e]

The natural sources of the stephaoxocanes are herbaceous perennial wines or climbers employed in diverse folk medicine systems of South America[5] and the Far East, including Traditional Chinese Medicine.[6] Their uses include indications as diuretic, antiphlogistic, antirheumatic, antiinflammatory, analgesic and stomachic agents, being also prescribed to treat different conditions, such as dysentery, leukopenia, bleeding, urinary infections, parotiditis, asthma, inflammation and fever.[7] Despite their scarcity, potential biological activity and intriguing structures, little work has been carried out in the area of synthesis of stephaoxocanes and their analogues.[8]

As part of our interest in the study of the synthesis and biological activity of the stephaoxocanes, we have reported the syntheses of 1,9-oxazafluoranthenes **4** and **5**,[9a–c] which embody the ABC-ring system of the stephaoxocanes and demonstrated that tricyclic lactone **5** and some of its derivatives are inhibitors of the enzyme acetylcholinesterase, a therapeutic target for the treatment of Alzheimer's disease, their potency being equivalent to that of a daffodil (*Narcissus pseudonarcissus*) extract enriched in the approved anti-Alzheimer's drug galanthamine.[9d]

More recently, we have also disclosed the sequential use of ring closing metathesis (RCM) and Jackson's cyclization for the preparation of compounds **6** and **7**, which correspond to the carbon framework of different stephaoxocanes.[10]

Herein, we describe a modification of our original strategic sequence that has culminated in the synthesis of cyclodeca[*ij*]isoquinoline derivative **7**, which embodies the carbon skeleton of the stephaoxocanes, displaying the nitrogenated ring as

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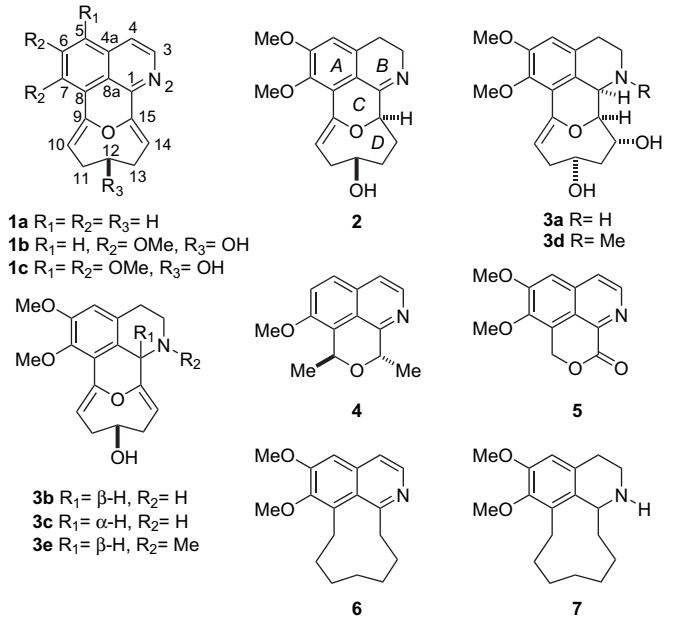


Figure 1. Chemical structures of the stephaoxocane skeleton **1a**, naturally occurring stephaoxocanes (**1b**, **1c**, **2** and **3a**–**e**), synthetic tricyclic analogues of the stephaoxocanes (**4**–**6**) and the proposed target (**7**).

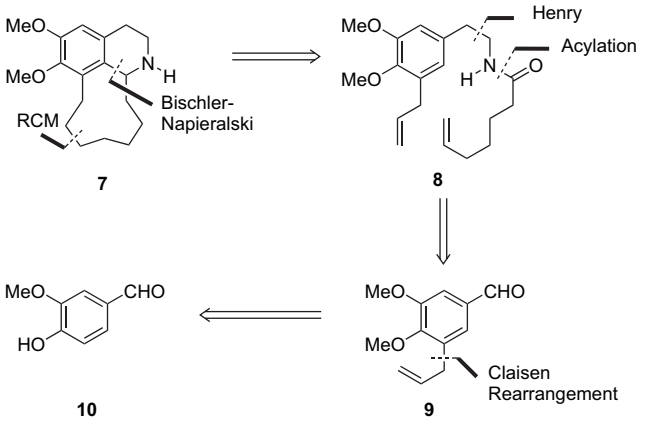
found in excentricine and stephalonganines A and B. This approach entails the use of a RCM for the preparation of macrocyclic compounds and Bischler–Napieralski's isoquinoline synthesis for accessing the nitrogen-bearing heterocyclic ring.

Although RCM has been employed in several strategies towards the elaboration of isoquinoline derivatives,[11] the combined use of RCM and Bischler–Napieralski cyclization has scarce precedents.[12] In principle, however, a sequence containing this association of synthetic transformations should be advantageous over our previously described approach to **7**,[10] resulting in shorter routes towards the target, which may also make less use of protecting groups or even avoid their utilization.

2. Results and discussion

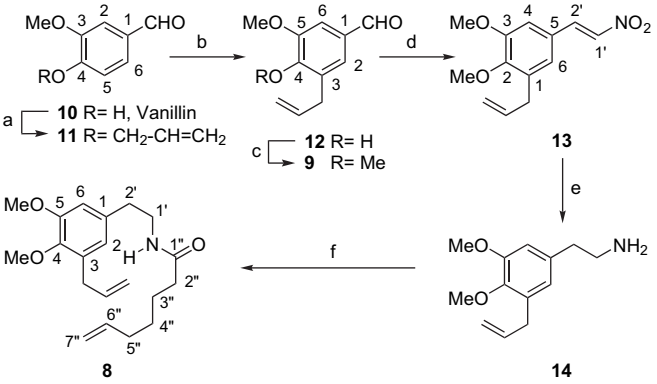
The synthetic plan towards tricycle **7** was based on the retrosynthetic analysis shown in Scheme 1, which hinged upon the use of RCM and Bischler–Napieralski cyclizations of precursor **8**, to build the macrocyclic and heterocyclic features of the target. It was expected that the amide chain of **8** could be easily constructed by acylation of the β-phenethylamino moiety with an ω-olefin substituted acyl chloride, while the β-ethylamino chain itself could be prepared by the Henry nitroaldol reaction of a suitably functionalized benzaldehyde derivative.

It was considered that the carbon–carbon disconnection shown in Scheme 1 represented the most convenient alternative to perform the RCM, since on one hand, this would entail the use of an allylbenzenoid precursor (**9**) and on the other, the proximity of one of the terminal double bonds to the carbonyl oxygen may affect the cyclization. In fact, there are literature precedents by the groups of Grubbs and Schrock, indicating that unproductive metal complexes can result when the terminal double bond is separated three bonds or less from the carbonyl moiety.[13] Finally, taking into account the neighbourhood of a phenolic group, **9** could be conveniently accessed by a Claisen rearrangement of the corresponding allyl phenyl ether. In turn, this early intermediate could result from the inexpensive and commercially available vanillin (**10**).



