

Synthesis of a tricyclic lactone embodying the ABC-ring system of stephaxocanidine, by tin(IV) chloride-assisted sulfonamidoacetal cyclization and an aromatization promoted by triethylamine

Darío A. Bianchi and Teodoro S. Kaufman*

*Instituto de Química Orgánica de Síntesis (IQUIOS, CONICET-UNR) and
Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario,
Suipacha 531, (S2002LRK) Rosario, Argentina
E-mail: tkaufman@fbioyf.unr.edu.ar*

**Dedicated to Professor Edmundo A. Rúveda on the occasion of his 70th birthday and to
Professor Roberto A. Rossi on occasion of his 60th birthday
(received 30 Jun 03; accepted 25 Aug 03; published on the web 26 Aug 03)**

Abstract

The synthesis of the polysubstituted 8-oxa-1-azaphenalene lactone **4**, which embodies the ABC-ring system of stephaxocanidine, a tetracyclic isoquinoline alkaloid recently isolated from the tubers of *Stephania cepharantha* Hayata, is reported. Elaboration of **4** was carried out by means of the camphorsulfonic acid-assisted lactonization of **9**, coupled to a titanium(IV) chloride-mediated acetal cyclization of the resulting lactone **10** to form the tricyclic intermediate **12**, followed by the base-promoted aromatization of the latter to **13** and final benzylic bromination. Lactone **4** constitutes an advanced key intermediate for the total synthesis of stephaxocanidine, the simplest stephaxocane.

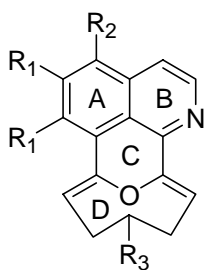
Keywords: Stephaxocanidine, natural products, synthesis, isoquinolines, cyclization

Introduction

The stephaxocanes constitute a new, small family of isoquinoline alkaloids sharing the tetracyclic stephaxocane¹ skeleton (**1a**). This family, which was independently uncovered during the past decade by Japanese,¹ Chinese² and Brazilian³ research groups, has only five members (**1b-1f**), all of which have been isolated from Menispermaceae employed in folk medicine.⁴ The structurally simplest stephaxocane is stephaxocanidine (**1b**), a *Stephania cepharantha* Hayata alkaloid which contains a fully unsaturated isoquinoline ring system like eletefine (**1c**), isolated from *Cissampelos glaberrima* (also known as *Cissampelos pareira*).

Other stephaxocanes such as stephaxocanine (**1d**), excentricine (**1e**) and *N*-methyl excentricine (**1f**) display their AB-ring systems in the dihydro- and tetrahydro- states, respectively.

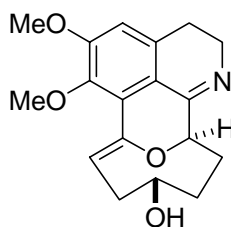
Structurally, the stephaxocanes are reminiscent of other tetracyclic isoquinoline natural products, such as the tropoloisoquinolines [for example: grandirubrine (**2a**) and imerubrine (**3b**)] and the azafluoranthenes [for example: rufescine (**3a**), norrufescine (**3b**) and imeluteine (**3c**)]. These are biosynthetically related alkaloids isolated from Menispermaceae, including *C. Pareira*, which have shown healing properties as well as interesting cytotoxic and antitumor activities.⁵



