Concise Synthesis of the ABC-Ring System of the Azafluoranthene, Tropoisoquinoline and Proaporphine Alkaloids: An Olefin Hydroacylation/Pomeranz–Fritsch Cyclization Approach

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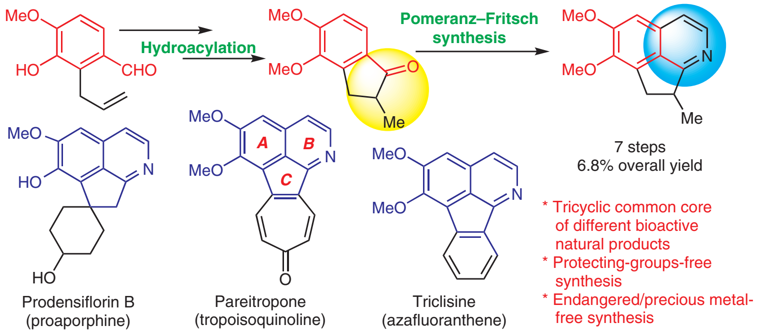
MeO
HO
CHO
Hydroacylation
MeO
MeO
O
Me
Pomeranz–Fritsch synthesis
MeO
MeO
N
Me
7 steps
6.8% overall yield
MeO
HO
N
HO
Prodensiflorin B
(proaporphine)
MeO
MeO
A
B
C
N
O
Pareitropone
(tropoisoquinoline)
MeO
MeO
N
Triclisine
(azafluoranthene)
* Tricyclic common core of different bioactive natural products
* Protecting-groups-free synthesis
* Endangered/precious metal-free synthesis

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Abstract A straightforward approach toward a decorated cyclopenta[*ij*]isoquinoline embodying the ABC-ring system characteristic of the azafluoranthene (triclisine), tropoisoquinoline (pareitropone) and proaporphine (prodensiflorin B) alkaloids, is reported. The synthetic sequence entailed a novel 40% KF/Al_2O_3-mediated hydroacylation of a 2-allyl-benzaldehyde derivative, obtained in two steps from isovanillin, through O-allylation and Claisen rearrangement to assemble the AC-ring system. This was followed by an O-methylation and a reductive amination of the resulting indanone with aminoacetal. A modified Pomeranz–Fritsch cyclization was next implemented to install ring B, through sulfonamidation, followed by acid-promoted cyclization and final desulfonylation *in situ*.

Key words natural products, azafluoranthenes, tropoisoquinolines and proaporphines, alkaloids, hydroacylation, Pomeranz–Fritsch cyclization

The extracts of many plants that are widely used in traditional medicine systems for treatment of various health conditions, have been found to contain alkaloids that display relevant biological activities.[1] The azafluoranthenes are a small class of naturally occurring alkaloids that are characterized by their unique indeno[1,2,3-*ij*]isoquinoline motif.[2] They differ in the pattern of their oxygen substituents. Phenolic members of this family are norimeluteine (**1a**), norrufescine (**1b**) and telitoxine (**1c**), isolated from the climbing shrubs *Cissampelos pareira, Abuta rufescens, A. imene, Telitoxicum peruvianum, T. glaziovii Stephania hernandifolia* and *Pericampylus glaucus*.[3,4] In addition, rufescine (**1d**), imeluteine (**1e**) and triclisine (**1f**), isolated from the Amazonian vines *Abuta rufescens, A. imene* and *Triclisia gilletii*, respectively,[5] are non-phenolic tetracycles that are also included in this group (Figure 1). These heterocycles were isolated from Menispermaceae; however, the tatarines A (**2a**) and D (**2b**) were recently reported from *Acorus tatarinowii* Schott, *A. graminei* (Araceae),[6] and the unusual azafluoranthenic acid **2c** (sarumine) was isolated from *Saruma henryi* (Aristolochiaceae).[7]