Scheme 1. Retrosynthetic analysis of target compound **7**.

Therefore, the synthesis began with the O-allylation of vanillin (**10**) with allyl bromide in refluxing EtOH, in the presence of K_2CO_3 as base, which afforded the known compound **11** in 99% yield as shown in Scheme 2.[14] In turn, **11** was subjected to a Claisen rearrangement in refluxing 1,2-dichlorobenzene as the inert, high boiling solvent, furnishing 85% of 5-allyl vanillin (**12**),[15] which was finally submitted to O-methylation of its phenolic moiety with methyl iodide in refluxing ethanol, with K_2CO_3 as base, quantitatively providing the projected aldehyde **9**.



Scheme 2. Reagents and conditions: (a) $CH_2{=}CHCH_2Br$, K_2CO_3, EtOH, reflux, 4 h (99%); (b) 1,2-Cl_2-C_6H_4, 185 °C, 13 h (85%); (c) MeI, K_2CO_3, EtOH, reflux, 6 h (100%); (d) $MeNO_2$, $(H_3NCH_2CH_2NH_3)^{+2}\cdot 2AcO^-$, *t*-BuOH, 80 °C, 24 h (95%); (e) $LiAlH_4$, THF, 0 °C→reflux, 5 h (90%); (f) 6-heptenoic acid, DCC, $DMAP_{(cat.)}$, $ClCH_2CH_2Cl$, 0 °C→reflux, 15 h (54%).

With the allyl benzaldehyde derivative **9** in hand, the next stage consisted in the preparation and further acylation of the 3,4-dimethoxy β-phenethylamine **14**. To that end, **9** was reacted with nitromethane under promotion of ethylenediammonium diacetate[16] yielding 95% of nitrostyrene **13**, to which the *E* configuration was assigned, in view of the value of the coupling constant (J=13.7 Hz) between both of its vinylic protons. The nitrostyrene was next subjected to reduction with $LiAlH_4$ in THF, providing β-phenethylamine **14**; however, due to its ready oxidizability, without further purification the latter was immediately acylated with 6-hexenoic acid and DCC in refluxing 1,2-dichloroethane under catalysis of DMAP, giving intermediate **8** in 54% overall yield.

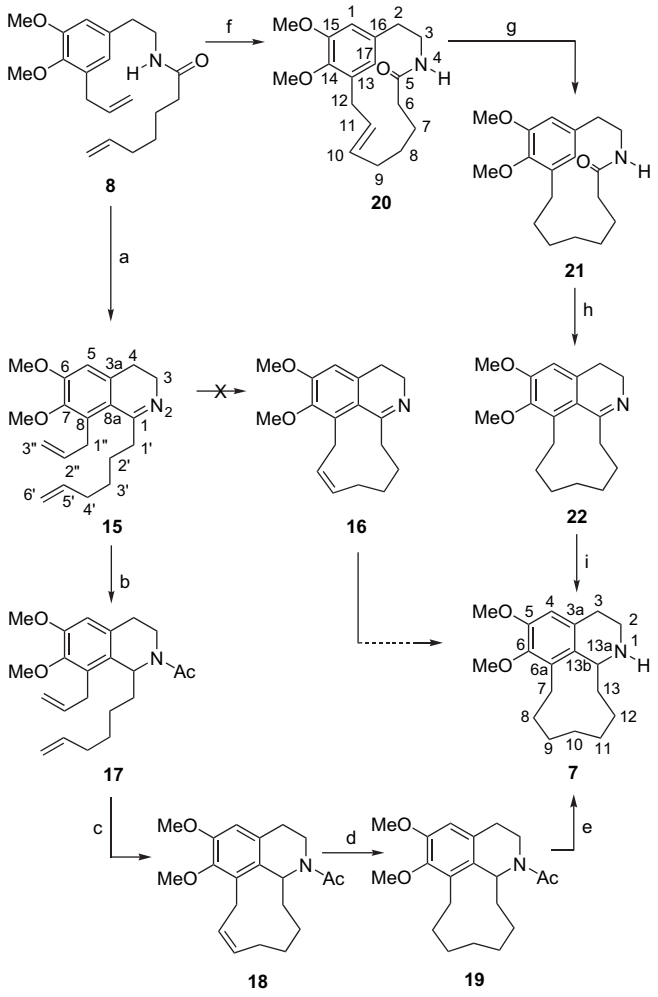
Now, the stage was set to carry out the projected cyclizations. A priori, performing the RCM before the Bischler–Napieralski synthesis was considered less likely to give satisfactory results, since it entailed the unusual formation of a 14-membered macrolactam ring, which would then need to be regioselectively cyclized.[17]

Therefore, **8** was subjected to a Bischler–Napieralski cyclization with phosphoryl chloride in refluxing acetonitrile, which smoothly

furnished in almost quantitative yield 1,2-dihydroisoquinoline intermediate **15** (Scheme 3), as concluded from the observation of NOE between H-4 and H-5 and by the value of the ^{13}C NMR resonance of OMe-6 (55.69 ppm); in case of formation of the undesired dihydroisoquinoline a 4–5 ppm downfield shift of this carbon atom should have been seen in its spectrum.[18a] The observed regioselectivity of the reaction most probably stems from the fact that cyclization *para* to the activating methoxy group is favoured over the alternative ring closing reaction, at the position *ortho* to the activating methyl ether. In the latter case, steric reasons may hinder cyclization or lower the degree of activation of the aromatic ring towards cyclization.[18b,c]

However, several attempts to perform the RCM of the di-olefin to obtain **16**, en route towards **7**, including with the addition of 20 mol % titanium isopropoxide in order to block coordination of the nitrogen atom of the dihydroisoquinoline to the ruthenium species,[19a] met with failure; despite that the interaction of imines with RCM catalysts leading to ring opening has been reported,[19b] no such products were observed, and only unreacted starting material was recovered.

Therefore, **15** was reduced with sodium borohydride and the resulting tetrahydroisoquinoline was immediately subjected to acylation with acetic anhydride and DMAP, providing 54% of the *N*-acetyl derivative **17** (from **15**), which was observed in its ^1H NMR spectrum as an approximately 1:1 mixture of amide rotamers, due to hindered rotation around the amide C–N bond, with the acetamido methyl group resonating at 2.11 and 2.13 ppm.[20]



Scheme 3. Reagents and conditions: (a) $POCl_3$, MeCN, reflux, 1 h (95%); (b) (1) $NaBH_4$, THF/MeOH, 0 °C, 1 h; (2) Ac_2O, C_5H_5N, $DMAP_{(cat.)}$, CH_2Cl_2, 0 °C, 4 h (54% from **15**); (c) Grubbs II catalyst, CH_2Cl_2, reflux, 22 h (68%); (d) H_2 (1 atm), $PtO_{2(cat.)}$, EtOH, RT, 23 h (99%); (e) 12 N HCl, MeOH (1:1, v/v), sealed tube, 90 °C, 52 h (25%); (f) Grubbs I catalyst, CH_2Cl_2, RT, 16 h (88%); (g) H_2 (1 atm), $PtO_{2(cat.)}$, EtOH, RT, 3–5 h (91%); (h) $POCl_3$, C_6H_6, reflux, 27 h (77%); (i) H_2 (1 atm), 10% $Pd/C_{(cat.)}$, MeOH, RT, 24 h (90%).

