Model Studies Towards Stephaoxocanes: Construction of the 2-Oxa-4-aza-phenalene Core of Stephaoxocanidine and Eletefine

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Dedicated to Professor Edmundo A. Rúveda on the occasion of his 70th birthday

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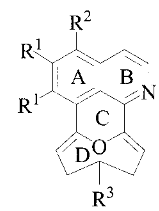
The construction of the polysubstituted 1*H*,3*H*-2-oxa-4-aza-phenalene **4** by means of consecutive oxa-Pictet–Spengler and Jackson cyclizations is reported. This compound contains the ABC ring system of the novel isoquinoline alkaloids stephaoxocanidine and eletefine, found in *Stephania cepharantha* and *Cissampelos glaberrima*. Both these species are Menispermaceæ used in folk medicine in the Far East and Brazil.

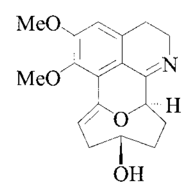
Introduction

The novel tetracyclic stephaoxocane skeleton **1a** is common to a small family of isoquinoline alkaloids, revealed in recent years through the work of Japanese,[1,2] Chinese[3,4] and Brazilian[5] research groups.

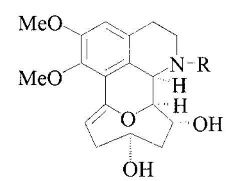
To date, the isolation of only five stephaoxocanes (**1b**−**f**) has been reported, their source being plants of the Menispermaceæ family employed in folk medicine.[6,7] Stephaoxocanidine (**1b**, isolated from *Stephania cepharantha*) and eletefine (**1c**, which occurs in *Cissampelos glaberrima*, better known as *C. pareira*), have fully unsaturated AB rings, whereas their congeners stephaoxocanine **1d**, eccentricine **1e**, and *N*-methyleccentricine **1f** display dihydro and tetrahydro-substituted AB ring systems, respectively. Most noteworthy is the fact that the stephaoxocanes bear a close structural relationship to other tetracyclic isoquinoline derivatives, such as the tropoloisoquinolines grandirubrine **2a** and imerubrine **2b**, and the azafluoranthenes, exemplified by telitoxine **3a** and imeluteine **3b**. These are biosynthetically related alkaloids isolated from Menispermaceæ (including *C. pareira*[8,9]), which have demonstrated interesting cytotoxic and antitumor activity as well as healing properties.[10,11]



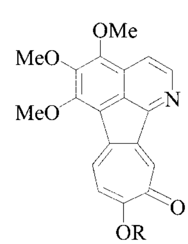
1a $R^1 = R^2 = R^3 = H$
1b $R^1 = OMe$, $R^2 = H$, $R^3 = OH$
1c $R^1 = R^2 = OMe$, $R^3 = OH$



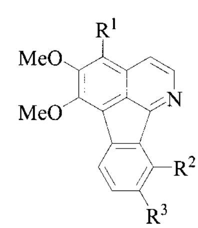
1d



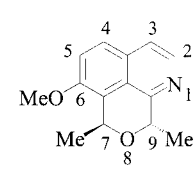
1e R = H
1f R = Me



2a R = H
2b R = Me



3a $R^1 = R^3 = H$, $R^2 = OH$
3b $R^1 = R^2 = R^3 = OMe$



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Previously, we have shown that appropriate modifications of the scarcely used Jackson sulfonamidoacetal cyclization protocol[12] result in useful intermediates for the elaboration of polysubstituted isoquinolines,[13] tetrahydroisoquinolines,[14,15] and tetahydroprotoberberines.[16] We have also reported the synthesis of a tetrahydro-2-oxa-4-azaphenalene lactone derivative related to the stephaoxocanes.[17]

We describe here a short synthesis of the substituted 2-oxa-4-azaphenalene **4** (which contains the ABC ring system of stephaoxocanidine **1b** and eletefine **1c**), starting from the aldehyde **5**. This tricyclic structural unit, unique to the stephaoxocanes, constitutes an unprecedented heterocyclic ring system.