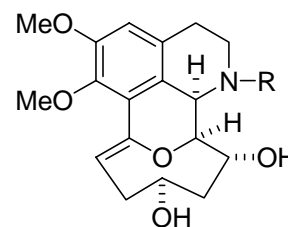
1a R₁ = R₂ = R₃ = H

1b R₁ = OMe, R₂ = H, R₃ = OH

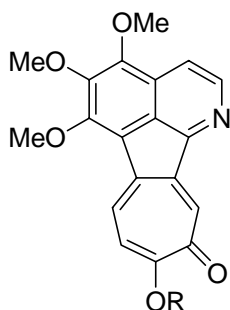
1c R₁ = R₂ = OMe, R₃ = OH



1d

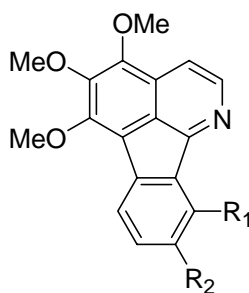


1e R = H
1f R = Me



2a R = H

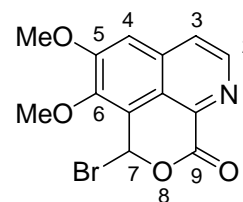
2b R = Me



3a R₁ = H, R₂ = OMe

3b R₁ = H, R₂ = OH

3c R₁ = R₂ = OMe



4

We have demonstrated that the cyclization of sulfonamido acetals originally reported by Jackson and coworkers⁶ is a versatile protocol, capable of providing useful intermediates towards polysubstituted isoquinolines, tetrahydroisoquinolines and tetrahydroprotoberberines.⁷ In addition, we have recently reported⁸ the synthesis of a tricyclic oxazaphenalene derivative related to the stephaxocanes, employing a reaction sequence entailing a Friedel-Crafts acylation in association with a benzylic functionalization strategy and a Jackson-type toluenesulfonamide acetal cyclization.⁶

As part of our ongoing project aimed to the synthesis of stephaxocanes, we describe here the elaboration of polysubstituted 8-oxa-1-azaphenalene-9-one **4** from the previously reported tricarbonylic compound **5**, in turn easily accessible from commercially available 2,3-dimethoxytoluene.⁸ Tricyclic lactone **4** embodies the ABC-ring system of stephaxocanine

(1b) and constitutes a convenient advanced key intermediate for its total synthesis. The 8-oxa-1-azaphenalene structure is a new and unprecedented heterocyclic ring system, being this unit unique to the stephaxocanes.

Results and Discussion

As shown in Scheme 1, the synthesis commenced with the selective reduction of tricarbonylic compound **5** to mandelate **6**. Sodium cyanoborohydride proved to be a more appropriate reducing agent than sodium borohydride, which caused partial removal of the acetate, furnishing the benzylic alcohol in 91% yield. Next, alcohol **6** was smoothly and efficiently transformed into the related chloride **7** in 82% yield by reaction with methanesulfonyl chloride, employing triethylamine as base.⁹ By analogy with similar processes, this transformation most probably proceeded through chloride ion displacement¹⁰ of a transient mesylate,¹¹ which was not isolated.

Benzylic chloride **7** was aminated with aminoacetaldehyde dimethyl acetal in a DMSO-toluene (1:4) solvent mixture,¹² to which *N*-ethyl diisopropylamine was added as HCl scavenger, furnishing secondary amine **8** in almost quantitative yield. In turn, this was uneventfully converted into the related sulfonamide (**9**) with tosyl chloride under forcing conditions,⁸ required to overcome the steric crowding surrounding the nitrogen atom.

We have previously reported that submission of **9** to Jackson's protocol for 1,2-dihydroisoquinoline formation (6 N HCl, dioxane, reflux) resulted only in moderate yields of tetrahydroisoquinoline derivative **10**. We have also recently disclosed that *N*-sulfonyl tetrahydroisoquinolines bearing a carbonyl substituent at C-1 are capable of undergoing aromatization of the heterocyclic ring on exposure to KF supported on alumina under microwave irradiation.¹³ With these precedents in mind, attempts were made to cyclize **9** under more efficient, alternative conditions; however, cyclization with HCl in dioxane to which EtOH was added¹⁴ did not yield improved results and reaction of sulfonamido acetal **9** with SnCl₄ at -40°C produced only scarce amounts of **10**, together with a complex mixture of decomposition products.

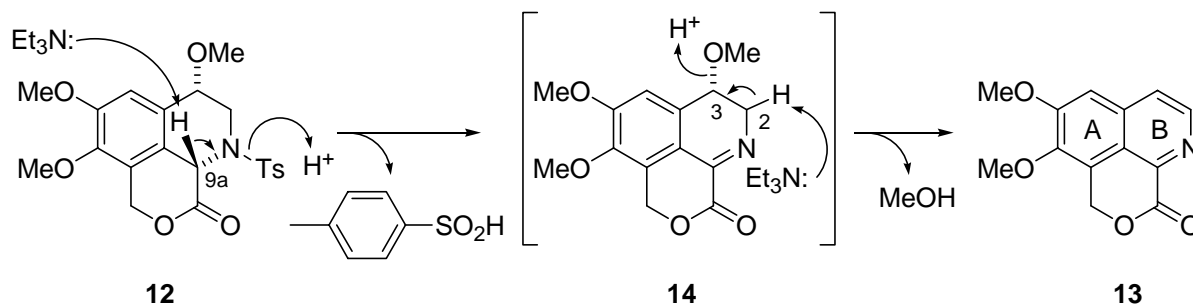
Thus, a stepwise approach towards the desired tricyclic compound was explored, consisting in the elaboration of lactone **11** as a first step, followed by its subsequent submission to an acetal cyclization protocol and a final B-ring aromatization. Not unexpectedly, however, initial attempts to lactonize **9** either by basic hydrolysis (LiOH, THF/H₂O and K₂CO₃, MeOH/H₂O) followed by acidic work-up or by transesterification under basic conditions (K₂CO₃ in MeOH)¹⁵ met with failure, probably due to the acidity of the tertiary benzylic proton, which resulted in oxidative desulfonylation of **9**, with loss of *para*-toluenesulfinic acid and subsequent hydrolysis of the resulting imine, to yield **5**. This side reaction is analogous to one previously reported in a similar environment.¹⁶

