DOI: 10.1002/ejoc.200700570

Synthesis of the Carbon Framework of the Stephaoxocanes Employing a Sequential RCM/Pomeranz–Fritsch Approach

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Keywords: Synthesis design / Cyclization / Stephaoxocanes / Carbon framework / Isoquinolines / Alkaloids

The syntheses of two cyclodeca[*ij*]isoquinoline derivatives, which embody the carbon framework of stephaoxocanidine, excentricine and the recently isolated stephalonganines A, B and C, are reported. The target tricyclic compounds were prepared from isovanillin, employing a ring-closing metathesis approach towards the synthesis of a benzocyclodecane-type common intermediate; different modifications of the Pomeranz–Fritsch protocol allowed the installation of the heterocyclic ring.

Introduction

Benzoannelated nitrogen heterocycles constitute the basic units of a wide variety of naturally occurring products and represent key elements in modern drug discovery endeavors.[1] Recent studies on Chinese, Japanese and Brazilian Menispermaceae unveiled a small and structurally unusual family of isoquinoline-type natural products carrying an oxocane ring, for which the name stephaoxocanes was coined.[2] The same designation was proposed for their common tetracyclic ring system **1a** (Figure 1).

To date, only eight stephaoxocanes are known, including stephaoxocanidine (**1b**)[2] and stephaoxocanine (**1c**),[3] obtained from *Stephania cepharantha*; excentricine (**1d**) and *N*-methylexcentricine (**1e**), from *S. excentrica*, eletefine (**1f**), isolated from *Cissampelos glaberrima*[4] and *Stephania longa* Lour, and the stephalonganines A (**1g**), B (**1h**) and C (**1i**), recently isolated from *S. longa*.[5] The natural sources of the stephaoxocanes are employed in folk medicine, including Traditional Chinese Medicine, for different purposes ranging from asthma to fever, inflammation, dysentery and urinary infections;[6] in addition, some plant extracts have also demonstrated interesting biological activities.[7]

Structurally, the stephaoxocanes are related to other tetracyclic Menispermaceae alkaloids, such as the azafluoranthenes represented by telitoxine (**2a**) and rufescine (**2b**), and the tropoloisoquinolines, exemplified by pareitropone (**3a**) and grandirubrine (**3b**). A number of publications report diverse synthetic efforts towards the long known azafluoranthene and tropoloisoquinoline alkaloids,[8] being this in contrast to the scarcity of synthetic work on stephaoxocanes.

We have previously developed two approaches to the synthesis of the ABC-ring system of the stephaoxocanes, which culminated with the synthesis of 1,9-oxazafluoranthene derivatives **4** and **5**.[9] More recently, we also demonstrated that lactone **5** and related compounds inhibit the enzyme acetylcholinesterase with potency comparable to that exhibited by a daffodil (*Narcissus pseudonarcissus*) extract enriched in galanthamine.[10] Acetylcholinesterase is a recognized therapeutic target for the treatment of cognitive disorders in Alzheimer's disease.

Pursuing our interest in the synthesis of isoquinoline derivatives related to the stephaoxocanes, here we wish to report the construction of the cyclodeca[*ij*]isoquinoline derivatives **6** and **7**, which contain the carbon framework of the stephaoxocanes. The former embodies the tetrahydroisoquinoline moiety characteristic of the excentricines and the stephalonganines, while compound **7** displays the related isoquinoline motif, common to stephaoxocanidine and eletefine.

As shown in the retrosynthetic analysis of **6** and **7** depicted in Scheme 1, we envisioned that these objectives could be reached from the common intermediate **8**, the overall strategy being centered on the sequential use of a ring closing metathesis (RCM) for building the macrocycle containing the carbon atoms of rings C and D of the natural products (**9**→**8**), and modern modifications of the Pomeranz–Fritsch isoquinoline synthesis for completing the nitrogen heterocycle (**8**→**6** and **8**→**7**). In turn, intermediate **9** would be derived from the readily available isovanillin (**10**).[11]

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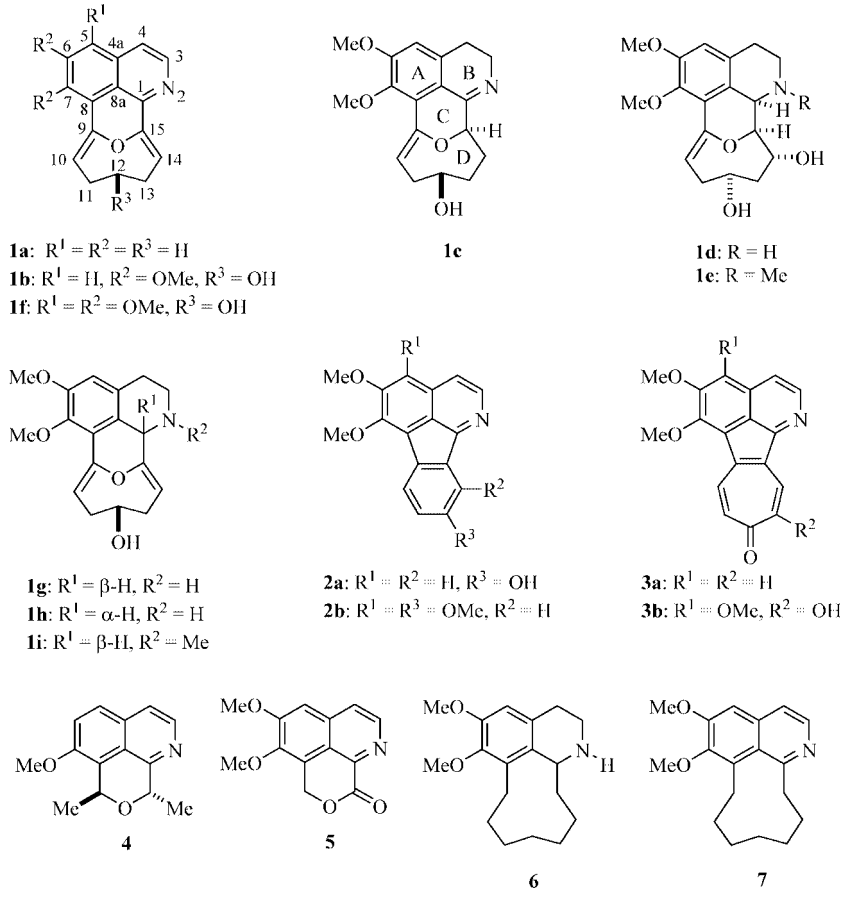
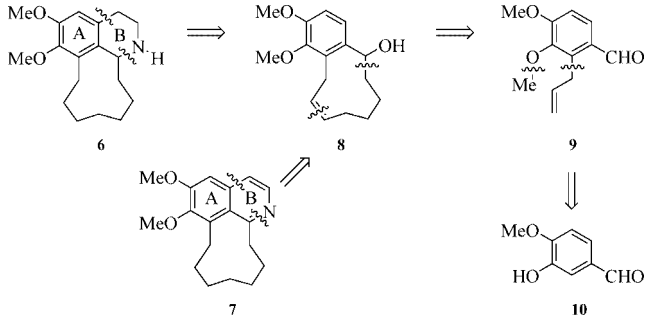


Figure 1. Chemical structures of the stephaoxocanes **1a**–**i**, related natural products **2** and **3**, synthetic tricyclic analogs **4** and **5** and proposed targets **6** and **7**.



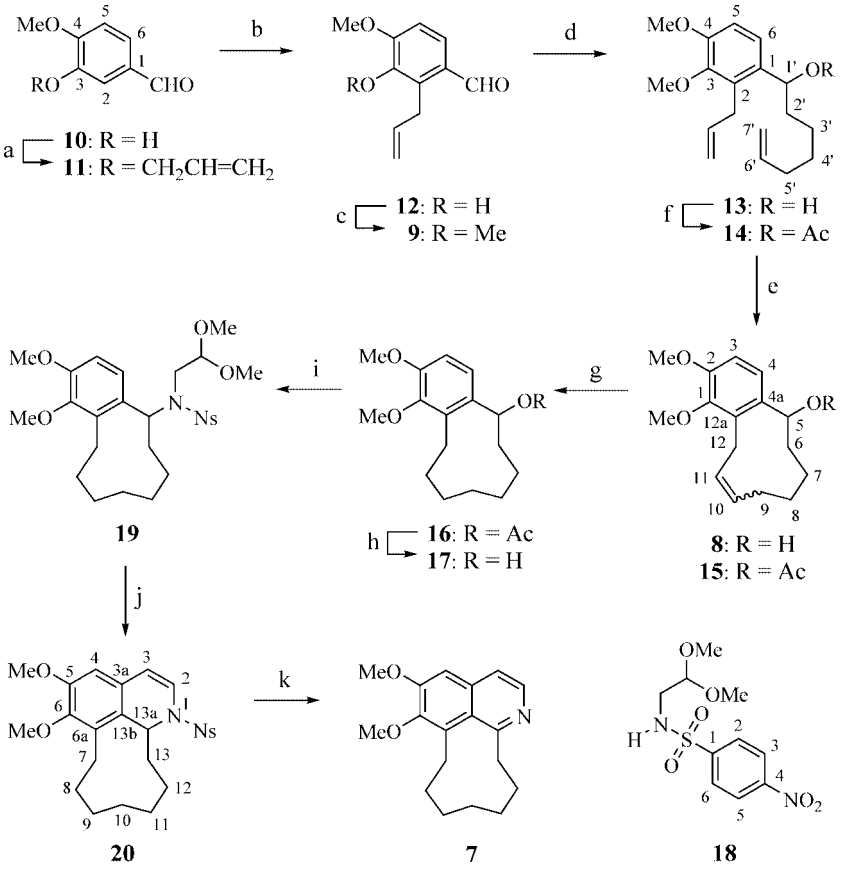
Scheme 1. Retrosynthetic analysis of compounds **6** and **7**.