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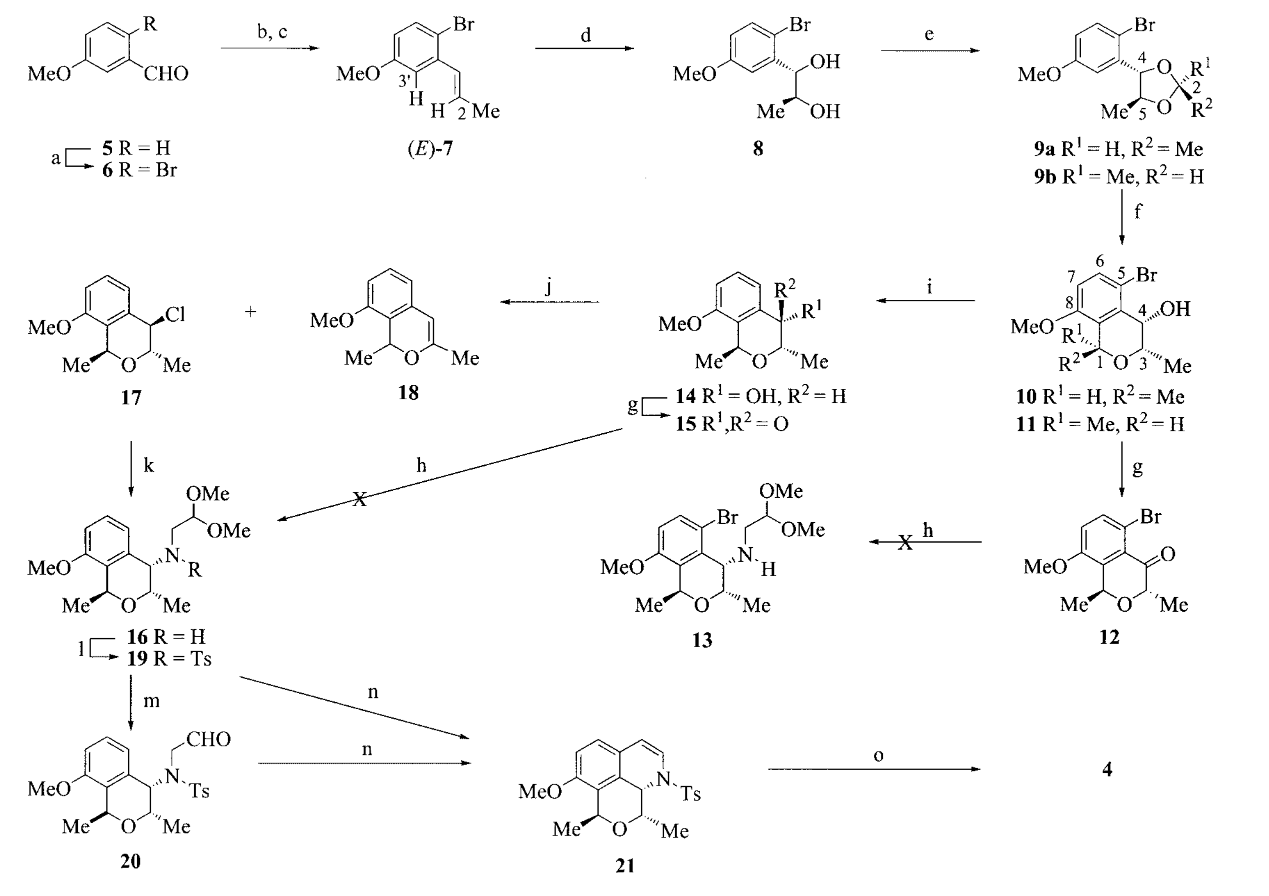
Our approach is based on the application of an intramolecular version of the poorly exploited oxa-Pictet−Spengler cyclization of β-phenethyl alcohols[18] for isochroman ring formation and the use of a novel modification[19] of the protocol originally reported by Jackson and co-workers[12,20] for the construction of the isoquinoline moiety.

Results and Discussion

In order to favor the construction of the required isochroman bearing a contiguously substituted aromatic moiety, the aldehyde **5** was first brominated,[21] furnishing **6** in 93 % yield,[22] as depicted in Scheme 1. Next, olefination of bromoaldehyde **6** with MeCH=PPh_3 afforded an inseparable mixture of isomeric β-methylstyrene derivatives (*E*/*Z* approx. 0.7:1) in 90 % yield, which was equilibrated to the most stable isomer (*E*)-**7** (*E*/*Z* > 20:1) with thiophenol in toluene at 80 °C under AIBN promotion, in almost quantitative yield. The stereochemical assignment of (*E*)-**7** was supported by ^1H NMR spectroscopic data ($J_{H-1,H-2}$ = 15.6 Hz), especially differential NOE spectroscopy. The H-2 proton coupled to the methyl group (J = 6.6 Hz) showed a signal enhancement of 14 % upon irradiation of its aromatic neighbor (H-3′), whereas irradiation of H-2 produced a 6 % increase in the size of H-3′ doublet.

Continuing with the synthesis, the OsO_4-catalyzed dihydroxylation of (*E*)-**7** [employing *N*-methyl morpholine *N*-oxide (NMO) as co-oxidant] cleanly furnished *threo*-diol **8** in 85 % yield. This was transacetalized with acetaldehyde dimethyl acetal and a catalytic amount of camphorsulfonic acid to provide the epimeric acetals **9a** and **9b** as an inseparable mixture in 95 % yield (**9a**:**9b** approx. 2.7:1).[23] Using the oxa-Pictet−Spengler conditions, this was cyclized with $TiCl_4$ at −78 °C to afford a 2:1 mixture of isochroman-4-ols in a combined yield of 84 %. These were identified as **10** and **11** on the basis of their NMR spectra, including differential NOE experiments and results from Giles and co-workers.[24] These authors studied in detail the isomerization of 4-phenyldioxolanes (related to **9**) to the corresponding isochroman-4-ols, and found that the stereochemistry at C-4 and C-5 was transferred unchanged to C-4 and