Therefore, we turned our attention to an acid catalyzed lactonization process,¹⁷ which to our delight provided lactone **11** in 94% yield, when performed with catalytic amounts of

isochroman-3-one system to the nucleophilic attack of the activated acetal by the aromatic moiety during the cyclization.⁸

In spite that tricyclic compound **12** tolerated basic work-up, it proved to be unstable and readily decomposed upon contact with silica gel; however, pretreatment of the chromatographic medium with 2% triethylamine in hexane caused efficient *in situ* transformation of **12** into oxazaphenalene **13**,¹⁸ this becoming the preferred method for accessing the isoquinoline.

Aromatization of the nitrogen containing heterocyclic ring may be the driving force of this transformation which, as shown in Scheme 2, could probably take place through an initial base-assisted oxidative desulfonylation of **12** entailing loss of *para*-toluenesulfonic acid to give intermediate **14**, a process favored by the acidity of H-9a. In turn, and after elimination of methanol, **14** would readily provide compound **13**, carrying a fully unsaturated AB ring system. The overall transformation is somehow reminiscent of the scarcely employed Pictet-Gams modification of the classical Bischler-Napieralski synthesis, capable of converting β -hydroxy- or β -methoxy-phenethylamine derivatives into isoquinolines.¹⁹



Scheme 2

The proposal that oxidative desulfonylation precedes the loss of methanol during the aromatization is supported by the relatively harsh conditions required to transform *N*-tosyl-1,2-dihydroisoquinolines into isoquinolines,¹³ compared to the observed ease with which the base-promoted desulfonylation reaction takes place.

Finally, benzylic bromination of **13** with NBS in refluxing CCl_4 , under the assistance of AIBN, furnished brominated derivative **4** in moderate but satisfactory yield.²⁰ Interestingly, in spite that the benzylic bromination of benzyl ethers has been studied in some detail,²¹ there are only scarce references to the bromination of lactones carrying a benzylic methylene attached to oxygen.²² Compound **4** has different C-7 and C-9 functionalities, suitable for the elaboration of the remaining oxocane-type D-ring of stephaoxocanidine.

Conclusions

The synthesis of polysubstituted 8-oxa-1-azaphenalene derivative **4** was successfully and efficiently achieved in 8 steps and 21% overall yield from tricarbonylic compound **5**. Efficient synthesis and amination of chloride **7**, coupled to lactonization of acetate **9** prior to acetal cyclization and use of tin(IV) chloride as cyclization promoter proved to be crucial for attaining good yields of tricyclic product **12**, while the unusual base-promoted aromatization of **12** was fundamental for accessing oxazaphenalene derivative **13** in good yields. Studies employing **4** as key intermediate for the total synthesis of stephaoxocanidine are under way and will be reported in due time.