Upon submission to reaction with Grubbs II catalyst, compound **17** quite efficiently underwent RCM, affording 68% of the tricyclic derivative **18**, to which the *Z* configuration was assigned on the basis of previous observations for an analogous transformation[10] and the observed value of the coupling constant (J=10.8 Hz) between the vinylic hydrogens H-8 and H-9. After conventional hydrogenation of the olefinic double bond with pre-reduced Adams catalyst, the resulting acetamide derivative **19** was exposed to a refluxing mixture of MeOH and 12 N HCl (1:1, v/v),[21] yielding the expected tricycle **7**, albeit in unsatisfactory 25% yield.

In view of the meager results of the deacetylation stage and in order to evaluate the challenging and more direct route towards the target compound **7**, di-olefin **8** was subjected to RCM, furnishing macrolactam **20** when the reaction was carried out with Grubbs I catalyst in CH_2Cl_2 at room temperature. Interestingly, yields were quite satisfactory (88%), and no need to protect the nitrogen of the diene-amide precursor was required, as suggested by previous studies.[22a]

The stereochemistry of **20** was deduced as *E* from the value of the observed coupling constant (J=17.6 Hz) between the vinylic protons H-10 and H-11 of the macrocycle. This is consistent with the observations of Weiler and co-workers on similarly sized lactams, who also found that within this group, the geometry of the double bond may be predicted.[22b] As expected, minor amounts of the corresponding *Z*-macrolactam (*Z*-**20**) were also observed;[22b] however, despite being inseparable from *E*-**20**, this was considered not to be an obstacle for the synthesis.

The literature contains many examples on the preparation of 14-membered lactam derivatives as intermediates towards natural products or for studying their properties.[23] However, despite the wide use and recent popularity of the RCM reaction, the synthesis of these macrolactams employing RCM has few and scattered precedents. Among them, the group of Hoveyda employed a molybdenum-based (Schrock) catalyst to prepare the *cis*-macrolactam unit of fluvirucin B_1,[24a] while Billard and co-workers have synthesized a 14-membered α-trifluoromethyl lactam[24b] and the group of Danishefsky has recently reported the RCM-mediated preparation of 14-membered lactones en route to radicicol and aigialomycin D,[24c] and the synthesis of a related 14-membered macrolactam.[24d]

The possibility of sequentially carrying out the RCM and the hydrogenation of the resulting olefin with Grubbs catalyst as a one-pot process was explored,[25] employing 1,2-dichloroethane as solvent; however, after performing the hydrogenation of **20** over the ruthenium catalyst during 24 h (70 °C, H_2 at 100 psi), it was observed that the reaction was not complete and more than one product was present in the reaction medium. Therefore, the double bond of **20** was hydrogenated under atmospheric pressure of hydrogen, with Adams catalyst in EtOH, uneventfully furnishing 91% of **21** after 3–5 h at room temperature. Once subjected to the proposed Bischler–Napieralski cyclization, with $POCl_3$ in refluxing benzene, lactam **21** regioselectively generated the 3,4-dihydroisoquinoline derivative **22** in 77% yield. Finally, atmospheric pressure hydrogenation of the dihydroisoquinoline with 10% Pd/C in MeOH completed the synthesis, furnishing 90% of compound **7**, the spectral data of which were in full agreement with those previously reported.[10]

In conclusion, two approaches towards the synthesis of tricyclic compound **7**, which embodies the carbon skeleton of excentricine and related stephaoxocanes, were implemented, using a combined RCM-Bischler–Napieralski strategy. Starting from the readily available vanillin, and employing macrolactam **20** as key intermediate, resulted in an efficient 10 steps sequence towards

the target, which was reached in 23% overall yield, without the need of protective groups.

3. Experimental

3.1. General conditions

Melting points were taken on an Ernst Leitz Wetzlar model 350 hot-stage microscope and are reported uncorrected. FTIR spectra were determined employing a Shimadzu Prestige 21 spectrophotometer as solid dispersions in KBr disks, or as thin films held between NaCl cells. The ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ in a Bruker Avance spectrometer (300.13 and 75.48 MHz for ^{1}H and ^{13}C, respectively), with tetramethylsilane (TMS) as internal standard. The chemical shifts are reported in parts per million downfield from TMS and coupling constants (*J*) are expressed in hertz. DEPT 135 and DEPT 90 experiments aided the interpretation and assignment of the fully decoupled ^{13}C NMR spectra. In special cases, 2D-NMR experiments (COSY, HMBC, HMQC and *J*-resolved spectra) were also employed. Pairs of signals marked with (#) or with an asterisk (*) indicate that their assignments may be exchanged. High-resolution mass spectral data were obtained from the University of California, Riverside (USA). The reactions were carried out under dry nitrogen or argon atmosphere, employing oven-dried glassware.

Reagents were used as received; dry THF and benzene were prepared by distillation from Na-benzophenone ketyl; anhydrous pyridine was prepared by distillation after refluxing the reagent 4 h over pellets of KOH; dry CH_2Cl_2 and MeCN were prepared by a 4 h reflux over P_2O_5 followed by distillation; anhydrous solvents were stored in dry Young ampoules. In the conventional work-up procedure, the reaction was diluted with brine (5–10 mL) and the products were extracted with EtOAc (4–5×20 mL); the combined organic extracts were then washed once with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was submitted to flash column chromatography with silica gel 60 H. Elution was carried out with hexane/EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques.

All new compounds gave single spots on TLC plates run in different hexane/EtOAc and CH_2Cl_2/toluene solvent systems. Chromatographic spots were detected by exposure to UV light (254 nm), followed by spraying with ethanolic ninhydrin (amines) or with ethanolic *p*-anisaldehyde/sulfuric acid reagent and careful heating of the plates for improving selectivity.