Scheme 1. Reagents and conditions: a) Br_2 (3 equiv.), AcOH, 5 °C → room temp., overnight (93 %); b) (1) NaH, DMSO/THF, 60 °C, 2 h, (2) $EtP^+Ph_3I^-$, THF, 60 °C, 20 min, (3) Bromoaldehyde **6**, 60 °C, 2 h, room temp., overnight (90 %, *E*/*Z* ≈ 0.7); c) PhSH, AIBN, $PhCH_3$, 80 °C, 2 h, (99 %, *E*/*Z* > 20); d) OsO_4 (0.02 equiv.), NMO (1.25 equiv.), acetone/H_2O (2:1), 0 °C → room temp., overnight (85 %); e) $CH_3CH(OCH_3)_2$ (3 equiv.), CSA (0.1 equiv.), CH_2Cl_2, 4 h, 35 °C (95 %); f) $TiCl_4$ (2 equiv.), CH_2Cl_2, −78 °C (84 %); g) (1) DMSO, TFAA, CH_2Cl_2, −60 °C, 20 min, (2) **10** or **14**, in CH_2Cl_2, 10 min, (3) Et_3N, −60 °C → room temp., 30 min (**10** → **12**, 96 %; **14** → **15**, 94 %); h) $NaCNBH_3$, $H_2NCH_2CH(OCH_3)_2$ (5 equiv.), AcOH, EtOH, room temp. (**12** → **10**, 84 %; **15** → **14**, 87 %); i) Bu_3SnH, C_6H_{12}, hν (254 nm), room temp., 2 h (97 %); j) MsCl, Et_3N, CH_2Cl_2, −10 °C, overnight (**17**, 84 %; **18**, < 5 %); k) $H_2NCH_2CH(OCH_3)_2$, *i*Pr_2NEt, DMSO−$PhCH_3$ (1:1), 70 °C, 48 h (79 %); l) TsCl, Et_3N, $CHCl_3$, reflux, 36 h (96 %); m) 6 N HCl, dioxane, reflux, 2.5 h (86 %); n) 6 N HCl, dioxane, EtOH, reflux, 2.5 h (**19** → **21**, 81 %; **20** → **21**, 79 %); o) K*t*BuO, pyridine, 100 °C, 1 h (97 %).

C-3, respectively. Isochroman-4-ol **10**[25] was then employed for the construction of the nitrogen-containing ring in a strategy involving Jackson's isoquinoline synthesis. However, initial efforts directed to effect a one-pot introduction of the aminoethyl residue (required to form the isoquinoline ring) by sulfonamidation of **10** with *N*-tosyl aminoacetal[26] were unsuccessful. In addition, in spite of the fact that oxidation of bromo alcohol **10** gave 96 % of ketone **12**, attempts to reductively aminate **12** with the aid of sodium cyanoborohydride[27] failed to provide aminoacetal **13**, furnishing instead precursor **10**. This outcome was presumably due to steric hindrance, which might have made the condensation step between the amine and the carbonyl to form a reducible imine intermediate difficult. Therefore, aryl bromide **10** was subjected to a photochemically assisted debromination with tributyltin hydride,[28] furnishing an excellent yield of **14**,[23] which was smoothly oxidized to the related ketone **15** in 90 % yield from **10**. Nevertheless, **15** was also reluctant to undergo reductive amination to **16**, being preferentially reduced to its precursor, the isochroman-4-ol **14**.

In the hope that amination of benzylic halide **17** would lead to successful C−N bond formation, alcohol **14** was halogenated with the novel thionyl chloride−benzotriazole reagent;[29] however, only low yields of **17** (15−20 %) were obtained. The non-inverted sulfite was the major reaction product, presumably because of steric crowding at the benzylic position. Therefore, **14** was treated with the methanesulfonyl chloride−triethylamine reagent, smoothly providing the inverted pseudoequatorial chloride **17**[30,31] in 84 % yield with perfect stereocontrol ($J_{H-3,H-4}$ = 8.9 Hz), presumably by nucleophilic inversion of the initially formed mesylate.

Excess methanesulfonyl chloride (3 equiv.) was required in order to achieve complete conversion, probably due to the poor stability of the sulfene intermediate. A similar transformation yielding a pseudoaxial chloride from the corresponding pseudoequatorial alcohol had previously been reported, employing a different set of reagents.[32] In our reaction, small amounts (< 5 %) of the dehydration product **18** were also isolated. This compound was recognized by the characteristic coupling between H-4 (δ = 5.51 ppm, q, *J* = 0.8 Hz) and Me-3 (δ = 1.89 ppm, d, *J* = 0.8 Hz).