Experimental Section

General Procedures. Melting points were taken on an Ernst Leitz Wetzlar model 350 hot-stage microscope apparatus and are informed uncorrected. FT-IR spectra were determined with Bruker IFS 25 or Beckman Acculab 8 spectrophotometers as thin films held between NaCl cells or as dispersions in KBr disks. The ^1H and ^{13}C -NMR spectra were acquired in CDCl_3 employing TMS as internal standard, with a Bruker AC200-E spectrometer operating at 200.13 and 50.33 MHz, respectively. DEPT 135 and DEPT 90 experiments aided the interpretation of the fully decoupled ^{13}C NMR spectra. HRMS and microanalytical data were obtained from Kent Electronics (UK), Atlantic Microlab (USA) and UMyMFOR (Argentina). Reactions were carried out under dry Nitrogen or Ar atmospheres, employing oven-dried glassware. Commercially obtained reagents were used without further purification. Dry THF and toluene were prepared by distillation from Na-benzophenone ketyl; anhydrous DMSO, *N*-ethyl diisopropylamine and Et_3N were accessed by reflux and distillation from CaH_2 ; CHCl_3 and CH_2Cl_2 were distilled from P_2O_5 and pyridine was dried over KOH pellets and then distilled; anhydrous solvents were stored in dry Schlenk bottles. All new compounds gave single spots on TLC plates run in different solvent systems. Spots were visualized by exposure to UV light (254 and 365 nm), followed by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent and careful heating. Standard work-up procedures consisted in diluting the reaction with brine (5 – 20 mL) and extracting the products with EtOAc (3 x 20 – 40 mL); the combined organic extracts were washed once with brine, dried over Na_2SO_4 , concentrated under reduced pressure and the respective residues were chromatographed. Flash column chromatographies were carried out with silica gel 60 H, eluting with hexane-EtOAc mixtures under positive pressure and employing gradient techniques. Mixtures of EtOAc-acetone and EtOAc-EtOH were used for the separation of **4** and **13**, respectively.

Ethyl{2-[(acetoxy)methyl]-3,4-dimethoxyphenyl}-(hydroxy)acetate (6). A solution of keto ester **5** (1001.4 mg, 3.23 mmol) in absolute ethanol (40 mL) was successively treated with glacial acetic acid (0.184 mL, 3.23 mmol) and sodium cyanoborohydride (223.7 mg, 3.55 mmol), and

the mixture was stirred overnight at room temperature. The reaction was quenched with 1N NaOH (5 mL) and submitted to the conventional work-up procedure, providing mandelate **6** (918 mg, 91 %), as an oil; IR (film): 3460, 2980, 2850, 1750, 1740, 1600, 1500, 1460, 1280, 1090 and 810 cm^{-1} ; ^1H NMR (δ): 1.22 (t, 3 H, $J= 7.1$, OCH_2Me), 1.57 (bs, $w_{1/2}= 10$ Hz, 1 H, OH), 2.07 (s, 3 H, MeCO_2), 3.84 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 4.20 (dq, 2 H, $J= 1.0, 7.1$, OCH_2Me), 5.35 (s, 2 H, ArCH_2O), 5.40 (s, 1 H, ArCHOH), 6.92 (d, 1 H, $J= 8.6$, H-5) and 7.10 (d, 1 H, $J= 8.6$, H-6); ^{13}C NMR (δ): 13.88, 20.86, 55.56, 57.60, 61.20, 61.97, 69.77, 112.71, 122.97, 128.03, 130.88, 148.46, 142.65, 170.73 and 173.60. HRMS m/z 312.12118; $\text{C}_{15}\text{H}_{20}\text{O}_7$ requires 312.12087.