3.2. 3-Allyl-4,5-dimethoxy-benzaldehyde 9

Allyl bromide (2.1 mL, 24.51 mmol) was added to a stirred suspension of vanillin (**10**, 2.87 g, 18.85 mmol) and K_2CO_3 (3.64 g, 26.4 mmol) in absolute EtOH (28 mL). The slurry was refluxed until complete consumption of the starting material was observed by TLC. Then, it was filtered through a pad of Celite, the filter was washed with EtOH (3×5 mL) and the combined organic filtrates were concentrated under reduced pressure. After addition of EtOAc (80 mL), the solution was washed with brine (2×15 mL); the organic phase was dried over Na_2SO_4 and concentrated in vacuo to give aldehyde **11** (3.61 g, 99%), as an oil. IR (NaCl) ν_{max}: 3100, 2939, 2835, 1684, 1586, 1424, 1394, 1258, 1136, 1033, 995, 809, 731 and 662 cm^{-1}; ^{1}H NMR (δ): 3.94 (s, 3H, OMe), 4.71 (dt, 2H, *J*=2.6 and 5.3, $OCH_2CH{=}CH_2$), 5.35 (ddd, 1H, *J*=1.3, 2.6 and 10.5, $OCH_2CH{=}CH_2$), 5.44 (ddd, 1H, *J*=1.3, 2.6 and 16.8, $OCH_2CH{=}CH_2$), 6.09 (dddd, 1H, *J*=5.3, 5.3, 10.5 and 16.8, $OCH_2CH{=}CH_2$), 6.97 (d, 1H, *J*=8.6, H-3), 7.40 (d, 1H, *J*=1.9, H-2), 7.43 (dd, 1H, *J*=1.9 and 8.6, H-2) and 9.85 (s, 1H, CHO); ^{13}C NMR (δ): 56.6 (OMe), 72.4 ($OCH_2CH{=}CH_2$), 112.0 (C-2),* 114.6 (C-5),* 121.3 ($OCH_2CH{=}CH_2$), 129.1 (C-6), 132.9 (C-1), 134.9 ($OCH_2CH{=}CH_2$), 152.5 (C-3), 156.1 (C-4) and 193.5 (CHO). A solution of aldehyde **11** (3.60 g, 18.8 mmol) in 1,2-dichlorobenzene (7 mL) was heated at 180–185 °C until complete consumption of the starting material was verified by TLC (12–16 h). Then, the solution was passed through a short silica gel column, eluting with hexanes in order to remove the 1,2-dichlorobenzene. Increasing solvent polarity allowed the elution of *ortho*-allylphenol **12** (3.042 g, 85%), which was recovered as a solid, mp 82–84 °C (hexane/EtOAc). IR (KBr) ν_{max}: 3250, 2968, 2852, 1675, 1589, 1469, 1303, 1259, 1146, 1072, 912, 849, 734 and 651 cm^{-1}; ^{1}H NMR (δ): 3.46 (br d, 2H, *J*=6.6, $ArCH_2CH{=}CH_2$), 3.96 (s, 3H, OMe), 5.11 (ddd, 1H, *J*=1.7, 3.0 and 9.7, $ArCH_2CH{=}CH_{2cis}$), 5.12 (ddd, 1H, *J*=1.7, 3.0 and 17.5, $ArCH_2CH{=}CH_{2trans}$), 6.01 (dddd, 1H, *J*=6.6, 6.6, 9.7 and 17.5, $ArCH_2CH{=}CH_2$), 6.26 (s, 1H, OH), 7.31 (s, 2H, H-2 and H-6) and 9.81 (s, 1H, CHO); ^{13}C NMR (δ): 36.3 ($ArCH_2CH{=}CH_2$), 59.1 (OMe), 110.0 (C-6), 119.2 ($ArCH_2CH{=}CH_2$), 129.0 (C-2), 130.8 (C-1),* 132.0 (C-3),* 138.4 ($ArCH_2CH{=}CH_2$), 149.8 (C-5), 152.3 (C-4) and 193.9 (CHO). Methyl iodide (1.4 mL, 22.5 mmol) was added to a mixture of allylphenol **12** (2.05 g, 10.66 mmol) and K_2CO_3 (2.06 g, 14.9 mmol) in absolute EtOH (20 mL). The resulting suspension was refluxed until the reaction was completed, as judged by TLC (4 h). Then, the solids were removed by filtration through Celite, the filtrate washed with EtOH (3×5 mL), and the combined organic filtrates were concentrated under reduced pressure. After addition of EtOAc (70 mL), the solution was successively washed with 20% aqueous K_2CO_3 (2×15 mL) and brine (2×15 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give **9** (2.20 g, 100%), as a colourless oil. IR (NaCl) ν_{max}: 3090, 2941, 2836, 1695, 1586, 1486, 1388, 1299, 1110, 1004, 915, 858 and 655 cm^{-1}; ^{1}H NMR (δ): 3.46 (br d, 2H, *J*=6.6, $ArCH_2CH{=}CH_2$), 3.90 (s, 3H, OMe), 3.92 (s, 3H, OMe), 5.04 (ddd, 1H, *J*=1.3, 3.0 and 17.1, $ArCH_2CH{=}CH_{2trans}$), 5.10 (ddd, 1H, *J*=1.3, 3.0 and 10.0, $ArCH_2CH{=}CH_{2cis}$), 5.97 (dddd, 1H, *J*=6.6, 6.6, 10.0 and 17.1, $ArCH_2CH{=}CH_2$), 7.31 (d, 1H, *J*=1.9, H-6),* 7.33 (d, 1H, *J*=1.9, H-2),* and 9.87 (s, 1H, CHO); ^{13}C NMR (δ): 36.8 ($ArCH_2CH{=}CH_2$), 58.7 (OMe-3), 63.6 (OMe-4), 112.0 (C-6), 119.14 ($ArCH_2CH{=}CH_2$), 129.30 (C-2), 135.14 (C-3), 137.2 (C-1), 139.2 ($ArCH_2CH{=}CH_2$), 155.5 (C-5), 156.1 (C-4) and 194.1 (CHO). Spectral data of compounds **9**, **11** and **12** were in good agreement with the literature.[14b]