To our delight, benzylic chloride **17** was cleanly and completely aminated[33] with 2,2-dimethoxyethylamine after two days at 70 °C in a 1:1 DMSO/toluene solvent mixture containing *N*-ethyl diisopropylamine as a promoter and acid scavenger. This afforded 86 % of acetal **16**, the spectroscopic data of which ($J_{H-3,H-4}$ = 2.4 Hz) provided evidence of configurational inversion.[32] Worthy of note is that the reaction proceeded without formation of the elimination product **18**. It has been observed that this transformation is highly sensitive to steric bulk;[34] therefore, assuming that the reaction time required for completion is a measure of the steric hindrance at the benzylic center, this unusually slow reaction may imply that steric crowding was responsible for the reluctance of **12** and **15** to undergo reductive amination.

Tosylation of aminoacetal **16** under forcing conditions then furnished a nearly quantitative yield of **19**, which, when submitted to the conventional Jackson cyclization protocol,[35] surprisingly resulted in only small amounts of the 1,2-dihydroisoquinoline **21**. The related aldehyde **20** (δ_{CHO} = 9.23 ppm, t, *J* = 2.2 Hz) accounted for the mass difference. After considerable experimentation, it was concluded that acetal hydrolysis and acetal cyclization were competing transformations and that the rigidity and strain introduced by the heterocyclic ring hindered cyclization of **19** in favor of aldehyde formation.[36] This would necessitate minimizing hydrolysis in order to drive the cyclization to completion.

The simplest and most expedient way of doing this consisted of adding excess ethanol to the reaction medium in order to regenerate the acetal in situ. Gratifyingly, this provided the tricyclic compound **21** in 81 % yield after 2.5 h. Interestingly enough, recycling of the aldehyde by addition of ethanol[37] to pure **20** in a mixture of dioxane and 6 N HCl was also successful, rapidly and efficiently turning the otherwise uncyclizable aldehyde **20** into the desired sulfonamide **21** in 79 % yield.[38] The final step was oxidative desulfonylation. However, submission of **21** to the conditions for elimination of sulfonamide (potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, as in the original literature procedure[35]) resulted in extensive decomposition; only small amounts of the desired oxazaphenalene **4** could be isolated. In a search for more effective conditions, it was observed that by performing the elimination in refluxing pyridine, clean and complete desulfonylation could be readily achieved. Moreover, when the reaction was performed in [D$_5$]pyridine in an NMR tube and the ^{1}H NMR spectrum of the mixture taken after 30 minutes at room temperature, approximately 10 % conversion was apparent. The structure and stereochemical assignment of compound **4** was unequivocally confirmed by NMR analysis, including 2D NMR (HETCOR) experiments.

Conclusion

The synthesis of 2-oxa-4-azaphenalene **4**, related to the ABC ring system of the novel stephaoxocanes stephaoxocanidine **1b** and eletefine **1c**, was conveniently achieved by sequential application of an intramolecular oxa-Pictet−Spengler reaction and Jackson's tosylacetal cyclization. Three simple but critical modifications to Jackson's original protocol resulted in (i) incorporation of the aminoethyl residue required for the construction of the nitrogen heterocycle in high yield, (ii) efficient formation of the 1,2-dihydroisoquinoline derivative **21**, and (iii) the clean transformation of this compound into the final product, the 2-oxa-4-azaphenalene **4**. Use of the above strategy for the synthesis of more advanced stephaoxocane intermediates is currently under investigation and will be reported in due course.

Experimental Section

General Remarks: Melting points are uncorrected and were taken on an Ernst Leitz Wetzlar model 350 hot-stage microscope apparatus. FT-IR spectra were taken with a Bruker IFS 25 spectrophotometer as dispersions in KBr disks (for solids) or as thin films held between NaCl cells (for oils). The ^{1}H NMR (200.13 MHz) and ^{13}C NMR (50.33 MHz) spectra were acquired in $CDCl_3$ with tetramethylsilane as the internal standard, employing a Bruker AC200-E spectrometer. Assignments were made with the aid of differential NOE and selective irradiation techniques, DEPT experiments and 2D NMR spectra; an asterisk means that assignments may be exchanged. HRMS data were obtained from Kent Electronics (UK) and UMyMFOR (Argentina). Reactions were carried out under dry N_2 or Ar atmospheres, employing oven-dried glassware. Commercially obtained reagents were used without further purification. Anhydrous CH_2Cl_2 and $CHCl_3$ were purified by refluxing over P_2O_5 and distillation; dry pyridine was purified by refluxing over NaOH pellets followed by distillation; anhydrous DMSO was obtained by distillation from CaH_2 under reduced pressure; toluene and cyclohexane were distilled from sodium benzophenone ketyl prior to use; dry solvents were stored in dry Schlenk flasks. All new compounds gave single spots on TLC plates run in different solvent systems. Spots were detected by exposure to UV light (254 and 365 nm), followed by spraying with ethanolic *p*-anisaldehyde/sulfuric acid and careful heating. Standard workup procedures consisted of adding brine (5−20 mL) and extracting the products with EtOAc (3 × 20−40 mL); the organic extracts were then combined, washed once with brine, dried over Na_2SO_4, concentrated under reduced pressure and the residue chromatographed. Flash column chromatography was carried out with silica gel 60 H, eluting with hexane/EtOAc mixtures of increasing polarity. Supporting Information for this article (Synthesis and spectroscopic data for compounds **6−9**, **12**, **15**, **18** and **20** and spectra of **4**, **10−12**, **14** and **16−21**) is available; see also the footnote on the first page of this article.