Results and Discussion

The synthesis commenced with the preparation of 2-allyl veratraldehyde derivative **9**, as illustrated in Scheme 2. Potassium carbonate mediated *O*-allylation of isovanillin (**10**), provided 92% of the allyl ether **11**,[11] which was subjected to a Claisen rearrangement in refluxing 1,2-dichlorobenzene and the resultant 2-allyl phenol **12**,[11] obtained in 97% yield, was transformed into the corresponding methyl ether **9** (90% yield) after conventional alkylation with methyl iodide. The use of 1,2-dichlorobenzene to affect the Claisen rearrangement proved to be more convenient than the previously employed dimethylacetamide.[11a]

Next, the aldehyde **9** was subjected to a 1,2-addition of 5-hexenylmagnesium bromide, prepared in situ from the alkyl bromide and magnesium,[12] which affected the incorporation of the required hexenyl moiety, furnishing the benzylic alcohol **13** and setting the stage for the anticipated ring-closing metathesis reaction. Interestingly, the Claisen rearrangement – RCM strategic sequence has been repeatedly employed for the synthesis of benzoannulated aromatics and other small carbon or heterocyclic rings attached to aromatic moieties including azepines, oxocines and oxepines,[13] but there is only one record of its use for benzocyclodecene derivatives.[14]

Disappointingly, however, when the reaction was carried out with Grubbs' first-generation catalyst $[Cl_2(PCy_3)_2Ru{=}CHPh]$ in refluxing CH_2Cl_2, the expected alcohol **8** was isolated in low yields, ranging from 27 to 35%. This was accompanied by considerable amounts of oligomeric products, resulting from cross-metathesis. Additional attempts to improve the yields, which included changing the solvent to toluene and raising the reaction temperature to 80 °C were fruitless, while modification of other experimental



Scheme 2. Nosylamide-based synthesis of compound **7**. Reagents and conditions: a) $BrCH_2CH=CH_2$, K_2CO_3, EtOH, reflux, 2 h (92%); b) 1,2-Cl_2-C_6H_4, reflux, 13 h (97%); c) MeI, K_2CO_3, EtOH, reflux (90%); d) 1. Mg, $Br(CH_2)_4CH=CH_2$, THF; 2. **12**, THF, room temp., 3 h, (60%); e) Grubbs I catalyst (6 mol-%), CH_2Cl_2, reflux, 6 h (**13**→**8**, 35%; **14**→**15**, 77%); f) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, room temp., 4 h (90%); g) H_2, 1 atm, PtO_2 (cat.), EtOH, room temp., 4 h (100%); h) NaOH, THF/MeOH, 50 °C, 6 h (91%); i) PPh_3, DIAD, 4-O_2N-C_6H_4-$SO_2NHCH_2CH(OCH_3)_2$ (**18**), THF, 60 °C, 4 h (65%); j) 6 N HCl, EtOH, dioxane, reflux, 30 min (68%); k) K*t*BuO, C_5H_5N, 60 °C, 1 h (28%).

conditions, such as increasing substrate dilution and performing slow addition of the catalyst, gave no substantial improvement.

Suspecting that the free hydroxy group may be interfering with the RCM reaction, being responsible for the observed low yields, the alcohol **13** was acylated with acetic anhydride and Et_3N providing the acetate **14** in 90% yield. In turn, this smoothly underwent the RCM reaction furnishing 77% of the cyclized product **15**, as an isomeric mixture (*Z*/*E* > 95:5) of olefins, barely separable by flash chromatography. Minor amounts of oligomeric material were also detected.

Interestingly, a functionalized benzo[10]annulene (benzocyclodecene) derivative has been prepared by oxidation and ring expansion, from 1,4,5,8,9,10-hexahydroanthracene,[14a] and compounds of this class endowed of antitumor activity have been prepared as analogs of the sarcodictyins, terpenoids extracted from the stoloniferan coral *Sarcodictyon roseum*.[14b]

In agreement with previous observations, the ^1H NMR spectrum of the purified major olefin confirmed its identity as the *Z*-isomer,[15] as stemmed from observation of a distinctive coupling constant of 10.8 Hz between both vinylic protons, whereas its isomer *E*-**15** exhibited a coupling constant of 15.6 Hz between its vinylic protons ($\delta_{10\text{-H}}$ = 5.00 and $\delta_{11\text{-H}}$ = 5.62 ppm). The literature records examples of successful RCM reactions in the presence of free alcohols;[16] therefore, it seems likely that acetylation of **13** may provide a more favorable conformational bias of the olefinic side chains for engaging in the intramolecular RCM reaction. Sometimes, RCM has shown to be highly sensitive to minor structural changes.[17]

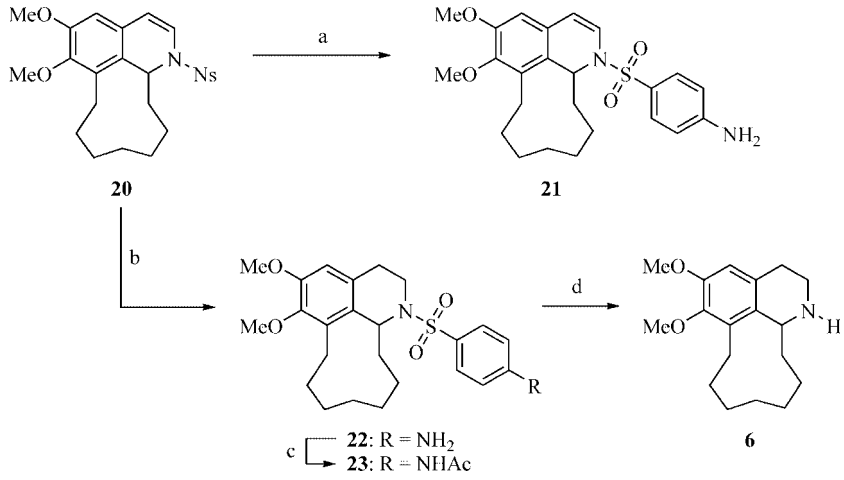
For our synthetic purposes and without previous isomerization, the mixture was submitted to catalytic hydrogenation with PtO_2 in EtOH under atmospheric pressure, furnishing **16** quantitatively. Completion of the sequence towards alcohol **17** was achieved by basic hydrolysis with NaOH in THF/methanol, which uneventfully furnished 91% of the required intermediate.

With a workable route to benzo[10]annulen-5-ol derivative **17**, we turned our attention to the task of building the heterocyclic ring by the use of a modern variation of the Pomeranz–Fritsch methodology.[18] Previous experience suggested that execution of the protocol optimized by Castedo[19] should be advantageous over the implementation of seemingly more straightforward Bobbitt-type strategy,[20]

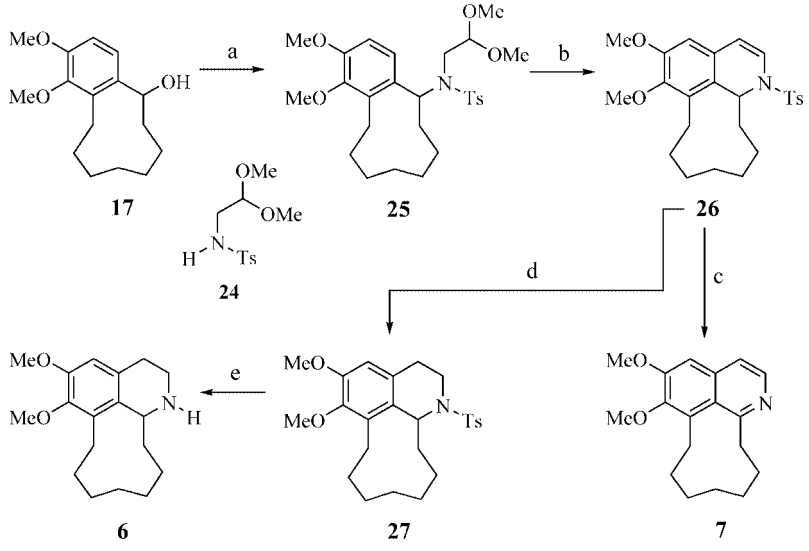
which would require oxidation of **17** to the corresponding ketone, followed by reductive amination and cyclization to the tetrahydroisoquinoline **6**. In fact, we have previously observed that in a similar embodiment the Bobbitt cyclization fails, probably due to insufficient activation of the aromatic ring; this is caused by the presence of two substituents *ortho* to the activating methyl ether located *para* to the ring closure position, which induce the latter to adopt an out-of-plane preferred conformation.[21] In the case of **17**, this is clearly reflected in the downfield shift of the ^{13}C NMR signal of the *ortho*-disubstituted methyl ether (δ = 60.92 ppm), compared with the chemical shift of its neighbor methyl group (δ = 56.12).