Ethyl {2-[(acetyloxy)methyl]-3,4-dimethoxyphenyl}[N-(2,2-dimethoxyethyl)amino]acetate (8). Triethylamine (1.66 mL, 11.97 mmol) was added to an ice-cooled solution of mandelate **6** (931 mg, 2.99 mmol) in CH_2Cl_2 (25 mL) and the resulting solution was treated dropwise with a freshly prepared solution of methanesulfonyl chloride (0.697 mL, 8.98 mmol) in CH_2Cl_2 (5 mL). After stirring overnight, the reaction was submitted to the conventional work-up procedure, furnishing chloride **7** (809 mg, 82 %) as a clear, slightly unstable oil. IR (film): 2982, 2941, 1748, 1735, 1683, 1583, 1497, 1378, 1323, 1288, 1177, 1086 and 978 cm^{-1} ; ^1H NMR (δ): 1.26 (t, 3 H, $J= 7.1$, OCH_2Me), 2.08 (s, 3 H, MeCO_2), 3.86 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 4.19 (dq, 2 H, $J= 7.1$, OCH_2Me), 5.29 (d, 1 H, $J= 12.2$, ArCH_2O), 5.37 (d, 1 H, $J= 12.2$, ArCH_2O), 5.66 (s, 1 H, ArCHCl), 6.96 (d, 1 H, $J= 8.8$, H-5) and 7.38 (d, 1 H, $J= 8.8$, H-6); ^{13}C NMR (δ): 13.79, 20.70, 55.10, 55.60, 57.21, 61.22, 62.29, 112.95, 124.53, 127.90, 128.34, 147.98, 153.11, 168.22 and 170.41. Without delay, chloride **7** was dissolved in a mixture of DMSO (5 mL) and toluene (20 mL), to which *N*-ethyl diisopropylamine (3.82 mL, 21.99 mmol) and aminoacetaldehyde dimethyl acetal (0.798 mL, 7.33 mmol) were successively added. The reaction was warmed to 60°C and stirred overnight until completion. Submission of the mixture to conventional work-up conditions gave secondary amine **8** (954 mg, 98 %), as a clear oil. IR (film): 3550-2700, 2960, 2840, 1740, 1280, 1090 and 820 cm^{-1} ; ^1H NMR (δ): 1.20 (t, 3 H, $J= 7.1$, OCH_2Me), 1.92 (bs, 1 H, NH), 2.05 (s, 3 H, MeCO_2), 2.59 (dd, 1 H, $J= 5.5, 13.0$, NCH_2), 2.74 (dd, 1 H, $J= 5.5, 13.0$, NCH_2), 3.34 (s, 3 H, CHOMe), 3.36 (s, 3 H, CHOMe), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 4.13 (dq, 2 H, $J= 1.0, 7.1$, OCH_2Me), 4.46 [t, 1 H, $J= 5.5$, $\text{CH}(\text{OMe})_2$], 4.61 (s, 1 H, ArCHCO_2Et), 5.34 (s, 2 H, ArCH_2O), 6.89 (d, 1 H, $J= 8.6$, H-5) and 7.10 (d, 1 H, $J= 8.6$, H-6); ^{13}C NMR (δ): 13.95, 20.86, 48.82, 53.46, 53.73, 55.59, 57.59, 60.76, 60.99, 61.22, 103.72, 112.78, 122.53, 128.38, 130.67, 148.42, 152.23, 170.65 and 172.72; HRMS m/z 399.1904; $\text{C}_{19}\text{H}_{29}\text{NO}_8$ requires 399.1893.

Ethyl {2-[(acetyloxy)methyl]- 3,4-dimethoxyphenyl}- {N-(2,2-dimethoxyethyl)- N-(4-methyl phenyl)sulfonyl}-amino}-acetate (9). Toluene-*p*-sulfonyl chloride (1133 mg, 5.94 mmol) was added all at once to a solution of amine **8** (947 mg, 2.38 mmol) in a mixture of dry chloroform (25 mL) and pyridine (0.862 mL, 10.69 mmol). The reaction was refluxed for 16 h and then it was submitted to the standard work-up protocol, providing sulfonamide **9** (1064 mg, 81%), as a solid mp $88.5\text{-}90^\circ\text{C}$ (hexane-EtOAc); IR (KBr): 2940, 2840, 1740, 1600, 1500, 1460, 1350, 1290, 1170, 1090, 1080, 830 and 670 cm^{-1} ; ^1H NMR (δ): 1.14 (t, 3 H, $J= 7.2$, OCH_2Me), 2.11 (s,

3 H, MeCO₂), 2.44 (s, 3 H, ArMe), 3.01 (s, 3 H, OMe), 3.21 (s, 3 H, OMe), 3.26 (dd, 1 H, *J*= 6.9, 15.7, NCH₂), 3.49 (dd, 1 H, *J*= 4.0, 15.7, NCH₂), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.82-4.10 (m, 3 H, NCH₂CH and OCH₂Me), 5.13 (d, 1 H, *J*= 11.9, ArCH₂O), 5.40 (d, 1 H, *J*= 11.9, ArCH₂O), 6.07 (s, 1 H, ArCHNTs), 6.77 (d, 1 H, *J*= 8.6, H-5), 6.85 (d, 1 H, *J*= 8.6, H-6), 7.29 (d, 2 H, *J*= 8.3, ArH of tosyl) and 7.72 (d, 2 H, *J*= 8.3, ArH of tosyl); ¹³C NMR (δ): 13.75, 20.92, 21.94, 47.44, 54.48, 54.93, 55.56, 57.50, 59.97, 61.15, 61.20, 104.37, 111.83, 124.70, 125.91, 127.65, 129.26, 130.41, 135.78, 143.55, 146.91, 153.32, 170.11 and 170.52; Anal. Calcd. for C₂₆H₃₅NO₁₀S: C, 56.41; H, 6.37; N, 2.53; S, 5.79. Found: C, 56.53; H, 6.34; N, 2.55; S, 5.83.