(1*S,3*S**,4*S**)-5-Bromo-8-methoxy-1,3-dimethylisochroman-4-ol (10) and (1*R**,3*S**,4*S**)-5-Bromo-8-methoxy-1,3-dimethylisochroman-4-ol (11):** A freshly prepared solution of $TiCl_4$ in CH_2Cl_2 (0.902 M, 3.85 mL, 3.47 mmol) was added to a mixture of dioxolanes **9a** and **9b** (453 mg, 1.58 mmol) in dry CH_2Cl_2 (33 mL) cooled to −78 °C. The reaction was stirred for 2 h at −78 °C under an argon atmosphere, quenched with MeOH (1.5 mL) and allowed to warm to room temperature. Saturated $NaHCO_3$ (5 mL) was added and the reaction was submitted to the standard workup procedure, furnishing isochroman-4-ol **11** (132 mg, 0.46 mmol, 29 %), as a colorless oil. IR: ṽ = 3430, 2976, 2836, 1577, 1466, 1367, 1285, 1253, 1193, 1166, 1117, 1066, 993, 812, 777, 622 cm^{-1}. ^{1}H NMR: δ = 1.40 (d, *J* = 6.4 Hz, 3 H, CH_2−3), 1.56 (d, *J* = 6.2 Hz, 3 H, CH_3−1), 2.09 (d, *J* = 9.6 Hz, 1 H, OH-4), 3.69 (dq, J_1 = 1.2, J_2 = 6.4 Hz, 1 H, H-3), 3.81 (s, 3 H, OCH_3), 4.49 (dd, J_1 = 1.2, J_2 = 9.6 Hz, 1 H, H-4), 4.93 (q, *J* = 6.2 Hz, 1 H, H-1), 6.72 (d, *J* = 8.8 Hz, 1 H, H-7) and 7.45 (d, *J* = 8.8 Hz, 1 H, H-6) ppm. ^{13}C NMR: δ = 16.69 (CH_3−3), 21.57 (CH_3−1), 55.23 (OCH_3), 68.33 (C-4), 70.83 (C-1), 71.98 (C-3), 111.58 (C-7), 115.73 (C-5), 130.52 (C-8a), 131.07 (C-6), 136.53 (C-4a), 155.23 (C-8) ppm. HRMS: calcd. $C_{12}H_{15}BrO_3$: 286.02046; found 286.02024. Increasing the solvent polarity allowed the isolation of isochroman-4-ol **10** (248 mg, 0.86 mmol, 55 %) as a white solid. M.p. 116−117 °C (hexane/EtOAc). IR: ṽ = 3415, 2976, 2932, 1577, 1464, 1438, 1399, 1355, 1323, 1285, 1256, 1195, 1152, 1125, 1098, 1061, 991, 954, 940, 852, 818, 809, 777, 721, 647, 614 cm^{-1}. ^{1}H NMR: δ = 1.40 (d, *J* = 6.4 Hz, 3 H, CH_3−3), 1.47 (d, *J* = 6.6 Hz, 3 H, CH_3−1), 2.00 (d, *J* = 8.9 Hz, 1 H, OH-4), 3.80 (s, 3 H, OCH_3), 4.11 (dq, J_1 = 1.7, J_2 = 6.4, 1 H, H-3), 4.44 (dd, J_1 = 1.7, J_2 = 8.9, 1 H, H-4), 5.08 (q, *J* = 6.6 Hz, 1 H, H-1), 6.69 (d, *J* = 8.7 Hz, 1 H, H-7), 7.45 (d, *J* = 8.7 Hz, 1 H, H-6) ppm. ^{13}C NMR: δ = 16.82 (CH_3−3), 17.80 (CH_3−1), 55.40 (OCH_3), 66.20 (C-4), 67.01 (C-1), 68.44 (C-3), 111.19 (C-7), 115.79 (C-5), 130.27 (C-8a), 131.36 (C-6), 135.46 (C-4a), 154.46 (C-8) ppm. HRMS: calcd. $C_{12}H_{15}BrO_3$: 286.02046; found 286.02039. $C_{12}H_{15}BrO_3$ (286.02): calcd. C 50.19, H 5.27; found C 50.03, H 5.37.