Therefore, compound **17** was subjected to a Mitsunobu type sulfonamidation with 4-nitrosulfonamidoacetal (**18**), which in a single operation installed the protected nitrogen and the required two carbon atom chain, ready for cyclization. A modification of the protocol originally conceived by the group of Jackson,[22] in which ethanol was added to improve the yields,[23] allowed transformation of **19** into the octahydro-1*H*-cyclodeca[*ij*]isoquinolin-1-yl sulfonamide derivative **20** in a moderate 68% yield.

It was expected that the use of nosylamido acetal **18** instead of the conventionally employed toluenesulfonyl acetal **24** would provide both, a more effective acidic component for the key C–N bond forming reaction and a more easily removable sulfonamide moiety en route to the synthesis of **7**. However, attempts to remove the nosyl group with the Cs_2CO_3/PhSH reagent met with failure, furnishing a complex mixture of denosylated products. We have recently shown that mild basic reagents such as potassium fluoride supported on alumina effect the oxidative desulfonylation



Scheme 3. Nosylamide-based synthesis of compound **6**. Reagents and conditions: a) H_2 (1 atm), 10% Pd/C, MeOH, room temp., 2.5 h (100%); b) H_2 (6 atm), 10% Pd/C, MeOH, room temp., 2.5 h; c) Ac_2O, pyridine, DMAP (cat.), CH_2Cl_2, r.t. (74% overall); d) 1. Na, NH_3, –33 °C; 2. NH_4Cl (96%).



Scheme 4. Tosylamide-based synthesis of compounds **6** and **7**. Reagents and conditions: a) $TsNHCH_2CH(OMe)_2$ (**24**), PPh_3, DIAD, THF, room temp., 12 h (68%); b) 6 N HCl, EtOH, dioxane, reflux (50%); c) K*t*BuO, 2,6-lutidine, 140 °C (70%); d) 1. H_2 (7 atm), 10% Pd/C, MeOH, r.t. 24 h (100%); e) 1. Na, NH_3, –33 °C; 2. NH_4Cl (98%).

of *N*-sulfonyl-dihydroisoquinoline derivatives to the corresponding isoquinolines;[24] however, this was also unsuitable for our purposes.

Conversely, submission of nosylamide **20** to potassium *tert*-butoxide in refluxing *tert*-butyl alcohol afforded the expected isoquinoline derivative **7** in only 13% yield, which was increased to 28% when pyridine was employed as solvent.

On the other hand, attempts of selective hydrogenation of the double bond in the heterocyclic ring of **20** proved fruitless, providing **21** quantitatively, as depicted in Scheme 3. However, upon reaction at 6 atm employing 10% Pd/C, sulfanilamide **22** was obtained, which was isolated as the *N*-acetyl derivative **23** in 74% overall yield. Submission of the latter to reductive desulfonylation with sodium in liquid ammonia furnished **6** in 96% yield (Scheme 4).

The troublesome conversion of **20** into **6** inclined us to explore a shorter and more efficient alternative. For that purpose, **17** was amidated with sulfonamide **24** resulting in 68% of tosylacetal **25**; in turn, this was submitted to Jackson cyclization, furnishing **26** in 50% yield. This was followed by 10% Pd/C mediated catalytic hydrogenation and mild reductive desulfonylation of the resulting sulfonamide **27** with sodium in liquid ammonia, which afforded tetrahydroisoquinoline derivative **6** in 98% yield.

On the other hand, neither oxidative desulfonylation of **26** with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol nor in pyridine furnished acceptable recoveries of the expected isoquinoline derivative **7**. However, after some experimentation, it was found that carrying out the reaction with potassium *tert*-butoxide in refluxing 2,6-lutidine smoothly effected the desired transformation, affording 70% of **7**.

Conclusions

The synthesis of the unique carbon framework of the stephaoxocanes excentricine and the stephalonganines A, B and C was effected in twelve steps and 10% overall yield from commercially available isovanillin, while the carbon skeleton of stephaoxocanidine was accessed in eleven steps and 7% yield. Further efforts to install the oxygen bridge are underway and will be disclosed in due time.

Experimental Section

General: Melting points were taken with an Ernst Leitz Wetzlar model 350 hot-stage microscope apparatus and are informed uncorrected. FT-IR spectra were determined with a Shimadzu Prestige 21 spectrophotometer as thin films held between NaCl cells or as solid dispersions in KBr disks. The ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ employing TMS as internal standard, with a Bruker AC200-E spectrometer (200.13 and 50.33 MHz for ^{1}H and ^{13}C, respectively) or with a Bruker Avance 300 apparatus (300.13 and 75.48 MHz, for ^{1}H and ^{13}C, respectively). The chemical shifts are consigned in ppm downfield from the internal standard, while coupling constants (*J*) are expressed in Hertz. DEPT 135, DEPT 90 aided the interpretation and assignment of the fully decoupled ^{13}C NMR spectra. In special cases, 2D-NMR experiments (COSY, HMBC and HMQC) were also employed. Pairs of signals, the assignments of which may be exchanged, are marked with # or with an asterisk *; letters d and u are used to designate downfield and upfield protons, respectively, attached to the same carbon atom. Proton and carbon signals belonging to nosyl, tosyl and 4-aminophenylsulfonyl groups are designated as H_{ar} and C_{ar}, respectively. High-resolution mass spectroscopic data were obtained from the Kent Mass Spectrometry Unit 1 (Kent, UK). The reactions were carried out under dry nitrogen or argon, employing oven-dried glassware. Reagents were used as received; dry THF was prepared by distillation from sodium benzophenone ketyl; anhydrous pyridine was prepared by distillation after refluxing the reagent 4 h over pellets of KOH; dry CH_2Cl_2 and Et_3N 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 with Na_2SO_4 and concentrated under reduced pressure. The residue was submitted to flash column chromatography with silica gel 60 H, eluting with hexane/EtOAc mixtures under positive pressure and employing gradient techniques. All new compounds gave single spots on TLC plates (Merck, article number 5554) 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 *p*-anisaldehyde/sulfuric acid reagent and careful heating of the plates for better selectivity.

2-Allyl-3,4-dimethoxybenzaldehyde (9): A mixture of isovanillin (**10**, 1000 mg, 6.58 mmol), allyl bromide (1035 mg, 8.55 mmol) and anhydrous potassium carbonate (1.271 g, 9.21 mmol) in absolute ethanol (10 mL) was refluxed for 3 h. At the end of this time the ethanol was evaporated, brine (20 mL) was added to the residue, and the product was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated, leaving an oil which was purified by chromatography, furnishing **11** (1160 mg, 92%), as an oil. IR (film): $\tilde{\nu}$ = 2934, 2841, 1686, 1585, 1436, 1397, 1268, 1134, 1018, 932, 811, 757, 641 cm^{-1}. ^{1}H NMR (200.13 MHz): δ = 3.96 (s, 3 H, OCH_3), 4.67 (dt, *J* = 1.3, 5.3 Hz, 2 H, $OCH_2CH{=}CH_2$), 5.32 (dd, *J* = 1.3 , 10.5 Hz, 1 H, $OCH_2CH{=}CH_2$), 5.44 (dd, *J* = 1.3, 17.3 Hz, 1 H, $OCH_2CH{=}CH_2$), 6.10 (dddd, *J* = 5.3, 10.5 , 17.3 Hz, 1 H, $OCH_2CH{=}CH_2$), 6.99 (d, *J* = 8.1 Hz, 1 H, 5-H), 7.41 (d, *J* = 1.9 Hz, 1 H, 2-H), 7.47 (dd, *J* = 1.9, 8.1 Hz, 1 H, 6-H), 9.84 (s, 1 H, CHO) ppm. ^{13}C NMR (50.33 MHz): δ = 56.06 (OCH_3), 69.64 ($OCH_2CH{=}CH_2$), 110.58 (C-5),* 110.82 (C-2),* 118.49 ($OCH_2CH{=}CH_2$), 126.67 (C-6), 129.92 (C-1), 132.40 ($OCH_2CH{=}CH_2$), 148.44 (C-3), 154.74 (C-4), 190.71 (CHO) ppm.[11]

Without further purification, a solution of 3-allyloxy-4-methoxybenzaldehyde (**11**, 1110 mg, 5.78 mmol) in 1,2-dichlorobenzene (6 mL) was purged with dry argon and then heated to reflux on a sand bath for 10 h. After cooling, most of the solvent was distilled off under reduced pressure and the remaining thick oil was submitted to chromatography, affording **12** (1080 mg, 97%) as a solid. M.p. 51–53 °C. IR (KBr): $\tilde{\nu}$ = 3425, 2954, 2850, 1679, 1600, 11575, 1492, 1345, 1279, 1165, 1084, 915, 804, 785, 656 cm^{-1}. ^{1}H NMR (200.13 MHz): δ = 3.88 (dt, *J* = 1.6 , 6.0 Hz, 2 H, $ArCH_2CH{=}CH_2$), 3.97 (s, 3 H, OCH_3), 4.99 (dd, *J* = 1.6 , 17.1 Hz, 1 H, $ArCH_2CH{=}CH_2$), 5.01 (dd, *J* = 1.6, 10.7 Hz, 1 H, $ArCH_2CH{=}CH_2$), 5.85 (s, 1 H, OH), 6.03 (dddd, *J* = 6.0, 10.7, 17.1 Hz, $ArCH_2CH{=}CH_2$, 1 H,), 6.87 (d, *J* = 8.4 Hz, 1 H, 5-H), 7.44 (d, *J* = 8.4 Hz, 1 H, 6-H), 10.07 (s, 1 H, CHO) ppm. ^{13}C NMR