3.3. *E*-1-Allyl-2,3-dimethoxy-5-(2′-nitrovinyl)-benzene 13

A solution of aldehyde **9** (670 mg, 3.25 mmol), $MeNO_2$ (1.05 mL, 19.5 mmol) and anhydrous $[NH_3CH_2CH_2NH_3]^{2+}\cdot 2AcO^-$ (59 mg, 0.33 mmol) in dry *t*-BuOH (15 mL) was heated at 65 °C. After 17 h, the mixture was concentrated in vacuo; Celite (200 mg) and EtOAc (20 mL) were added to the oily residue and the resulting suspension was filtered through a short pad of Celite. The filter was washed with EtOAc (2×5 mL) and the combined filtrates were concentrated under reduced pressure, yielding a yellow oil, which slowly solidified, affording nitrostyrene derivative **13** (729 mg, 90%), as a bright yellow solid, mp 76–78 °C. IR (KBr) ν_{max}: 2976, 2834, 1634, 1559, 1490, 1334, 1293, 1153, 1007, 970 and 832 cm^{-1}; ^{1}H NMR (δ): 3.41 (br d, 2H, *J*=6.5, $ArCH_2CH{=}CH_2$), 3.88 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.08 (ddd, 1H, *J*=1.7, 3.0 and 16.7, $ArCH_2CH{=}CH_{2trans}$), 5.09 (ddd, 1H, *J*=1.7, 3.0 and 10.3, $ArCH_2CH{=}CH_{2cis}$), 5.95 (dddd, 1H, *J*=6.4, 6.4, 10.3 and 16.7, $ArCH_2CH{=}CH_2$), 6.93 (d, 1H, *J*=2.1, H-4),* 7.01 (d, 1H, *J*=2.1, H-6),* 7.51 (d, 1H, *J*=13.7, H-2′) and 7.93 (d, 1H, *J*=13.7, H-1′); ^{13}C NMR (δ): 33.9 ($ArCH_2CH{=}CH_2$), 55.9 (OMe-3), 60.9 (OMe-2), 110.4 (C-4), 116.5 (–$CH{=}CH_2$), 124.4 (C-6), 125.5 (C-5), 135.0 (C-1), 136.1 ($ArCH_2CH{=}CH_2$),* 136.3 (C-1′),* 139.2 (C-2′), 150.8 (C-2) and 153.2 (C-3); HRMS (CI) Calcd for $C_{13}H_{16}NO_4$ (MH^+): 250.1079; found: 250.1071.

3.4. Hept-6-enoic acid [2-(3-allyl-4,5-dimethoxy-phenyl)-ethyl]-amide 8

A solution of nitrostyrene **13** (857 mg, 3.44 mmol) in THF (3.5 mL) was introduced via cannula during 5 min into an ice-cooled suspension of $LiAlH_4$ (784 mg, 20.6 mmol) in anhydrous THF (27 mL). The system was submitted to reflux during 5 h, then cooled to room temperature, diluted with Et_2O (10 mL) and carefully treated with H_2O (0.81 mL), 15% NaOH (1.16 mL) and saturated KF solution (2.64 mL). The mixture was stirred for 30 min and then filtered through Celite. The Celite was washed with Et_2O (4×5 mL) and the combined organic filtrates were concentrated in vacuo to furnish the unstable 2-(3-allyl-4,5-dimethoxy-phenyl)-ethylamine **14**, as an oil. IR (NaCl) ν_{max}: 3361, 3299, 2936, 2834, 1639, 1588, 1489, 1290, 1148, 1010, 912 and 736 cm^{-1}; ^1H NMR (δ): 1.67 (br s, 2H, NH_2), 2.68 (t, 2H, J=6.9, H-2′), 2.94 (t, 2H, J=6.9, H-1′), 3.38 (d, 2H, J=6.5, ArCH_2CH=CH_2), 3.79 (s, 3H, OMe), 3.85 (s, 3H, OMe), 5.04 (ddd, 1H, J=1.3, 3.0 and 10.1, ArCH$_2$CH=CH_{2cis}), 5.06 (ddd, 1H, J=1.3, 3.0 and 17.0, ArCH$_2$CH=CH_{2trans}), 5.96 (dddd, 1H, J=6.5, 6.5, 10.1 and 17.0, ArCH$_2$CH=CH$_2$), 6.60 (d, 1H, J=1.5, H-6)* and 6.62 (d, 1H, J=1.5, H-2);* ^{13}C NMR (δ): 34.0 (ArCH$_2$CH=CH$_2$), 39.7 (C-2′), 43.3 (C-1′), 55.7 (OMe-5), 60.6 (OMe-4), 111.1 (C-6), 115.5 (ArCH$_2$CH=CH$_2$), 122.1 (C-2), 133.7 (C-3), 135.3 (C-1), 137.3 (ArCH$_2$CH=CH$_2$), 145.4 (C-4) and 152.6 (C-5). Without further purification, the crude amine **14** (684 mg, 3.10 mmol) was dissolved in $ClCH_2CH_2Cl$ (41 mL) and cooled to 0 °C in an ice-water bath. 6-Heptenoic acid (210 μL, 1.55 mmol) and $DMAP_{(cat.)}$ were successively added; the mixture was stirred for 5 min, and then solution of DCC (478 mg, 2.32 mmol) in $ClCH_2CH_2Cl$ (2 mL) was introduced via cannula. The cooling bath was removed and after the reaction reached room temperature (1 h) it was submitted to reflux (12 h) until complete consumption of the starting amine was ascertained by TLC. The solvent was removed under vacuum, and the oily residue was chromatographed to give amide **8** (274 mg, 54%), as a colourless oil. IR (NaCl) ν_{max}: 3303, 3078, 2933, 2859, 1729, 1641, 1549, 1490, 1289, 1148, 1011, 911 and 733 cm^{-1}; ^1H NMR (δ): 1.41 (dd, 2H, J=8.2 and 15.4, H-4″),* 1.65 (ddd, 2H, J=5.7, 7.9 and 15.4, H-3″),* 2.06 (br dd, 2H, J=7.6 and 14.4, H-5″), 2.14 (t, 2H, J=7.6, H-2″), 2.74 (t, 2H, J=7.0, H-2′), 3.39 (dt, 2H, J=1.4 and 6.6, ArCH_2CH=CH$_2$), 3.50 (dd, 2H, J=7.0 and 12.9, H-1′), 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.95 (ddd, 1H, J=1.0, 2.0 and 10.2, H-7″$_{cis}$), 5.00 (ddd, 1H, J=1.0, 2.0 and 17.2, H-7″$_{trans}$), 5.05 (ddd, 1H, J=1.5, 3.0 and 10.3, ArCH$_2$CH=CH_{2cis}), 5.06 (ddd, 1H, J=1.5, 3.0 and 17.0, ArCH$_2$CH=CH_{2trans}), 5.44 (br s, $w_{1/2}$=15 Hz, NH), 5.78 (dddd, 1H, J=6.7, 6.7, 10.3 and 17.0, ArCH$_2$–CH=CH$_2$), 5.95 (dddd, 1H, J=6.3, 6.3, 10.2 and 17.2, H-6″), 6.58 (d, 1H, J=2.1, H-2) and 6.62 (d, 1H, J=2.1, H-6); ^{13}C NMR (δ): 25.2 (C-3″), 28.5 (C-4″), 33.4 (C-5″), 34.0 (ArCH$_2$CH=CH$_2$), 35.6 (C-2′), 36.6 (C-2″), 40.6 (C-1′), 55.8 (OMe-5), 60.7 (OMe-4), 110.9 (C-6), 114.7 (=CH$_2$), 115.6 (=CH$_2$), 122.1 (C-2), 133.8 (C-3), 134.6 (C-1), 137.3 (ArCH$_2$CH=CH$_2$),* 138.4 (CH$_2$CH=CH$_2$),* 145.6 (C-4), 152.8 (C-5) and 173.0 (C-1″); HRMS (CI) Calcd for $C_{20}H_{30}NO_3$ (MH^+): 332.2218; found: 332.2226.