(1*S,3*S**,4*S**)-8-Methoxy-1,3-dimethylisochroman-4-ol (14):** A suspension of bromo alcohol **10** (125 mg, 0.44 mmol) in dry, oxygen-free cyclohexane (7.35 mL) was treated with Bu_3SnH (0.35 mL, 1.31 mmol) under a dry argon atmosphere and the reaction was irradiated (254 nm radiation) for 2 h. The resultant pale yellow solution was concentrated under reduced pressure; chromatography of the residue furnished debrominated alcohol **14** (88 mg, 0.42 mmol, 97 %) as a white solid. M.p. 58−60 °C (hexane/EtOAc). IR: ṽ = 3429, 3384, 2973, 2938, 2928, 2919, 2904, 1590, 1473, 1461, 1436, 1353, 1257, 1129, 1105, 1082, 1065, 1048, 987, 832, 808, 756, 748 cm^{-1}. ^{1}H NMR: δ = 1.37 (d, *J* = 6.4 Hz, 3 H, CH_3−3), 1.50 (d, *J* = 6.6 Hz, 3 H, CH_3−1), 1.83 (d, *J* = 10.1 Hz, 1 H, OH-4), 3.82 (s, 3 H, OCH_3), 4.14 (dq, J_1 = 1.8, J_2 = 6.4 Hz, 1 H, H-3), 4.19 (dd, J_1 = 1.8, J_2 = 10.1 Hz, 1 H, H-4), 5.11 (q, *J* = 6.6 Hz, 1 H, H-1), 6.81 (dd, J_1 = 1.0, J_2 = 8.2, 1 H, H-7), 7.01 (dd, J_1 = 1.0, J_2 = 7.6, 1 H, H-5), 7.26 (dd, J_1 = 7.6, J_2 = 8.2, 1 H, H-6) ppm. ^{13}C NMR: δ = 16.81 (CH_3−3), 17.87 (CH_3−1), 55.10 (OCH_3), 66.03 (C-3), 68.00 (C-4)*, 68.63 (C-1)*, 109.64 (C-7), 121.88 (C-5), 127.34 (C-8a), 127.68 (C-6), 136.70 (C-4a), 154.94 (C-8) ppm. HRMS: calcd. $C_{12}H_{16}O_3$: 208.10995; found 208.10988.

(1*S,3*S**,4*S**)-(2,2-Dimethoxyethyl)(8-methoxy-1,3-dimethylisochroman-4-yl)amine (16):** An ice-water-cooled solution of methanesulfonyl chloride (0.19 mL, 2.41 mmol) in CH_2Cl_2 (7 mL) was slowly (3 h) added to a mixture of triethylamine (0.50 mL, 3.62 mmol) and alcohol **14** (251 mg, 1.21 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred overnight under an argon atmosphere at −10 °C. The reaction was submitted to the standard workup procedure, furnishing chloride **17** (230 mg, 1.02 mmol, 84 %) as a slightly unstable, colorless oil. IR: ṽ = 2976, 2934, 2898, 2838, 1588, 1472, 1456, 1440, 1384, 1360, 1348, 1304, 1262, 1202, 1148, 1114, 1084, 1066, 1024, 802, 790, 754, 720 cm^{-1}. ^{1}H NMR: δ = 1.44 (d, *J* = 6.1 Hz, 3 H, CH_3−3), 1.56 (d, *J* = 6.6 Hz, 3 H, CH_3−1), 3.82 (s, 3 H, OCH_3), 4.14 (dq, J_1 = 6.1, J_2 = 8.8 Hz, 1 H, H-3), 4.72 (d, *J* = 8.8 Hz, 1 H, H-4), 5.08 (q, *J* = 6.6 Hz, 1 H, H-1), 6.76 (dd, J_1 = 0.6, J_2 = 8.4 Hz, 1 H, H-7), 7.19 (dd, J_1 = 0.6, J_2 = 7.7 Hz, 1 H, H-5), 7.25 (dd, J_1 = 7.7, J_2 = 8.4, 1 H, H-6) ppm. ^{13}C NMR: δ = 18.62 (CH_3−1), 19.21 (CH_3−3), 55.19 (OCH_3), 59.57 (C-4)*, 68.14 (C-1)*, 68.67 (C-3), 109.00 (C-7), 120.94 (C-5), 127.48 (C-6), 128.57 (C-8a), 134.30 (C-4a), 154.47 (C-8) ppm. Without delay, *N*-ethyldiisopropylamine (0.306 mL, 1.76 mmol) was added to a solution of chloride **17** (203 mg, 0.90 mmol) and 2,2-dimethoxyethylamine (0.5 mL, 4.4 mmol) in anhydrous toluene/DMSO (1:1, 4 mL). The reaction was heated for 2 days at 70 °C; 10 % NaOH (20 mL) was then added and the reaction was submitted to the standard workup procedure, furnishing amine **16** (208 mg, 0.70 mmol, 79 %) as an oil. IR: ṽ = 3500, 2972, 2932, 2906, 2834, 2540, 1586, 1470, 1440, 1354, 1258, 1196, 1132, 1110, 1066, 1024, 746 cm^{-1}. ^{1}H NMR: δ = 1.36 (d, *J* = 6.4 Hz, 3 H, CH_3−3), 1.47 (d, *J* = 6.5 Hz, 3 H, CH_3−1), 1.56 (s, 1 H, NH), 2.59 (dd, J_1 = 5.0, J_2 = 12.1 Hz, 1 H, CH_2CH), 2.83 (dd, J_1 = 6.2, J_2 = 12.1 Hz, 1 H, CH_2CH), 3.29 (s, 3 H, CHOCH_3), 3.31 (s, 3 H, CHOCH_3), 3.36 (d, *J* = 2.4 Hz, 1 H, H-4), 3.81 (s, 3 H, OCH_3−8), 4.16 (dq, J_1 = 2.4, J_2 = 6.4 Hz, 1 H, H-3), 4.38 (dd,