(50.33 MHz): δ = 28.27 (Ar*C*H_2CH=CH_2), 55.00 (OCH_3), 108.01 (C-5), 115.24 (ArCH_2CH=*C*H_2), 125.30 (C-6), 127.48 (C-1), 128.21 (C-2), 136.11 (ArCH_2*C*H=CH_2), 143.72 (C-3), 150.65 (C-4), 191.29 (CHO) ppm.[11]

A mixture of the so obtained 2-allyl-3-hydroxy-4-methoxybenzaldehyde (**12**, 1000 mg, 6.58 mmol), methyl iodide (1078 mg, 5.62 mmol) and anhydrous potassium carbonate (1085 mg, 7.86 mmol) in absolute ethanol (10 mL) was submitted to reflux for 8 h. Then the solvent was evaporated and the residue was submitted to the conventional work-up procedure giving **9** (1040 mg, 90%), as an oil. IR (film): $\tilde{\nu}$ = 2939, 2842, 1687, 1637, 1589, 1490, 1282, 1085, 975, 811, 771 cm^{-1}. ^1H NMR (200.13 MHz): δ = 3.81 (s, 3 H, 3-OCH_3), 3.86 (dt, *J* = 1.7 , 5.3 Hz, Ar*C*H_2CH=CH_2), 3.93 (s, 3 H, 4-OCH_3), 4.92 (dd, *J* = 1.7, 16.6 Hz, 1 H, Ar*C*H_2CH=C*H*$_2$), 5.02 (dd, *J* = 1.7, 11.6 Hz, 1 H, Ar*C*H_2CH=C*H*$_2$), 6.04 (dddd, *J* = 5.3, 11.6, 16.6 Hz, 1 H, Ar*C*H_2C*H*=CH_2), 6.92 (d, *J* = 8.6 Hz, 1 H, 5-H), 7.64 (d, *J* = 8.6 Hz, 1 H, 6-H), 10.06 (s, 1 H, CHO) ppm. ^{13}C NMR (50.33 MHz): δ = 28.60 (Ar*C*H_2CH=CH_2), 55.69 (4-OCH_3), 60.84 (3-OCH_3), 109.82 (C-5), 115.50 (Ar*C*H_2CH=*C*H_2), 127.96 (C-1), 128.86 (C-6), 136.10 (C-2), 137.03 (Ar*C*H_2*C*H=CH_2), 147.26 (C-3), 157.42 (C-4), 190.76 (CHO) ppm. MS (EI, 70 eV): *m/z* (%) = 206 (60) [M^+], 191 (100), 175 (30), 163 (20), 147 (21), 131 (24), 115 (17), 103 (38), 91 (30).

The spectroscopic data of the product were in agreement with those informed in ref.[11]

(*Z*)-1,2-Dimethoxy-5,6,7,8,9,12-hexahydrobenzocyclodecen-5-ol (8): A solution of **9** (980 mg, 4.77 mmol) in dry THF (10 mL) was added to a flask containing a cold (0 °C) stirred solution of 5-hexenylmagnesium bromide, prepared from 5-hexenyl bromide (933 mg, 5.72 mmol) and magnesium turnings (273 mg, 11.4 mmol) in THF (8 mL). The resulting reaction mixture was stirred at room temperature for 3 h and then quenched with saturated aqueous NH_4Cl (20 mL). The product was extracted with EtOAc (3 × 40 mL) and the combined organic phases were washed with brine (10 mL) and dried with sodium sulfate. Removal of the solvent under reduced pressure gave an oil which was purified by chromatography, affording **13** (789 mg, 60%), as an oil. IR (film): $\tilde{\nu}$ = 3404, 2931, 2855, 1637, 1601, 1489, 1275, 1080, 995 cm^{-1}. ^1H NMR (200.13 MHz): δ = 1.20–1.80 (m, 7 H, O*H*, 2-H, 3′-H, 4′-H), 2.05 (dd, *J* = 6.7, 10.2 Hz, 2 H, 5′-H), 3.43 (dd, *J* = 4.9, 16.7 Hz, 1 H, Ar*C*H_2CH=CH_2), 3.59 (dd, *J* = 4.9, 16.7 Hz, 1 H, Ar*C*H_2CH=CH_2), 3.80 (s, 3 H, 3-OCH_3), 3.86 (s, 3 H, 4-OCH_3), 4.82 (dd, *J* = 4.6, 7.1 Hz, 1 H, 1′-H), 4.88–5.08 (m, 4 H, 7-H, Ar*C*H_2CH=C*H*$_2$), 5.80 (dddd, *J* = 6.7, 6.7, 10.2, 16.9 Hz, 1 H, 6′-H), 6.00 (dddd, *J* = 5.5, 5.5, 11.4, 16.5 Hz, 1 H, Ar*C*H_2C*H*=CH_2), 6.85 (d, *J* = 8.6 Hz, 1 H, 6-H), 7.20 (d, *J* = 8.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50.33 MHz): δ = 25.56 (C-3′), 28.61 (C-4′), 29.51 (Ar*C*H_2CH=CH_2), 33.43 (C-5′), 38.01 (C-2′), 55.41 (4-OCH_3), 60.50 (3-OCH_3), 69.77 (C-1′), 110.54 (C-5), 114.08 (C-7′), 114.75 (Ar*C*H_2CH=*C*H_2), 121.10 (C-6), 130.53 (C-2), 136.25 (C-1), 137.53 (Ar*C*H_2*C*H=CH_2), 138.63 (C-6′), 146.74 (C-3), 151.53 (C-4) ppm.

Without further purification, alcohol **13** (25 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (22 mL); the solution was stirred under reflux while Grubbs I catalyst (7 mol-%) dissolved in CH_2Cl_2 (1 mL) was added via syringe pump during 2 h. Stirring continued 4 h after the addition; then, the solvent was evaporated under reduced pressure and the residue was chromatographed, furnishing **8** (8 mg, 35%), as an oil. IR (film): $\tilde{\nu}$ = 3397, 2926, 2853, 1601, 1580, 1487, 1279, 1175, 1080, 984, 808, 739 (and 692) cm^{-1}. ^1H NMR (300.13 MHz): δ = 0.80–0.92 (m, 1 H, 7u-H), 1.27–1.36 (m, 1 H, 7d-H), 1.40–1.65 (m, 2 H, 8-H), 1.65–1.80 (br. s, 1 H, OH), 1.87–1.98 (m, 2 H, 6-H), 2.06 (ddd, *J* = 4.8, 8.9, 13.5 Hz, 1 H, 9u-H), 2.60 (ddt, *J* = 3.5, 12.5, 13.5 Hz, 1 H, 9d-H), 3.37 (dt, *J* = 6.3, 12.8 Hz, 1 H, 12u-H), 3.53 (dd, *J* = 11.0, 12.8 Hz, 1 H, 12d-H), 3.86 (s, 3 H, OCH_3-2), 3.88 (s, 3 H, 1-OCH_3), 5.17 (dt, *J* = 4.8, 11.0 Hz, 1 H, 10-H), 5.43 (dd, *J* = 5.7, 10.1 Hz, 1 H, 5-H), 5.77 (dt, *J* = 6.3, 11.0 Hz, 1 H, 11-H), 6.86 (d, *J* = 8.6 Hz, 1 H, 3-H), 7.17 (d, *J* = 8.6 Hz, 1 H, 4-H) ppm. ^{13}C NMR: δ = 20.01 (C-7), 24.47 (C-12), 26.57 (C-9), 29.77 (C-8), 41.38 (C-6), 55.52 (2-OCH_3), 60.54 (1-OCH_3), 69.58 (C-5), 110.87 (C-3), 121.73 (C-4), 128.58 (C-10, C-11), 133.07 (C-12a), 135.19 (C-4a), 145.91 (C-1), 151.46 (C-2) ppm. HRMS calcd. $C_{16}H_{22}O_3$: 262.15689; found 262.15658.