3.5. 14,15-Dimethoxy-4-aza-bicyclo[11.3.1]heptadeca-1(16),13(17),14-trien-5-one 21

A solution of Grubbs I catalyst (42 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) was added dropwise, in 90 min, to a refluxing solution of amide **8** (158 mg, 0.478 mmol) in CH_2Cl_2 (260 mL). The mixture was further refluxed during 18 h; then the volatiles were removed under reduced pressure. The remaining dark oil was chromatographed, affording macrolactam **20** (128 mg, 88%), as colourless needles, mp 126–128 °C (hexane/EtOAc). IR (KBr) ν_{max}: 3259, 3078, 2934, 2844, 1637, 1559, 1485, 1358, 1287, 1143, 1080, 1005 and 665 cm^{-1}; ^1H NMR (δ): 1.45–1.56 (m, 2H, H-8), 1.62–1.72 (m, 3H, H-6 and H-7), 2.08 (dt, 1H, J=8.0 and 9.7, H-6), 2.11 (dd, 2H, J=5.5 and 13.1, H-9), 2.68 (t, 2H, J=4.6 and 8.6, H-2), 3.37 (d, 2H, J=6.5, H-12), 3.40 (ddd, 2H, J=4.6, 8.6 and 11.4, H-3), 3.79 (s, 3H, OMe-14), 3.86 (s, 3H, OMe-15), 5.35 (br s, 1H, $w_{1/2}$=15 Hz, NH), 5.45 (ddd, 1H, J=9.4, 15.7 and 17.6, H-10), 5.56 (ddd, 1H, J=6.5, 16.2 and 17.6, H-11) and 6.56 (s, 2H, H-1 and H-17); ^{13}C NMR (δ): 24.4 (C-7), 26.8 (C-8), 30.4 (C-9), 31.1 (C-12), 35.3 (C-2), 35.7 (C-6), 39.7 (C-3), 55.8 (OMe-15), 60.9 (OMe-14), 110.2 (C-1), 123.5 (C-17), 131.2 (C-10),* 131.3 (C-11),* 134.5 (C-13),# 134.7 (C-16),# 145.3 (C-14), 153.2 (C-15) and 173.3 (C-4); HRMS (CI) Calcd for $C_{18}H_{26}NO_3$ (MH^+): 304.1913; found: 304.1906. Without further purification, macrolactam **20** (87 mg, 0.287 mmol) was dissolved in absolute ethanol (10 mL). The resulting solution was transferred to a suspension of PtO_2 (4 mg, 0.018 mmol) in EtOH (4 mL) and the reaction was stirred under H_2 at atmospheric pressure until complete consumption of the olefin was verified by TLC. The suspension was filtered through a small pad of Celite and the filter was washed with EtOH (1 mL); the combined filtrates were concentrated in vacuo and the residue was chromatographed, affording amide **21** (80 mg, 91%), as a solid, mp 127–129 °C (hexane/EtOAc). IR (KBr) ν_{max}: 3269, 2928, 2855, 1639, 1560, 1488, 1357, 1231, 1148 and 1017 cm^{-1}; ^1H NMR (δ): 1.18–1.28 (m, 4H, H-9 and H-10), 1.30–1.41 (m, 2H, H-7), 1.62–1.75 (m, 4H, H-8 and H-11), 2.09–2.19 (m, 2H, H-6), 2.69 (dd, 2H, J=6.2 and 12.0, H-12), 2.80 (br t, 2H, J=5.9, H-2), 3.56 (dd, 2H, J=5.9 and 11.7, H-3), 3.77 (s, 3H, OMe-14), 3.86 (s, 3H, OMe-15), 5.26 (br s, 1H, $w_{1/2}$=15 Hz, NH), 6.59 (d, 1H, J=2.0, H-1) and 6.63 (d, 1H, J=2.0, H-17); ^{13}C NMR (δ): 25.0 (C-11), 26.2 (C-7), 26.7 (C-10), 27.0 (2C, C-9 and C-8), 27.6 (C-12), 34.7 (C-2), 36.4 (C-6), 39.6 (C-3), 55.7 (C-15), 60.5 (C-14), 109.8 (C-1), 122.2 (C-17), 133.8 (C-16),* 135.6 (C-13),* 146.2 (C-14), 153.1 (C-15) and 173.2 (C-4); HRMS (CI) Calcd for $C_{18}H_{28}NO_3$ (MH^+): 306.2069; found: 306.2059.

3.6. 5,6-Dimethoxy-2,3,7,8,9,10,11,12,13,13a-decahydro-1*H*-cyclodeca[*ij*]isoquinoline 7 from 3,4-dihydro-isoquinoline derivative 22

Recently, distilled $POCl_3$ (0.24 mL) was slowly added to a refluxing solution of amide **21** (18 mg, 0.058 mmol) in anhydrous benzene (3.0 mL). After 28 h, when the reaction was completed (TLC), the volatiles were removed under reduced pressure and the oily residue was alkalinized with aqueous Na_2CO_3 (2 mL). The product was extracted with EtOAc (5×2 mL) and the organic extracts were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography, furnishing tricyclic derivative **22** (13 mg, 77%), as an oil. IR (NaCl) ν_{max}: 2933, 2847, 1669, 1590, 1464, 1311, 1293, 1133, 1020, 910 and 731 cm^{-1}; ^1H NMR (δ): 1.42–1.60 (m, 4H, H-8 and H-11), 1.61–1.75 (m, 4H, H-9 and H-10), 1.76–1.95 (m, 2H, H-12), 2.40–2.70 (m, 2H, H-3), 2.50 (dt, 2H, J=6.8 and 13.5, H-13), 3.02 (dt, 2H, J=7.6 and 15.2, H-7), 3.30–3.59 (m, 2H, H-2), 3.78 (s, 3H, OMe-6), 3.89 (s, 3H, OMe-5) and 6.63 (s, 1H, H-5); ^{13}C NMR (δ): 22.4 (H-10), 23.3 (H-11), 23.6 (C-7), 25.5 (C-12), 26.3 (C-8), 28.5 (H-9), 28.8 (C-13), 33.7 (C-3), 46.6 (C-2), 55.6 (OMe-5), 60.9 (OMe-6), 108.4 (C-4), 123.9 (C-13b), 135.9 (C-3a), 137.6 (C-6a), 146.4 (C-5), 153.3 (C-6) and 169.8 (C-13a); HRMS (CI) Calcd for $C_{18}H_{26}NO_2$ (MH^+): 287.19645; found: 288.1957. Without further purification, dihydroisoquinoline derivative **22** (3.0 mg, 0.0104 mmol) was dissolved in MeOH (1 mL), 10% Pd/C (1 mg) was added and the resulting suspension was vigorously stirred 7 h under a H_2 atmosphere. The catalyst was separated by filtration through a short pad of Celite and the filter was washed with EtOH (6×1 mL). The filtrates were combined and concentrated under reduced pressure, affording tetrahydroisoquinoline derivative **7** (2.7 mg, 90%), as a solid, mp 216–218 °C. IR (KBr) ν_{max}: 3650–3320, 3200–2400, 1588, 1475, 1308, 1235, 1122, 1022, 921, 842, 731 and 644 cm^{-1}; ^1H NMR (δ): 1.21–1.48 (m, 4H, H-9, H-10 and H-11), 1.52–1.77 (m, 5H, H-8, H-9, H-11 and H-12), 1.80–2.06 (m, 2H, H-8 and H-13), 2.13–2.39 (m, 1H, H-13), 2.59 (ddd, 1H, J=3.4, 3.5 and 10.5, H-7), 2.90 (ddd, 1H, J=3.4, 3.6 and 10.5, H-7), 3.03 (ddd, 2H, J=3.4, 6.1 and 17.7, H-3), 3.31 (ddd, 1H, J=3.4, 6.1 and 9.6,