J_1 = 5.0, J_2 = 6.2 Hz, 1 H, CH_2CH), 5.08 (q, J = 6.5 Hz, 1 H, H-1), 6.74 (dd, J_1 = 0.9, J_2 = 8.2 Hz, 1 H, H-7), 6.85 (dd, J_1 = 0.9, J_2 = 7.6 Hz, 1 H, H-5), 7.18 (dd, J_1 = 7.6, J_2 = 8.2 Hz, 1 H, H-6) ppm. ^{13}C NMR: δ = 17.49 (CH_3–1), 18.58 (CH_3–3), 48.41 (CH_2CH), 53.69 ($CHOCH_3$), 53.53 ($CHOCH_3$), 54.97 (OCH_3–8), 56.41 (C-4), 66.53 (C-1), 68.45 (C-3), 104.43 (CH_2CH), 108.69 (C-7), 121.28 (C-5), 126.72 (C-6), 127.54 (C-8a), 136.89 (C-4a), 155.19 (C-8) ppm. HRMS: calcd. $C_{16}H_{26}NO_4$ (MH^+): 296.18618; found 296.18639.

(1*S,3*S**,3a*S**)-9-Methoxy-1,3-dimethyl-4-(tolyl-4-sulfonyl)-3,3a-dihydro-1*H*,4*H*-2-oxa-4-azaphenalene (21):** Amine **16** (110 mg, 0.37 mmol) was dissolved in anhydrous $CHCl_3$ (10 mL) and successively treated with triethylamine (0.26 mL, 1.9 mmol) and tosyl chloride (210 mg, 1.11 mmol). After heating 8 h at 60 °C, the reaction was submitted to the standard workup protocol, affording sulfonamide **19** (160 mg, 0.36 mmol, 96 %) as a colorless oil. IR: ṽ = 2924, 2872, 2854, 1590, 1470, 1438, 1380, 1340, 1314, 1288, 1262, 1204, 1186, 1164, 1114, 1088, 1068, 1032, 1020, 976, 932, 894, 816, 748, 712, 688, 662, 650 cm^{-1}. ^{1}H NMR: δ = 1.17 (d, J = 6.5 Hz, 3 H, CH_3–3), 1.45 (d, J = 6.6 Hz, 3 H, CH_3–1), 2.46 (s, 3 H, Ar-CH_3), 3.01 (dd, J_1 = 4.9, J_2 = 15.4 Hz, 1 H, CH_2CH), 3.06 (s, 3 H, $CHOCH_3$), 3.09 (s, 3 H, $CHOCH_3$), 3.60 (dd, J_1 = 5.6, J_2 = 15.4 Hz, 1 H, CH_2CH), 3.80 (s, 3 H, OCH_3–8), 4.05 (dd, J_1 = 4.9, J_2 = 5.6 Hz, 1 H, CH_2CH), 4.17 (dq, J_1 = 3.3, J_2 = 6.5 Hz, 1 H, H-3), 4.81 (d, J = 3.3 Hz, 1 H, H-4), 5.07 (q, J = 6.6 Hz, 1 H, H-1), 6.56 (dd, J_1 = 0.8, J_2 = 7.9 Hz, 1 H, H-7), 6.73 (dd, J_1 = 0.8, J_2 = 8.2 Hz, 1 H, H-5), 7.06 (dd, J_1 = 7.9, J_2 = 8.2 Hz, 1 H, H-6), 7.32 (dd, J_1 = 1.9, J_2 = 8.0 Hz, 2 H, tosyl H-3′ and H-5′), 7.86 (dd, J_1 = 1.9, J_2 = 8.0, 2 H, tosyl H-2′ and H-6′) ppm. ^{13}C NMR: δ = 17.69 (CH_3–1), 17.75 (CH_3–3), 21.40 (Ar-CH_3), 46.98 (CH_2CH), 53.43 ($CHOCH_3$), 54.01 ($CHOCH_3$), 55.05 (OCH_3–8), 55.40 (C-4), 66.34 (C-1), 68.11 (C-3), 102.96 (CH_2CH), 109.12 (C-7), 121.77 (C-5), 127.39 (C-6), 127.89 (C-3′ and C-5′), 129.13 (C-2′ and C-6′), 129.53 (C-8a), 132.49 (C-1′), 138.54 (C-4a), 142.95 (C-4′), 154.83 (C-8) ppm. Tosylacetal **19** (56 mg, 0.12 mmol) was dissolved in dioxane (2 mL) and treated with 6 N HCl (0.2 mL, 1.2 mmol) and EtOH (0.1 mL, 1.74 mmol). The mixture was heated at 105 °C under a nitrogen atmosphere for 2.5 h. The reaction was then allowed to cool to room temperature, 10 % $NaHCO_3$ (3 mL) was added and after standard workup conditions, sulfonamide **21** (39 mg, 0.10 mmol, 81 %) was obtained as a colorless oil. IR: ṽ = 2958, 2924, 2854, 1598, 1488, 1466, 1406, 1380, 1364, 1352, 1324, 1266, 1250, 1228, 1186, 1170, 1120, 1092, 1052, 1024, 980, 818, 736, 706, 674, 648 cm^{-1}. ^{1}H NMR: δ = 1.18 (d, J = 6.5 Hz, 3 H, CH_3–3), 1.38 (d, J = 6.4 Hz, 3 H, CH_3–1), 2.43 (s, 3 H, Ar-CH_3), 3.76 (s, 3 H, OCH_3), 4.62 (d, J = 4.5 Hz, 1 H, H-3a), 4.93 (q, J = 6.4 Hz, 1 H, H-1), 5.00 (dq, J_1 = 4.5, J_2 = 6.5 Hz, 1 H, H-3), 5.56 (d, J = 8.2 Hz, 1 H, H-6), 6.62 (d, J = 8.4 Hz, 1 H, H-8), 6.73 (d, J = 8.2 Hz, 1 H, H-5), 6.75 (d, J = 8.4 Hz, 1 H, H-7), 7.36 (dd, J_1 = 1.9, J_2 = 8.0 Hz, 2 H, tosyl H-3′ and H-5′), 7.76 (dd, J_1 = 1.9, J_2 = 8.0 Hz, 2 H, tosyl H-2′ and H-6′) ppm. ^{13}C NMR: δ = 12.83 (CH_3–3), 21.34 (CH_3–1)*, 21.45 (Ar-CH_3)*, 55.08 (OCH_3), 55.79 (C-3a), 65.17 (C-1), 70.78 (C-3), 106.74 (C-6), 109.08 (C-8), 121.39 (C-6a), 123.64 (C-5), 124.34 (C-7), 125.06 (C-9a), 126.39 (C-6b), 127.72 (C-1′), 129.84 (C-3′ and C-5′), 132.61 (C-2′ and C-6′), 144.28 (C-4′), 154.41 (C-9) ppm. HRMS: calcd. $C_{21}H_{23}NO_4S$: 385.13478; found 385.13493.