***N*-(2,2-Dimethoxyethyl)-4-methyl-*N*-(3-oxo-3,4-dihydro-7,8-dimethoxy-1*H*-isochromen-4-yl)-benzenesulfonamide (11).** A solution of acetate **9** (734 mg, 1.33 mmol) in dry methanol (20 mL) was treated with camphorsulfonic acid (154.2 mg, 0.66 mmol) and the reaction was stirred at room temperature until complete disappearance of the starting material (10 h). Then, most of the solvent was removed under reduced pressure and the residue was submitted to the conventional work-up procedure, furnishing isochroman-3-one **11** (580 mg, 94 %), as a white solid mp 123-125°C (hexane-EtOAc). IR (KBr): 2940, 2850, 1750, 1610, 1500, 1460, 1320, 1290, 1170, 1060, 1000, 830 and 670 cm⁻¹; ¹H NMR (δ): 2.44 (s, 3 H, ArMe), 3.00 (s, 3 H, CHOMe), 3.17 (dd, 1 H, *J*= 5.7, 15.2, CH₂CH), 3.17 (s, 3 H, CHOMe), 3.42 (dd, 1 H, *J*= 4.7, 15.2, CH₂CH), 3.66 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 4.16 (dd, 1 H, *J*= 4.7, 5.7, CH₂CH), 5.33 (d, 1 H, *J*= 15.6, ArCH₂), 5.52 (d, 1 H, *J*= 15.6, ArCH₂), 5.87 (s, 1 H, ArCHCO₂), 6.94 (d, 1 H, *J*= 8.6, H-6), 7.14 (d, 1 H, *J*= 8.6, H-5), 7.32 (d, 2 H, *J*= 8.1, ArH of tosyl) and 7.90 (d, 2 H, *J*= 8.1, ArH of tosyl); ¹³C NMR (δ): 21.46, 47.29, 53.94, 54.23, 55.78, 56.18, 60.54, 65.93, 103.26, 112.69, 122.30, 122.64, 124.48, 127.88, 129.40, 136.76, 143.64, 151.42 and 167.67. Anal. Calcd. for C₂₂H₂₇NO₈S: C, 56.76; H, 5.85; N, 3.01; S, 6.89. Found: C, 56.83; H, 5.80; N, 2.95; S, 6.93.

5,6-Dimethoxy-7*H*,9*H*-pyrano[3,4,5-*ij*]isoquinolin-9-one (13). A freshly prepared solution of SnCl₄ in CH₂Cl₂ (6.5 mL, 2.61 mmol) was added dropwise to sulfonyl acetal **11** (578 mg, 1.24 mmol) was dissolved in dry CH₂Cl₂ (14 mL) and cooled to -30°C. The resulting yellow mixture was stirred 20 min at -30°C, then it was quenched with saturated NaHCO₃ solution (5 mL) and subjected to the conventional extractive work-up procedure, affording a crude consisting essentially in the unstable sulfonamide **12**. ¹H NMR (δ): 2.44 (s, 3 H, ArMe), 2.66 (dd, 1 H, *J*= 10.1, 13.3, H-2_{ax}), 3.58 (s, 3 H, CHOMe), 3.86 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 4.14 (dd, 1 H, *J*= 4.8, 13.3, H-2_{eq}), 4.39 (dd, 1 H, *J*= 4.8, 10.1, H-3), 5.26 (d, 1 H, *J*= 14.1, H-7_{ax}), 5.55 (s, 1 H, H-9a), 5.59 (d, 1 H, *J*= 14.1, H-7_{eq}), 7.12 (s, 1 H, H-4), 7.34 (d, 2 H, *J*= 8.2, ArH of tosyl) and 7.96 (d, 2 H, *J*= 8.2, ArH of tosyl); ¹³C NMR (δ): 21.45, 43.43, 53.45, 55.88, 57.55, 61.24, 64.25, 73.29, 109.47, 118.50, 124.44, 127.82, 129.53, 132.08, 136.64, 143.86, 144.87, 152.00 and 168.92. Submission of the crude reaction product to chromatography on a silica gel column pre-treated with 2% Et₃N in hexane, afforded oxazaphenalene lactone **13** (263 mg, 86%), as white needles mp 222-223°C (EtOH-EtOAc); IR (KBr): 2950, 2920, 1745, 1630, 1590, 1475, 1380, 1295, 1150, 1065, 980 and 880 cm⁻¹; ¹H NMR (δ): 3.98 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 5.85 (s, 2 H, H-7), 7.15 (s, 1 H, H-4), 7.71 (d, 1 H, *J*= 5.6, H-3) and 8.72 (d, 1 H, *J*= 5.6, H-2); ¹³C NMR (δ): 55.94, 60.73, 66.57, 104.16, 119.95, 121.64, 122.80, 133.98, 139.18, 144.23,