H-2), 3.71 (ddd, 1H, J=3.4, 6.1 and 9.6, H-2), 3.80 (s, 3H, OMe-6), 3.84 (s, 3H, OMe-5), 4.95 (t, 1H, J=6.8, H-13a), 6.58 (s, 1H, H-4) and 9.58 (br s, 1H, $w_{1/2}$=9 Hz, NH); ^{13}C NMR (δ): 23.7 (C-9),* 25.2 (C-10), 25.4 (C-3), 25.8 (C-12), 26.0 (C-7), 27.7 (C-11),* 28.1 (C-8), 31.5 (C-13), 37.0 (C-2), 51.4 (C-13a), 55.4 (OMe-5), 60.1 (OMe-6), 110.6 (C-4), 124.1 (C-6a),* 127.8 (C-13b),* 134.9 (C-3a), 146.9 (C-6) and 152.1 (C-5); HRMS Calcd for $C_{18}H_{28}NO_2$: 290.2120 (MH^+); found: 290.2124. Data of **7** were in agreement with the literature.[10]

3.7. 1-(8-Allyl-1-hex-5-enyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanone 17

Freshly distilled $POCl_3$ (0.43 mL) was added dropwise to a refluxing solution of amide **8** (92 mg, 0.278 mmol) in anhydrous MeCN (5.3 mL), and the mixture was stirred (ca. 1 h) until complete consumption of the starting material (TLC). The volatiles were removed under reduced pressure, the oily residue was diluted with EtOAc (2 mL) and basified with saturated aqueous $NaHCO_3$ (5 mL). The reaction products were extracted with EtOAc (5×2 mL), the organic extracts were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue furnished **15** (83 mg, 95%), as an oil. IR (NaCl) ν_{max}: 2935, 2853, 1640, 1591, 1464, 1308, 1291, 1139, 1022, 910 and 943 cm^{-1}; ^{1}H NMR (δ): 1.00–1.90 (m, 4H, H-2′ and H-3′), 2.01 (dd, 2H, J=7.3 and 14.4, H-4′), 2.55 (t, 2H, J=6.6, H-4), 2.80 (t, 2H, J=7.3, H-1′), 3.46 (t, 2H, J=6.6, H-3), 3.63 (d, 2H, J=5.3, H-1″), 3.79 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.86–5.08 (m, 4H, H-6′ and H-3″), 5.75 (dddd, 1H, J=6.8, 6.8, 10.6 and 17.0, H-5′),* 5.99 (dddd, 1H, J=5.3, 5.3, 10.6 and 15.5, H-3″),* and 6.70 (s, 1H, H-5); ^{13}C NMR (δ): 27.9 (C-4), 28.6 (2C, C-2′ and C-3′), 31.5 (C-1″), 33.5 (C-4′), 38.5 (C-1′), 45.9 (C-3), 55.7 (OMe-6), 60.8 (OMe-7), 109.4 (C-5), 114.4 (C-3″),* 114.6 (C-8a), 115.7 (C-6′),* 123.2 (C-4a), 131.3 (C-8), 136.9 (C-2″),# 137.1 (C-6), 138.7 (C-5′),# 146.7 (C-7) and 154.0 (C-1); HRMS (CI) Calcd for $C_{20}H_{28}NO_2$ (MH^+): 314.2120; found: 314.2116. Without further purification, dihydroisoquinoline **15** (80 mg, 0.255 mmol) was dissolved in a mixture of dry THF (6.1 mL) and anhydrous MeOH (93 μL); the solution was cooled in an ice bath and treated with $NaBH_4$ (22 mg, 0.582 mmol). After consumption of the imine was verified by TLC, the solvent was removed in vacuo and the resulting white gum was suspended in CH_2Cl_2 (4.3 mL), cooled at 0 °C and dry pyridine (0.23 mL, 2.97 mmol), Ac_2O (0.14 mL, 1.54 mmol) and a catalytic amount of DMAP were successively added. After 5 h, the mixture was diluted with CH_2Cl_2 (20 mL) and successively washed with saturated aqueous solutions of $NaHCO_3$ (5 mL), NH_4Cl (5 mL) and NaCl (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, giving a residue, which was chromatographed, affording acetamide derivative **17** (54 mg, 54% from **8**), as a white solid, mp 220–222 °C (hexane/EtOAc), which was observed as a roughly 1:1 mixture of rotamers by ^{1}H and ^{13}C NMR. IR (KBr) ν_{max}: 2933, 2856, 1641, 1598, 1429, 1339, 1235, 1120, 1028, 911 and 735 cm^{-1}; ^{1}H NMR (δ): 1.30–1.50 (m, 4H, H-2′ and H-3′), 1.60–1.70 (m, 2H, H-1′), 1.96–2.09 (m, 1H, H-4′), 2.11 (s, 1.5H, *Me*CO), 2.13 (s, 1.5H, *Me*CO), 2.70–2.99 (m, 2H, H-4), 3.14–3.25 (m, 1H, H-3), 3.33–3.42 (m, 0.5H, H-3), 3.50–3.60 (m, 0.5H, H-3), 3.62–3.71 (m, 2H, H-1″), 3.79 (s, 3H, OMe-7), 3.84 (s, 3H, OMe-6), 4.66 (dd, 0.5H, J=4.1 and 7.6, H-1), 4.79 (dd, 0.5H, J=3.8 and 10.6, H-1), 4.86–5.09 (m, 4H, H-3″ and H-6′), 5.78 (dddd, 1H, J=6.8, 6.8, 10.0 and 16.7, H-2″),* 5.96 (dddd, 1H, J=6.2, 10.3 and 16.7, H-5′),* 6.56 (s, 0.5H, H-5) and 6.58 (s, 0.5H, H-5); ^{13}C NMR (δ): 21.9 and 22.1 (*Me*CO), 25.0 and 25.9 (C-2′), 26.1 and 27.6 (C-3′), 28.7 (C-1″), 29.8 and 30.3 (C-4), 33.5 and 33.6 (C-1′), 34.0 and 35.1 (C-3), 35.3 and 35.5 (C-4′), 49.0 and 54.4 (C-1), 55.6 (OMe-6), 60.7 and 60.9 (OMe-7), 110.7 and 111.2 (C-5), 114.3 and 114.8 (C-6′),* 115.33 and 115.4 (C-3″),* 128.9 and 129.0 (C-8a),# 129.4 and 129.8 (C-4a),# 130.2 and 130.6 (C-8),# 136.8 and 137.2 (C-2″),* 138.4 and 138.9 (C-5′),* 145.7 and 146.1 (C-6), 151.2 and 151.4 (C-7) and 169.4 and 169.7 (Me*C*O); HRMS (CI) Calcd for $C_{22}H_{32}NO_3$ (MH^+): 358.2382; found: 328.2375.