(*Z*)-1,2-Dimethoxy-5,6,7,8,9,12-hexahydrobenzocyclodecen-5-yl Acetate (15): Alcohol **13** (700 mg, 2.54 mmol) was dissolved in dry CH_2Cl_2 (30 mL); pyridine (0.82 mL, 10.2 mmol), DMAP (5 mg) and acetic anhydride (0.723 mL, 7.62 mmol) were successively added and the mixture was stirred at room temperature for 10 h. Then, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography to afford **14** (727 mg, 90%), as an oil. IR (film): $\tilde{\nu}$ = 2933, 2857, 1732, 1637, 1601, 1493, 1371, 1279, 1020, 995, 806 cm^{-1}. ^1H NMR (200.13 MHz): δ = 1.20–1.50 (m, 4 H, 3′-H, 4′-H), 1.50–1.90 (m, 2 H, 2′-H), 1.95–2.15 (m, 2 H, 5′-H), 2.02 (s, 3 H, CH_3CO_2), 3.57 (bd, *J* = 5.1 Hz, 2 H, Ar*C*H_2CH=CH_2), 3.80 (s, 3 H, 3-OCH_3),* 3.85 (s, 3 H, 4-OCH_3),* 4.87–5.07 (m, 4 H, 7′-H, Ar*C*H_2CH=C*H*$_2$), 5.77 (dddd, *J* = 6.6, 6.6, 10.3, 16.9 Hz, 1 H, 6′-H), 5.90 (dd, *J* = 3.6, 7.5 Hz, 1 H, 5′-H), 5.97 (dddd, *J* = 5.1, 5.1, 11.4, 22.1 Hz, 1 H, Ar*C*H_2C*H*=CH_2), 6.82 (d, *J* = 8.5 Hz, 1 H, 6-H), 7.10 (d, *J* = 8.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50.33 MHz): δ = 21.16 (*C*H_3CO_2), 25.30 (C-3′), 28.47 (C-4′), 29.91 (Ar*C*H_2CH=CH_2), 33.42 (C-5′), 36.07 (C-2′), 55.53 (4-OCH_3), 60.65 3-OCH_3), 72.48 (C-1′), 110.51 (C-5), 114.29 (C-7′), 115.06 (Ar*C*H_2CH=*C*H_2), 121.93 (C-6), 131.54 (C-1), 132.64 (C-2), 137.12 (Ar*C*H_2*C*H=CH_2), 138.60 (C-6′), 146.93 (C-3), 152.02 (C-4), 170.27 (CH_3*C*O_2) ppm.

Compound **14** (97 mg, 0.31 mmol) was dissolved in anhydrous CH_2Cl_2 (120 mL) and the stirred solution was submitted to refux, while a solution of Grubbs I catalyst (15 mg, 6 mol-%) in dry CH_2Cl_2 (3 mL) was added via syringe pump during 1 h. Stirring and refluxing continued for 8 h after the addition was completed. Then, the solvent was evaporated and the residue was chromatographed, furnishing *Z*-**15** (68 mg, 77%), as an oil. IR (film): $\tilde{\nu}$ = 2930, 2837, 1730, 1601, 1493, 1371, 1242, 1020, 961, 795 cm^{-1}. ^1H NMR (200.13 MHz): δ = 0.86 (dd, *J* = 13.5, 24.7 Hz, 1 H, 7u-H), 1.30 (dd, *J* = 8.0, 13.5 Hz, 1 H, 7d-H), 1.40–1.68 (m, 2 H, 8-H), 1.85 (ddt, *J* = 1.5, 4.5, 12.6 Hz, 1 H, 6u-H), 1.92–2.15 (m, 2 H, 6d-H, 9u-H), 2.01 (s, 3 H, CH_3CO_2), 2.74 (ddd, *J* = 3.8, 10.8, 24.7 Hz, 1 H, 9d-H), 3.40 (dd, *J* = 6.2, 13.0 Hz, 1 H, 12u-H), 3.68 (dd, *J* = 10.8, 13.0 Hz, 1 H, 12d-H), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.17 (dt, *J* = 4.8, 10.8 Hz, 1 H, 10-H), 5.79 (dt, *J* = 6.2, 10.8 Hz, 1 H, 11-H), 6.43 (dd, *J* = 4.5, 11.8 Hz, 1 H, 5-H), 6.82 (d, *J* = 8.6 Hz, 1 H, 3-H), 7.07 (d, *J* = 8.6 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50.33 MHz): δ = 19.25, 21.18 (*C*H_3CO_2), 24.55, 26.51, 29.58, 38.12 (C-6), 55.37 (2-OCH_3), 60.40 (1-OCH_3), 71.91 (C-5), 110.47 (C-3), 122.28 (C-4), 128.31 (C-10),* 128.64 (C-11),* 131.25 (C-12a), 134.01 (C-4a), 145.80 (C-1), 151.71 (C-2), 170.09 (CH_3*C*O_2) ppm. HRMS calcd. $C_{18}H_{24}O_4$: 304.16746; found 304.16753.

1,2-Dimethoxy-5,6,7,8,9,10,11,12-octahydrobenzocyclodecen-5-ol (17): PtO_2 (26 mg) was added to a solution of **15** (548 mg, 1.89 mmol) in EtOH (40 mL) and the mixture was submitted to hydrogenation at atmospheric pressure and room temperature during 4 h; then, the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure and the resulting oily residue

was chromatographed, providing **16** (550 mg, 100%), as an oil. IR (film): $\tilde{\nu}$ = 2933, 2857, 1733, 1601, 1493, 1372, 1239, 1083, 961, 801 cm^{-1}. ^{1}H NMR (200.13 MHz): δ = 0.70–0.98 (m, 2 H), 1.00–1.40 (m, 2 H), 1.45–1.70 (m, 4 H), 1.85–2.17 (m, 4 H), 1.97 (s, 3 H, CH_3CO_2), 2.95 (dt, J = 7.2, 14.2 Hz, 1 H, 12-H), 3.00 (dt, J = 5.1, 14.2 Hz, 1 H, 12-H), 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.43 (dd, J = 5.9, 11.0 Hz, 1 H, 5-H), 6.85 (d, J = 8.6 Hz, 1 H, 3-H), 7.09 (d, J = 8.6 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50.33 MHz): δ = 20.50, 20.90, 21.29 (CH_3CO_2), 23.35, 24.60, 26.17, 27.95, 35.63 (C-6), 55.41 (2-OCH_3), 60.24 (1-OCH_3), 71.61 (C-5), 110.41 (C-3), 122.16 (C-4), 131.96 (C-4a), 134.84 (C-12a), 146.95 (C-1), 152.02 (C-2), 170.24 (CH_3CO_2) ppm.

Without further purification, **16** (234 mg, 0.80 mmol) was dissolved in THF/MeOH (10:1, 16.5 mL), treated with a solution of NaOH (2.75 N, 1.75 mL), and the resulting biphasic system was stirred 6 h at 50 °C. The mixture was submitted to the conventional work-up procedure, furnishing **17** (220 mg, 91%), as an oil. IR (film): $\tilde{\nu}$ = 3477, 2921, 2857, 1600, 1487, 1271, 1082, 974, 824 cm^{-1}. ^{1}H NMR (200.13 MHz): δ = 0.85 (dt, J = 2.2, 10.3 Hz, 1 H, 8u-H), 1.00–1.20 (m, 2 H, 8d-H, 7u-H), 1.30–1.52 (m, 5 H, 7d-H, 9-H, 10-H), 1.52–1.78 (m, 2 H, OH, 11u-H), 1.90 (ddd, J = 2.5, 5.9, 11.4 Hz, 1 H, 11d-H), 1.93–2.07 (m, 2 H, 6-H), 2.78 (ddd, J = 5.1, 12.1, 13.6 Hz, 1 H, 12u-H), 2.95 (ddd, J = 3.1, 6.0, 13.7 Hz, 1 H, 12d-H), 3.83 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.37 (t, J = 8.1 Hz, 1 H, 5-H), 6.88 (d, J = 8.8 Hz, 1 H, 3-H), 7.15 (d, J = 8.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50.33 MHz): δ = 21.56 (C-7), 21.82 (C-8), 23.97 (C-12), 25.61 (C-9),* 27.15 (C-11), 28.59 (C-10),* 39.47 (C-6), 56.12 (2-OCH_3), 60.92 (1-OCH_3), 63.32 (C-5), 111.50 (C-3), 121.93 (C-4), 134.30 (C-12a), 136.71 (C-4a), 147.57 (C-1), 152.28 (C-2) ppm. HRMS calcd. $C_{16}H_{24}O_3$: 264.17255; found 264.17283.

***N*-(2,2-Dimethoxyethyl)-4-nitrobenzenesulfonamide (18):** Et_3N (1.6 mL, 11.4 mmol) and 4-nitrobenzenesulfonyl chloride (929 mg, 4.2 mmol) were successively added to a solution of aminoacetaldehyde dimethyl acetal (400 mg, 3.89 mmol) in CH_2Cl_2 (25 mL) cooled to –20 °C. The reaction mixture was stirred 6 h at room temperature, when it was diluted with brine (10 mL) and extracted with EtOAc (4 × 25 mL). The organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and chromatographed, yielding **18** (1001 mg, 91%), as an oil. IR (film): $\tilde{\nu}$ = 3700–3300, 3209, 2958, 2899, 1609, 1538, 1464, 1346, 1167, 1095, 970, 858, 735, 612 cm^{-1}. ^{1}H NMR (200.13 MHz): δ = 3.12 (dd, J = 5.3, 5.8 Hz, 2 H, NCH_2), 3.34 (s, 6 H, 2 × OCH_3), 4.36 (t, J = 5.3 Hz, 1 H, CH_2CH), 5.07 (t, J = 5.8 Hz, 1 H, NH), 8.06 (d, J = 8.8 Hz, 2 H, 2-H_{ar}, 6-H_{ar}), 8.37 (d, J = 8.8 Hz, 2 H, 3-H_{ar}, 5-H_{ar}) ppm. ^{13}C NMR (50.33 MHz): δ = 44.49 (NCH_2), 54.64 (2 C, OCH_3), 102.34 [$CH(OCH_3)_2$], 124.22 (C_{ar}-3, C_{ar}-5), 128.17 (C_{ar}-2, C_{ar}-6), 145.77 (C_{ar}-1), 149.96 (C_{ar}-4) ppm. HRMS calcd. $C_{10}H_{14}N_2O_6S$: 290.05726; found 290.05758.