145.12, 156.12 and 161.24. Anal. Calcd. for C₁₃H₁₁NO₄: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.63; H, 4.57; N, 5.69.

7-Bromo-5,6-dimethoxy-7H,9H-pyrano[3,4,5-ij]isoquinolin-9-one (4). To a solution of **13** (16 mg, 0.065 mmol) in CCl₄ (2 mL) were successively added NBS (12.1 mg, 0.068 mmol) and a 0.015 M solution of AIBN (0.2 mL, 0.003 mmol) in CCl₄, and the resulting mixture was gently refluxed during 2.5 h. Then, the reaction was submitted to the standard work-up procedure, providing **4** (10.1 mg, 47%), as a white solid (EtOAc) mp > 300°C (with decomposition). IR (KBr): 2900, 1730, 1620, 1580, 1480, 1350, 1280, 1190, 1030, 990, 875, 750 and 680 cm⁻¹; ¹H NMR (δ): 3.97 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 7.26 (s, 1 H, H-4), 7.49 (s, 1 H, H-7), 7.76 (d, 1 H, *J*= 5.5, H-3) and 8.77 (d, 1 H, *J*= 5.5, H-2); ¹³C NMR (δ): 56.04, 60.99, 74.80, 85.98, 106.03, 117.35, 122.95, 133.22, 144.19, 155.82 and 174.39. HRMS *m/z* 322.9797 C₁₃H₁₀BrNO₄ requires 322.9793.

Acknowledgments

The authors gratefully acknowledge CONICET, ANPCyT, SECyT-UNR and Fundación Antorchas for generous financial support. D.A.B. thanks CONICET for a Doctoral Fellowship.

References

1. (a) Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M. *J. Nat. Prod.* **1996**, *59*, 803. (b) Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M.; Toda, J.; Suzuki, H.; Sano, T. *Nat. Prod. Lett.* **1997**, *9*, 177.
2. (a) Deng, J.-Z.; Zhao, S.-X.; Miao, Z.-Ch. *Nat. Prod. Lett.* **1993**, *2*, 283. (b) Deng, J.-Z.; Zhao, S.-X. *J. Nat. Prod.* **1997**, *60*, 294.
3. da-Cunha, E. V. L.; Cornélio, M. L.; Barbosa-Filho, J. M.; Braz-Filho, R.; Gray, A. I. *J. Nat. Prod.* **1998**, *61*, 1140.
4. (a) Pío-Corrêa, M. In *Dicionário das Plantas Úteis do Brasil e das Exóticas Cultivadas*; Ministério da Agricultura: Rio de Janeiro, Brazil, Ed., 1984, Vol. 2, p 282. (b) Nawawi, A.; Ma, C.; Nakamura, N.; Hattori, M.; Kurokawa, M.; Shiraki, K.; Kashiwaba, N.; Ono, M. *Biol. Pharm. Bull.* **1999**, *22*, 268. (c) *Zhong-yao-dai-ci-dian (Dictionary of Chinese Crude Drugs)*. Chiang Su New Medicine College, Ed.; Shanghai Scientific Technologic Publisher, Shanghai, China, 1978; p 2141. (d) Makidono, R.; Makidono, A.; Matsuura, K. *Nippon Acta Radiologica* **1977**, *37*, 1153.
5. (a) Buck, K. T. Azafluoranthene and Tropoloisoquinoline Alkaloids. In *The Alkaloids*, Brossi, A. Ed.; Academic Press, Inc.; New York: 1984; Vol. 23, pp 303-325. (b) Paris, R. R.; Moyse, H. In *Matiere Medicale*; Masson: Paris, 1967; Vol. 2, p 178. (c) Lewis, W. H.; Stonard, R. J.; Porras-Reyes, B.; Mustoe, T. A. U. S. Patent 5, 156, 847, 1992; *Chem. Abstr.*