(1*S,3*S**)-9-Methoxy-1,3-dimethyl-1*H*,3*H*-2-oxa-4-azaphenalene (4):** Freshly sublimed potassium *tert*-butoxide (120 mg, 1.1 mmol) was added to a solution of sulfonamide **21** (40 mg, 0.1 mmol) in dry pyridine (2.5 mL) and the reaction was heated to 60 °C under an argon atmosphere. After 2 h, NaOH (10 %, 1 mL) was added and the mixture was submitted to the standard workup procedure, furnishing **4** (23 mg, 0.1 mmol, 97 %) as a colorless oil. IR: ṽ = 2975, 2934, 2840, 1590, 1574, 1504, 1449, 1430, 1309, 1260, 1133, 1106, 1095, 1073, 1049, 1041, 1018, 843 cm^{-1}. ^{1}H NMR: δ = 1.61 (d, J = 6.7 Hz, 3 H, CH_3–1), 1.78 (d, J = 6.4 Hz, 3 H, CH_3–3), 3.97 (s, 3 H, OCH_3), 5.30 (q, J = 6.4 Hz, 1 H, H-3), 5.51 (q, J = 6.7 Hz, 1 H, H-1), 7.44 (d, J = 9.0 Hz, 1 H, H-8), 7.48 (d, J = 5.8 Hz, 1 H, H-6), 7.74 (d, J = 9.0 Hz, 1 H, H-7), 8.34 (d, J = 5.8 Hz, 1 H, H-5) ppm. ^{13}C NMR: δ = 18.30 (CH_3–1), 18.76 (CH_3–3), 56.02 (OCH_3), 67.06 (C-3), 67.25 (C-1), 116.94 (C-8), 118.78 (C-6), 121.69 (C-6a), 124.11 (C-9a), 126.06 (C-7), 129.94 (C-6b), 139.49 (C-5), 151.16 (C-9), 158.06 (C-3a) ppm. $C_{14}H_{15}NO_2$ (229.28): calcd. C 73.34, H 6.59, N 6.11; found C 73.29, H 6.64, N 6.07.

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