3.8. 1-(5,6-Dimethoxy-2,3,7,8,9,10,11,12,13,13a-deca-hydro-cyclodeca[*ij*]isoquinolin-1-yl)ethanone 19

A solution of Grubbs II catalyst (3 mg, 3.52 μmol) in CH_2Cl_2 (2 mL) was added dropwise during 120 min to a refluxing solution of amide **17** (25.2 mg, 0.0.71 mmol) in CH_2Cl_2 (35.8 mL) and the mixture was further refluxed for 24 h. Then, the solution was concentrated under reduced pressure and the remaining dark oil was chromatographed, furnishing macrocycle **18** (16 mg, 68%) as a colourless oil, which was observed as a 2:1 mixture of rotamers by ^{1}H and ^{13}C NMR. IR (NaCl) ν_{max}: 2933, 2857, 1623, 1600, 1419, 1332, 1234, 1120, 1030, 910 and 732 cm^{-1}; ^{1}H NMR (δ): 1.02–1.50 (m, 4H, H-11 and H-12), 1.65–2.19 (m, 4H, H-10 and H-13), 2.09 (s, 2H, *Me*CO), 2.30 (s, 1H, *Me*CO), 2.69–2.90 (m, 1H, H-3), 3.02–3.46 (m, 2H, H-3 and H-4), 3.55–3.65 (m, 1H, H-7), 3.78–3.88 (m, 2H, H-4 and H-7), 3.85 (s, 2H, OMe), 3.86 (s, 3H, OMe), 3.88 (s, 1H, OMe), 5.28 (dd, 0.34H, J=5.7 and 11.0, H-13a), 5.34 (ddd, 1H, J=5.2, 10.8 and 10.9, H-9), 5.81–5.95 (m, 1H, H-8), 6.12 (dd, 0.66H, J=5.4 and 10.4, H-13a), 6.63 (s, 0.66H, H-4) and 6.64 (s, 0.34H, H-4); ^{13}C NMR (δ): 20.7 and 21.0 (C-11),* 22.0 and 22.4 (*Me*CO), 25.4 (C-12),* 26.5 and 26.6 (C-7),# 27.9 and 28.8 (C-4),# 29.1 and 29.2 (C-10),# 35.8 and 37.0 (C-13), 40.2 and 43.2 (C-2), 50.4 and 54.9 (C-13a), 55.7 (OMe-5), 60.6 (OMe-6), 110.3 and 110.8 (C-4), 127.9 and 128.2 (C-8),* 129.0 and 129.8 (C-9),* 131.0 (C-13b),* 131.5 and 131.9 (C-3a),* 133.1 (C-6a),* 145.7 and 146.0 (C-5), 151.2 and 151.4 (C-6), and 169.3 and 169.5 (Me*C*O); HRMS (CI) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2069; found: 330.2062. A solution of **18** (23 mg, 0.068 mmol) in absolute EtOH (2.0 mL) was submitted to hydrogenation at atmospheric pressure, employing PtO_2 (1.1 mg) as catalyst. After 24 h, the mixture was filtered through a short pad of Celite and the filtrate was concentrated in vacuo. The residue was chromatographed, affording compound **19** (23 mg, 99%) as an oil, which was observed as a 1.4:1 mixture of rotamers by ^{1}H and ^{13}C NMR. IR (NaCl) ν_{max}: 2932, 2859, 1640, 1598, 1482, 1312, 1234, 1120, 1026 and 734 cm^{-1}; ^{1}H NMR (δ): 1.03–2.00 (m, 10H, H-8, H-9, H-10, H-11 and H-12), 2.08 (s, 1.75H, *Me*CO), 2.24 (s, 1.25H, *Me*CO), 2.55–3.60 (m, 8H, H-7, H-13, H-2 and H-3), 3.80 (s, 3H, OMe-6), 3.86 (s, 3H, OMe-5), 5.19 (dd, 0.58H, J=5.7 and 10.0, H-13a), 6.04 (dd, 0.42H, J=5.7 and 10.0, H-13a) and 6.63 (s, 0.58H, H-4) and 6.65 (s, 0.42H, H-4); ^{13}C NMR (δ): 21.8 and 22.4 (*Me*CO), 23.1 and 23.6 (C-11), 24.5 and 25.0 (C-12), 26.1 and 26.2 (C-10), 26.5 and 26.6 (C-7), 28.0 (2C, C-8, C-9), 28.8 (C-3), 33.6 and 34.2 (C-13), 40.3 and 43.3 (C-2), 48.7 and 53.1 (C-13a), 55.6 (OMe-5), 60.1 and 60.2 (OMe-6), 110.1 and 110.6 (C-4), 128.8 and 129.8 (C-13b), 130.6 and 131.0 (C-3a), 133.6 and 134.9 (C-6a), 146.3 and 146.6 (C-5), 151.2 and 151.4 (C-6), and 169.3 and 169.6 (C=O); HRMS (CI) Calcd for $C_{20}H_{29}NO_3$ (MH^+): 332.2226; found: 332.2216.

3.9. 3,4-Dihydroisoquinoline 7 from acetamide 19

Acetamide **19** (17 mg, 0.051 mmol) was dissolved in a 1:1 (v/v) mixture of MeOH and 12 N HCl (0.94 mL), confined in a sealed ampoule and subjected to hydrolysis at 95 °C during 20 h. Then, the reaction mixture was made alkaline with a saturated aqueous $NaHCO_3$ solution and the products were extracted with Et_2O (5×5 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated under reduced pressure; the residue was chromatographed to afford compound **7** (3.65 mg, 25%), as a solid, mp 216–218 °C. The spectral data of this product were in full agreement with the literature[10] and with those recorded for compound **7**, obtained from **22**.

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