{4-[(5,6-Dimethoxy-7,8,9,10,11,12,13,13a-octahydro-1*H*-cyclodeca-[*ij*]isoquinolin-1-yl)sulfonyl]phenyl}amine (21): Triphenylphosphane (273 mg, 1.04 mmol), *N*-nosylaminoacetal (18, 302 mg, 1.04 mmol) and DIAD (0.20 mL, 1.01 mmol) were sequentially added to a solution of alcohol **17** (87 mg, 0.35 mmol) in dry THF (4 mL) and the solution was stirred 4 h at 60 °C. Then, the solvent was removed under reduced pressure, leaving an oily residue, which was chromatographed furnishing **19** (115 mg, 65%), as an oil. IR (film): $\tilde{\nu}$ = 2938, 2844, 1604, 1531, 1490, 1385, 1275, 1157, 1055, 958, 855, 736, 686 cm^{-1}. ^{1}H NMR (200.13 MHz): δ = 0.80–0.93 (m, 1 H, 7-H), 1.00–1.20 (m, 2 H), 1.30–1.68 (m, 7 H), 1.84 (ddd, J = 4.4, 12.5, 13.5 Hz, 1 H, 6-H), 2.31 (dt, J = 6.0, 12.5 Hz, 1 H, 6-H), 2.71 (ddd, J = 4.9, 14.0, 20.4 Hz, 1 H, 12-H), 2.70–2.80 (m, 1 H, 12-H), 3.30 (dd, J = 3.5, 15.7 Hz, 1 H, CH_2CH), 3.33 (s, 3 H, $CHOCH_3$), 3.37 (s, 3 H, $CHOCH_3$), 3.57 (dd, J = 6.3, 15.7 Hz, 1 H, CH_2CH), 3.80 (s, 3 H, OCH_3-1), 3.82 (s, 3 H, OCH_3-2), 4.39 (dd, J = 3.5, 6.3 Hz, 1 H, $CHOCH_3$), 5.75 (dd, J = 4.7, 12.4 Hz, 1 H, 5-H), 6.68 (d, J = 8.7 Hz, 1 H, 4-H), 7.14 (d, J = 8.7 Hz, 1 H, 3-H), 7.74 (d, J = 8.9 Hz, 2 H, H_{ar}-2, H_{ar}-6), 8.16 (d, J = 8.9 Hz, 2 H, 3-H_{ar}, 5-H_{ar}) ppm. ^{13}C NMR (50.33 MHz): δ = 20.39 (C-9), 20.54 (C-8), 23.39 (C-7), 25.24 (C-12), 26.86 (C-10), 27.71 (C-11), 34.51 (C-6), 46.92 (CH_2CH), 54.87 ($CHOCH_3$), 55.40 ($CHOCH_3$),* 55.48 (2-OCH_3),* 56.71 (C-5), 60.44 (1-OCH_3), 105.11 ($CHOCH_3$), 109.83 (C-3), 122.90 (C-4), 123.49 (C_{ar}-3, C_{ar}-5), 128.14 (C_{ar}-2, C_{ar}-6), 129.80 (C-12a), 135.53 (C-4a), 146.87 (C-1), 147.47 (C_{ar}-1), 149.38 (C_{ar}-4), 152.27 (C-2) ppm.

Without further purification, EtOH (0.22 mL) and 6 N HCl (0.23 mL) were successively added to a cold solution of tosyl acetal **19** (121 mg, 0.23 mmol) in dioxane (1 mL) and the resulting solution submitted to reflux until complete dissapearence of the starting material (30 min). The reaction was then diluted with EtOAc (25 mL) and successively washed with brine (5 mL) containing 10% Na_2CO_3 (0.5 mL) and brine (5 mL). The organic phase was dried with Na_2SO_4, concentrated under reduced pressure and chromatographed, furnishing **20** (73 mg, 68%), as a solid. M.p. 137–139 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 2956, 2861, 1605, 1589, 1479, 1349, 1231, 1174, 1099, 998, 852, 739, 619 cm^{-1}. ^{1}H NMR (200.13 MHz): δ = 0.80–1.10 (m, 1 H, 10d-H), 1.20–1.35 (m, 2 H, 9d-H, 10u-H), 1.35–1.48 (m, 2 H, 11-H), 1.48–1.72 (m, 4 H, 8d-H, 9u-H, 12-H), 1.75–2.15 (m, 3 H, 8u-H, 13-H), 2.63 (ddd, J = 7.4, 14.4, 14.5 Hz, 1 H, 7d-H), 2.67 (ddd, J = 7.4, 14.0, 14.4 Hz, 1 H, 7u-H), 3.70 (s, 3 H, 6-OCH_3), 3.75 (s, 3 H, 5-OCH_3), 5.50 (dd, J = 5.1, 10.1 Hz, 1 H, 13a-H), 6.15 (d, J = 7.1 Hz, 1 H, 3-H), 6.37 (s, 1 H, 4-H), 6.54 (d, J = 7.1 Hz, 1 H, 2-H), 7.77 (d, J = 8.8 Hz, 2 H, H_{Ar}-2, H_{Ar}-6), 8.07 (d, J = 8.8 Hz, 2 H, H_{Ar}-3, H_{Ar}-5) ppm. ^{13}C NMR (50.33 MHz): δ = 21.20 (C-10), 24.14 (C-11), 25.99 (C-12), 26.62 (C-7), 27.33 (C-13), 27.90 (C-9), 31.81 (C-8), 53.10 (C-13a), 54.43 (5-OCH_3), 59.96 (6-OCH_3), 107.61 (C-3), 117.57 (C-4), 121.92 (C-2), 122.06 (C-6a), 123.44 (C_{Ar}-3, C_{Ar}-5), 124.73 (C-13b), 127.43 (C_{Ar}-2, C_{Ar}-6), 132.88 (C-3a), 144.67 (C-6), 148.11 (C_{Ar}-1), 148.60 (C_{Ar}-4), 151.38 (C-5) ppm.

Sulfonamide **20** (13 mg, 0.027 mmol) was dissolved in EtOH (1 mL), 10% Pd/C (2 mg) was added and the resultant mixture was submitted to room temperature hydrogenation at 1 atm. After 4 h, the catalyst was removed by filtration and washed with EtOAc (2 mL). The combined organic fractions were concentrated under reduced pressure and the residue was purified through a short pad of silica, furnishing sulfanilamine **21** (12.1 mg, 100%), as a solid. M.p. 65–67 °C (EtOAc). IR (KBr): $\tilde{\nu}$ = 3472, 3378, 2921, 2850, 1627, 1596, 1479, 1310, 1231, 1153, 1092, 830, 726 cm^{-1}. ^{1}H NMR (200.13 MHz): δ = 0.93 (dt, J = 6.2, 12.0, 12.5 Hz, 1 H), 1.10–1.30 (m, 4 H), 1.33–1.46 (m, 3 H), 1.45–1.75 (m, 3 H), 1.80–2.05 (m, 3 H), 2.61 (ddd, J = 2.6, 10.0, 20.0 Hz, 1 H, 7-H), 2.68 (ddd, J = 10.0, 12.8, 20.0 Hz, 1 H, 7-H), 3.74 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 5.46 (dd, J = 4.4, 9.8 Hz, 1 H, 13a-H), 6.42 (s, 1 H, 4-H), 6.43 (d, J = 8.6 Hz, 2 H, H_{ar}-3, H_{ar}-5), 6.56 (d, J = 7.3 Hz, 1 H, 3-H), 6.78 (d, J = 8.6 Hz, 1 H, 2-H), 7.41 (d, J = 8.6 Hz, 2 H, H_{ar}-2, H_{ar}-6) ppm. ^{13}C NMR (50.33 MHz): δ = 21.19, 24.30, 26.10, 26.44, 27.40, 27.90, 31.44 (C-13), 52.38 (C-13a), 55.43 (5-OCH_3), 60.27 (6-OCH_3), 107.19 (C-3), 113.45 (2 C, C_{ar}-3, C_{ar}-5), 114.01 (C-4), 122.42 (C-2),* 122.99 (C-13b),* 123.20 (C-6a), 125.66 (C_{ar}-1), 127.77 (C-3a), 128.46 (2 C, C_{ar}-2, C_{ar}-6), 132.93 (C-2), 147.57 (C-6), 150.17 (C_{ar}-4), 151.22 (C-5) ppm. HRMS calcd. $C_{24}H_{30}N_2O_4S$: 475.19028 [MH$^+$]; found 475.19075.