- 1992, 117, 245630t. (d) For a proposal on the formation of azafluoranthene alkaloids from tropoloisoquinolines, see: Silverton, J. V.; Kabuto, C.; Buck, K. T.; Cava, M. P. *J. Am. Chem. Soc.* **1977**, 99, 6708.
6. (a) Jackson, A. H.; Stewart, G. W. *J. Chem. Soc., Chem. Commun.* **1971**, 149. (b) Charnock, S. A.; Jackson, A. H.; Martin, J. A.; Stewart, G. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1911. (c) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2185.
 7. (a) Bianchi, D. A.; Kaufman, T. S. *Can. J. Chem.* **2000**, 78, 1165. (b) Kaufman, T. S. *Molecules* **2000**, 5, 491. (c) Larghi, E. L.; Kaufman, T. S. *Tetrahedron Lett.* **1997**, 38, 3159. (d) Ponzo, V. L.; Kaufman, T. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3131. (e) Ponzo, V. L.; Kaufman, T. S. *Tetrahedron Lett.* **1995**, 36, 9105.
 8. Kaufman, T. S. *Heterocycles* **2001**, 55, 323.
 9. (a) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, 36, 3044. (b) Hwang, C. K.; Li, W. S.; Nicolau, K. C. *Tetrahedron Lett.* **1984**, 2295.
 10. (a) Snyder, D. C. *J. Org. Chem.* **1995**, 60, 2638. (b) Munyemana, F.; Frisque-Hesbain, A.-M.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* **1989**, 30, 3077. (c) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, 4, 553. (d) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, 55, 2183.
 11. Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, 35, 3195.
 12. (a) Uenishi, J.; Tomoko, T.; Ueno, T.; Hiraoka, T.; Yonemitsu, O.; Tsukube, H. *Synlett* **1999**, 41. (b) Hrubiec, R. T.; Smith, M. B. *Tetrahedron Lett.* **1983**, 24, 5031. (c) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner-Jones, R. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, 56, 763. (d) Du Priest, M. T.; Zinke, P. W.; Conrow, R. E.; Kuzmich, D.; Dantanarayana, A. P.; Sproull, S. *J. Org. Chem.* **1997**, 62, 9372.
 13. (a) Silveira, C. C.; Bernardi, C. R.; Braga, A. L.; Kaufman, T. S. *Synlett* **2002**, 906. (b) Silveira, C. C.; Bernardi, C. R.; Braga, A. L.; Kaufman, T. S. *Tetrahedron Lett.* **2001**, 42, 8947.
 14. (a) MacLean, D. B.; Cundasawmy, N. E. *Can. J. Chem.* **1972**, 50, 3028. (b) Nagata, H.; Miyazawa, N.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **2001**, 1094.
 15. (a) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, 57, 2888. (b) Castagnani, R.; De Angelis, R.; De Fusco, E.; Gianessi, F.; Misiti, D.; Meloni, D.; Tinti, M. O. *J. Org. Chem.* **1995**, 60, 8318.
 16. Ponzo, V. L.; Kaufman, T. S. *Tetrahedron Lett.* **1995**, 36, 9105.
 17. (a) Taylor, S. K.; Fried, J. A.; Grassi, Y. N.; Marolewski, A. E.; Pelton, E. A.; Poel, T.-J.; Rezanka, D. S.; Whittaker, M. R. *J. Org. Chem.* **1993**, 58, 7304. (b) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, 59, 7849.
 18. Preliminary assays demonstrated that compound **13** is a potent acetylcholinesterase inhibitor, with $IC_{50} = 23 \mu M$.
 19. (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, 6, 74. (b) Herz, W.; Tsai, L. J.

- Am. Chem. Soc.* **1955**, 77, 3529. (c) Biandra, A. A.; Wadia, M. S.; Dutta, N. L. *Tetrahedron Lett.* **1968**, 2677.
20. (a) Dubey, S. K.; Kumar, S. *J. Org. Chem.* **1986**, 51, 3407. (b) Pizey, J. S. In *Synthetic Reagents*, J. Wiley & Sons: New York, 1974, Vol. 2, pp 15-21.
21. (a) Lovins, R. E.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1963**, 28, 2847. (b) Lovins, R. E.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1965**, 30, 1577.
22. Blair, J.; Logan, W. R.; Newbold, G. T. *J. Chem. Soc.* **1956**, 2443.