***N*-{4-[(5,6-Dimethoxy-2,3,7,8,9,10,11,12,13,13a-decahydro-1*H*-cyclodeca[*ij*]isoquinolin-1-yl)sulfonyl]phenyl}acetamide (23):** 10% Pd/C

(9 mg) was added to a solution of sulfonamide **20** (45.4 mg, 0.096 mmol) in MeOH/EtOAc (1.5:1, 1.7 mL) and the resultant mixture was submitted to room temperature hydrogenation at 6 atm. After 2.5 h, the catalyst was removed by filtration, washed with EtOAc (2 mL) and the combined organic fractions were concentrated under reduced pressure. Without further purification, the oily residue containing **22** was dissolved in CH_2Cl_2 (2 mL) and treated with pyridine (0.034 mL, 0.43 mmol) acetic anhydride (0.03 mL, 0.32 mmol) and a catalytic amount of DMAP. After stirring 3 h at room temperature, brine (5 mL) was added and the organic products were extracted with EtOAc (3 × 25 mL). Drying (Na_2SO_4), concentration under reduced pressure and chromatography of the combined extracts furnished **23** (39 mg, 74%), as a solid. M.p. 168–170 °C (EtOAc). IR (KBr): $\tilde{\nu}$ = 3323, 2938, 2862, 1676, 1591, 1481, 1316, 1260, 1157, 1093, 829, 729, 616 cm^{-1}. ^1H NMR (200.13 MHz): δ = 0.98–1.18 (m, 1 H), 1.27–1.48 (m, 5 H), 1.50–1.73 (m, 4 H), 1.80–2.01 (m, 4 H), 2.14 (s, 3 H, C*H*$_3$CO), 2.52–2.68 (m, 2 H), 2.76 (ddd, *J* = 5.9, 13.0, 15.0 Hz, 1 H), 3.03 (ddd, *J* = 5.9, 9.8, 15.0 Hz, 1 H), 3.20 (ddd, *J* = 5.9, 9.8, 10.5 Hz, 1 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 5.29 (dd, *J* = 8.4, 8.6 Hz, 1 H, 13a-H), 6.43 (s, 1 H, 4-H), 7.45 (d, *J* = 8.8 Hz, 2 H, H_{ar}), 7.53 (d, *J* = 8.8 Hz, 2 H, H_{ar}), 7.71 (br. s, 1 H, $w_{1/2}$ = 9, NH) ppm. ^{13}C NMR (50.33 MHz): δ = 23.21 (*C*H$_3$CO), 24.24, 24.74, 25.92 (C-3), 26.17, 27.58, 27.90, 28.02, 35.42 (C-13), 41.51 (C-2), 52.82 (C-13a), 55.36 (5-O*C*H$_3$), 60.12 (6-O*C*H$_3$), 110.36 (C-4), 118.71 (2 C, C_{ar}-3, C_{ar}-5), 128.00 (2 C, C_{ar}-2, C_{ar}-6), 128.58 (C-13b),* 129.61 (C-6a),* 133.49 (C-3a),# 133.74 (C_{ar}-1),# 141.47 (C_{ar}-4), 145.99 (C-6), 151.09 (C-5), 168.55 (CH$_3$*C*O) ppm. HRMS calcd. $C_{26}H_{23}N_2O_5S$: 487.22667 [MH^+]; found 487.22702.

Synthesis of 5,6-Dimethoxy-2,3,7,8,9,10,11,12,13,13a-decahydro-1*H*-cyclodeca[*ij*]isoquinoline (6) from Acetanilide 23: Anhydrous ammonia (8 mL) was condensed in a three necked flask fitted with a gas inlet tube and a dry ice/acetone condenser protected with a NaOH tube, and containing a solution of **23** (37 mg, 0.08 mmol) in anhydrous THF (1.5 mL). With rapid stirring, sodium metal contained in a graduated glass tube was added portionwise to the reaction mixture until the characteristic blue color persisted for ca. 10 min. The reaction was quenched by addition of NH_4Cl (80 mg), and the ammonia was allowed to evaporate. MeOH (1 mL) and silica gel were then added, the solvent was evaporated under reduced pressure and the adsorbed reaction products were chromatographed (EtOAc/EtOH), furnishing **6** (21 mg, 96%), the spectroscopic data of which were in agreement with those of the tetrahydroisoquinoline derivative obtained from **27**, as described below.

5,6-Dimethoxy-1-[(4-methylphenyl)sulfonyl]-7,8,9,10,11,12,13,13a-octahydro-1*H*-cyclodeca[*ij*]isoquinoline (26): Triphenylphosphane (322 mg, 1.23 mmol), *N*-tosylamino acetal (**24**, 318 mg, 1.23 mmol) and DIAD (0.23 mL, 1.19 mmol) were sequentially added to a solution of alcohol **17** (108 mg, 0.41 mmol) in dry THF (5 mL), and the resulting solution was stirred for 3 h at room temp. Then, the solvent was removed under reduced pressure, leaving an oily residue, which upon chromatography furnished **25** (156 mg, 68%), as an oil. IR (film): $\tilde{\nu}$ = 2937, 2858, 1599, 1491, 1340, 1275, 1156, 1082, 958, 813, 732, 662 cm^{-1}. ^1H NMR (200.13 MHz): δ = 0.66 (dd, *J* = 12.2, 20.6 Hz, 1 H, 7-H), 1.00–1.90 (m, 11 H), 2.37 (s, 3 H, ArCH$_3$), 2.73 (dd, *J* = 3.8, 8.9 Hz, 2 H, 12-H), 3.19 (dd, *J* = 4.5, 15.7 Hz, 1 H, NC*H*$_2$), 3.48 (dd, *J* = 12.4, 15.7 Hz, 1 H, NC*H*$_2$), 3.29 [s, 3 H, CH(OC*H*$_3$)$_2$], 3.41 [s, 3 H, CH(OC*H*$_3$)$_2$], 3.82 (s, 3 H, 1-OCH$_3$),* 3.84 (s, 3 H, 2-OCH$_3$),* 4.41 (dd, *J* = 3.6, 6.2 Hz, 1 H, 5-H), 5.73 [dd, *J* = 4.5, 12.4 Hz, 1 H, C*H*(OCH$_3$)$_2$], 6.74 (d, *J* = 8.6 Hz, 1 H, 3-H), 7.08 (d, *J* = 8.6 Hz, 1 H, 4-H), 7.17 (d, *J* = 8.2 Hz, 2 H, H_{ar}-3, H_{ar}-5), 7.55 (d, *J* = 8.2 Hz, 2 H, H_{ar}-2, H_{ar}-6) ppm. ^{13}C NMR (50.33 MHz): δ = 20.40 (C-9), 21.30 (arCH$_3$), 22.98 (C-8), 25.10 (C-7),# 26.85 (C-12),# 27.92 (C-10), 34.17 (C-6, C-11), 46.52 (N-CH$_2$), 55.12 [CH(O*C*H$_3$)$_2$],* 55.36 [CH(O*C*H$_3$)$_2$],* 55.71 (C-5),* 55.90 (2-OCH$_3$),* 60.42 (1-OCH$_3$), 105.73 [*C*H(OCH$_3$)$_2$], 109.47 (C-3), 123.38 (C-4), 127.10 (C_{ar}-2, C_{ar}-6), 129.14 (C_{ar}-3, C_{ar}-5), 130.14 (C-12a), 135.72 (C-4a), 137.87 (C_{ar}-1), 142.66 (C_{ar}-4), 147.36 (C-1), 152.03 (C-2) ppm.

A cold solution of tosyl acetal **25** (509 mg, 1.0 mmol) and EtOH (1 mL) in dioxane (12 mL) was treated with 6 N HCl (1 mL) and submitted to reflux until complete dissapearence of the starting material. The reaction was then diluted with EtOAc (100 mL) and successively washed with brine containing Na_2CO_3 (5 mL) and brine (5 mL). The organic phase was dried with Na_2SO_4, concentrated under reduced pressure and chromatographed, furnishing **26** (223 mg, 50%), as a solid. M.p. 118–120 °C (hexane/EtOAc). IR (film): $\tilde{\nu}$ = 2920, 1622, 1593, 1480, 1345, 1293, 1163, 1040, 923, 816, 720, 693 cm^{-1}. ^1H NMR (200.13 MHz): δ = 0.80–1.05 (m, 1 H), 1.10–1.45 (m, 4 H), 1.45–1.75 (m, 4 H), 1.75–2.12 (m, 3 H), 2.26 (s, 3 H, ArCH$_3$), 2.60 (ddd, *J* = 6.0, 7.0, 14.4 Hz, 1 H, 7-H), 2.67 (ddd, *J* = 7.0, 7.5, 14.4 Hz, 1 H, 7-H), 3.72 (s, 3 H, 5-OCH$_3$), 3.78 (s, 3 H, 6-OCH$_3$), 5.49 (dd, *J* = 5.1, 10.3 Hz, 1 H, 13a-H), 6.01 (d, *J* = 7.3 Hz, 1 H, 3-H), 6.40 (s, 1 H, 4-H), 6.56 (d, *J* = 7.3 Hz, 1 H, 2-H), 7.05 (d, *J* = 8.0 Hz, 2 H, H_{ar}-3, H_{ar}-5), 7.52 (d, *J* = 8.0 Hz, 2 H, H_{ar}-2, H_{ar}-6) ppm. ^{13}C NMR (50.33 MHz): δ = 21.18 (C-10), 21.25 (C_{ar}-H$_3$), 24.28 (C-11), 26.09 (C-12), 26.47 (C-9), 27.39 (C-8), 27.90 (C-7), 31.59 (C-13), 52.59 (C-13a), 55.43 5-OCH$_3$), 59.87 (6-OCH$_3$), 107.27 (C-3), 114.73 (C-4), 122.31 (C-6a), 122.87 (C-2), 125.46 (C-13b), 126.34 (C_{ar}-2, C_{ar}-6), 129.00 (C_{ar}-3, C_{ar}-5), 132.94 (C-3a), 136.95 (C_{ar}-1), 143.05 (C_{ar}-4), 147.66 (C-6), 151.24 (C-5) ppm. HRMS calcd. $C_{25}H_{31}NO_4S$: 442.20519 [MH^+]; found 442.20475.

5,6-Dimethoxy-2,3,7,8,9,10,11,12,13,13a-decahydro-1*H*-cyclodeca-[*ij*]isoquinoline (6): 10% Pd/C (5 mg) was added to a solution of **26** (50 mg, 0.11 mmol) in EtOAc/MeOH (2:1, 3 mL) containing 6 N HCl (0.01 mL) and the reaction was submitted to room temperature hydrogenation at 7 atm during 6 h. Then, the catalyst was removed by filtration, washed with EtOAc (2 mL) and the combined organics were filtered through a short path of silica, furnishing **27** (50 mg, 100%), as an oil. IR (film): $\tilde{\nu}$ = 2933, 2855, 1599, 1483, 1339, 1231, 1160, 1089, 986, 817, 731, 689 cm^{-1}. ^1H NMR (300.13 MHz): δ = 0.95–1.07 (m, 1 H), 1.10–1.50 (m, 5 H), 1.50–1.80 (m, 3 H), 1.80–2.06 (m, 3 H), 2.31 (s, 3 H, Ar*C*H$_3$), 2.54–2.67 (m, 2 H, 7-H), 2.74 (ddd, *J* = 6.9, 13.9, 14.4 Hz, 1 H, 3u-H), 2.99 (ddd, *J* = 6.2, 10.8, 14.4 Hz, 1 H, 3d-H), 3.21 (ddd, *J* = 6.2, 10.3, 10.8 Hz, 1 H, 2u-H), 3.70–3.85 (m, 1 H, 2d-H), 3.75 (s, 3 H, 6-OCH$_3$), 3.79 (s, 3 H, 5-OCH$_3$), 5.29 (dd, *J* = 6.2, 9.1 Hz, 1 H, 13a-H), 6.42 (s, 1 H, 4-H), 7.08 (d, *J* = 7.4 Hz, 2 H, H_{ar}-3, H_{ar}-5), 7.49 (d, *J* = 7.4 Hz, 2 H, H_{ar}-2, H_{ar}-6) ppm. ^{13}C NMR (75.4 MHz): δ = 21.37 (ar*C*H$_3$), 23.37, 24.90, 26.05, 26.30, 27.80, 28.06, 28.16, 35.57 (C-13), 41.70 (C-2), 52.87 (C-13a), 55.55 (5-OCH$_3$), 60.17 (6-OCH$_3$), 110.45 (C-4), 127.03 (C_{ar}-2, C_{ar}-6), 128.92 (C-13b), 129.19 (C-6a), 129.82 (C_{ar}-3, C_{ar}-5), 133.71 (C-3a), 136.41 (C_{ar}-4), 142.64 (C_{ar}-1), 146.13 (C-6), 151.16 (C-5) ppm.

The tetrahydroisoquinoline derivative **27** (50 mg, 0.11 mmol) was dissolved in anhydrous THF (1.5 mL) and transferred to a three-necked flask fitted with a gas inlet tube and a dry ice/acetone condenser protected with a NaOH tube in which anhydrous ammonia (8 mL) was condensed. With rapid stirring, sodium metal contained in a graduated glass tube was added portionwise to the reaction mixture until the characteristic blue color persisted for ca. 10 min. The reaction was quenched by addition of NH_4Cl (100 mg), and the ammonia was evaporated. MeOH (1 mL) and silica gel were then added, the solvent was evaporated under reduced pressure and

the adsorbed reaction products were chromatographed (EtOAc/EtOH), furnishing **6** (32.5 mg, 98%), as a solid. M.p. 216–218 °C. IR (KBr): $\tilde{\nu}$ = 3650–3320, 3200–2400, 1588, 1475, 1308, 1235, 1122, 1022, 921, 842, 731, 644 cm^{-1}. ^1H NMR (200.13 MHz): δ = 1.21–1.48 (m, 4 H, 9-H, 10-H, 11-H), 1.52–1.77 (m, 5 H, 8-H, 9-H, 11-H, 12-H), 1.80–2.06 (m, 2 H, 8-H, 13-H), 2.13–2.39 (m, 1 H, 13-H), 2.59 (ddd, J = 3.4, 3.5, 10.5 Hz, 1 H, 7-H), 2.90 (ddd, J = 3.4, 3.6, 10.5 Hz, 1 H, 7-H), 3.03 (ddd, J = 6.1, 17.7 Hz, 2 H, 3-H), 3.31 (ddd, J = 3.4, 6.1, 9.6 Hz, 1 H, 2-H), 3.71 (ddd, J = 3.4, 6.1, 9.6 Hz, 1 H, 2-H), 3.80 (s, 3 H, 6-OCH_3), 3.84 (s, 3 H, 5-OCH_3), 4.95 (t, J = 6.8 Hz, 1 H, 13a-H), 6.58 (s, 1 H, 4-H), 9.58 (br. s, 1 H, $w_{1/2}$ = 9, NH) ppm. ^{13}C NMR (50.33 MHz): δ = 23.74 (C-9),* 25.19 (C-10), 25.44 (C-3), 25.81 (C-12), 25.97 (C-7), 27.71 (C-11),* 28.12 (C-8), 31.49 (C-13), 36.98 (C-2), 51.36 (C-13a), 55.42 (5-OCH_3), 60.05 (6-OCH_3), 110.59 (C-4), 124.14 (C-6a),* 127.79 (C-13b),* 134.86 (C-3a), 146.85 (C-6), 152.05 (C-5) ppm. HRMS calcd. $C_{18}H_{28}NO_2$: 290.21200 [MH^+]; found 290.21235.

5,6-Dimethoxy-8,9,10,11,12,13-hexahydro-7*H*-cyclodeca[*ij*]isoquinoline (7): A solution of **20** (31 mg, 0.07 mmol) in freshly distilled pyridine (1 mL) was treated with potassium *tert*-butoxide (81 mg, 0.72 mmol) and the reaction was stirred under reflux for 2 h. Then, the reaction was submitted to the conventional work-up procedure, furnishing **7** (5.3 mg, 28%), as a solid. M.p. 94–96 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 2924, 2845, 1604, 1589, 1466, 1370, 1262, 1150, 1027, 963, 868, 797, 642 cm^{-1}. ^1H NMR (200.13 MHz): δ = 0.85–0.95 (m, 1 H), 1.15–1.40 (m, 2 H), 1.40–1.88 (m, 4 H), 1.90–2.22 (m, 4 H), 2.85–3.15 (m, 1 H, 7-H), 3.20–3.60 (m, 2 H, 13-H), 3.89 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 7.00 (s, 1 H, 4-H), 7.39 (d, J = 5.4 Hz, 1 H, 3-H), 8.25 (d, J = 5.4 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50.33 MHz): δ = 21.66, 24.11, 26.92, 27.55, 28.71, 28.82, 36.10 (C-13), 55.41 (5-OCH_3), 61.05 (6-OCH_3), 105.18 (C-4), 119.27 (C-3), 122.48 (C-13b), 134.05 (C-6a), 137.10 (C-3a), 140.08 (C-2), 148.56 (C-6), 154.29 (C-5), 162.08 (C-13a) ppm. HRMS calcd. $C_{18}H_{23}NO_2$: 286.18069 [MH^+]; found 286.18042.

Synthesis of 5,6-Dimethoxy-8,9,10,11,12,13-hexahydro-7*H*-cyclodeca[*ij*]isoquinoline (7) from Tosylamide 26: A solution of **26** (60 mg, 0.14 mmol) in freshly distilled 2,6-lutidine (2 mL) was treated with potassium *tert*-butoxide (135 mg, 1.22 mmol) and the reaction was stirred under reflux for 3 h. Then, the reaction was submitted to the conventional work-up procedure, furnishing **7** (28 mg, 70%), the melting point and spectroscopic data of which were in agreement with those of the tetrahydroisoquinoline derivative obtained from **20**.

Supporting Information (see also the footnote on the first page of this article): Copies of the ^{13}C NMR spectra of the target compounds and synthetic intermediates are provided.

Acknowledgments

The authors are indebted with the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Universidad Nacional de Rosario (UNR) and Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) for financial support (projects PIP N° 5439, PICT N° 06-12532 and PICT N° 06-38165). A. B. J. B. is also thankful to CONICET for a doctoral fellowship.

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Received: June 20, 2007
Published Online: August 28, 2007