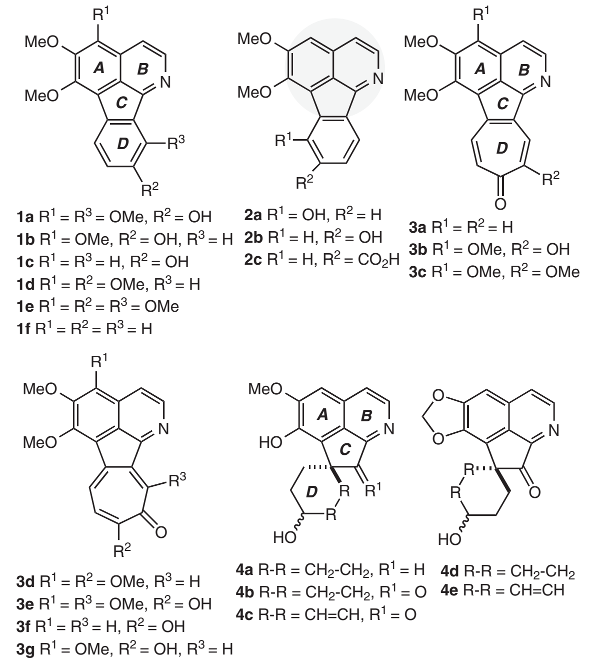

R1
MeO
MeO
A
B
C
D
N
R3
R2
1a R1 = R3 = OMe, R2 = OH
1b R1 = OMe, R2 = OH, R3 = H
1c R1 = R3 = H, R2 = OH
1d R1 = R2 = OMe, R3 = H
1e R1 = R2 = R3 = OMe
1f R1 = R2 = R3 = H
MeO
MeO
N
R1
R2
2a R1 = OH, R2 = H
2b R1 = H, R2 = OH
2c R1 = H, R2 = CO2H
R1
MeO
MeO
A
B
C
D
N
O
R2
3a R1 = R2 = H
3b R1 = OMe, R2 = OH
3c R1 = OMe, R2 = OMe
R1
MeO
MeO
N
R3
R2
O
3d R1 = R2 = OMe, R3 = H
3e R1 = R3 = OMe, R2 = OH
3f R1 = R3 = H, R2 = OH
3g R1 = OMe, R2 = OH, R3 = H
MeO
HO
A
B
C
D
N
R
R
R1
HO
4a R-R = CH2-CH2, R1 = H
4b R-R = CH2-CH2, R1 = O
4c R-R = CH=CH, R1 = O
O
O
N
R
R
O
HO
4d R-R = CH2-CH2
4e R-R = CH=CH

Figure 1 Chemical structures of some natural products carrying the cyclopenta[*ij*]isoquinoline motif

The azafluoranthenes exhibit promising antidepressant, healing, cytotoxic, anti-HIV and antifungal activity;[3d,8] in addition, triclisine and rufescine have been predicted to display a number of relevant biological activities.[9] The interest in these natural products has resulted in different synthetic and medicinal chemistry endeavors.[5a,10,11]

Some azafluoranthenes have environmental impact, being considered air pollutants and priority contaminants,[12] while others display potentially valuable technological applications in luminescent and electroluminescent devices.[13]

Analogously, the tropo- and tropolo-isoquinolines are a biogenetically related reduced group of Menispermaceae natural products, bearing a poly-substituted 9*H*-azuleno[1,2,3-*ij*]isoquinoline framework, which differ in the decoration of oxygenated functions along the molecular periphery.[14] Pareitropone (**3a**), grandirubrine (**3b**), and isoimerubrine (**3c**), as well as imerubrine (**3d**), the pareirubrines A (**3e**) and B (**3f**), and granditropone (**3g**),[4b,15] are its most recognized members.

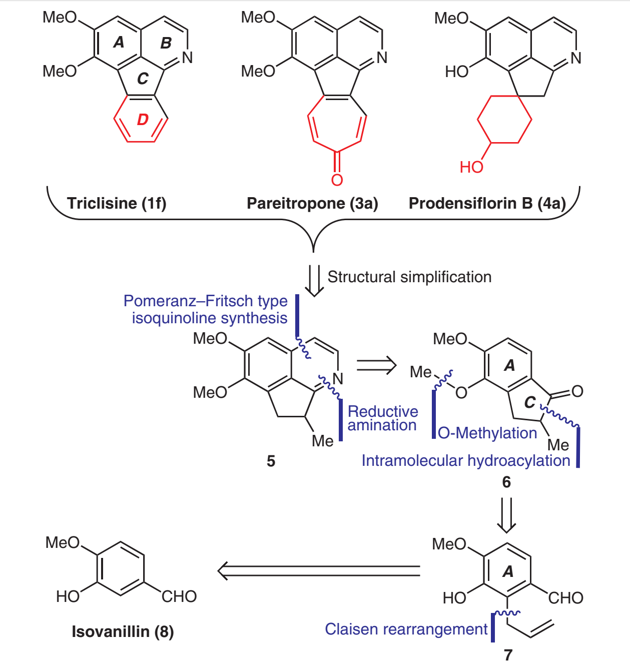
The sources of these heterocycles were *Abuta rufescens*, *A. imene*, *A. concolor*, *A. grandifolia*, and *Cissampelos pareira*. The compounds exhibited cytotoxic properties and antileukemic activity against P-388 cells,[16] and a number of efforts have been made towards their synthesis.[17]

In addition, proaporphine alkaloids that display a fully aromatic isoquinoline framework, are rather scarce. This family includes prodensiflorin B (**4a**), compound **4b** and their oxidized congeners including prooxocryptochine (**4c**), grandine A (**4d**) and scortechiniine B (**4e**), which have been isolated from various ethnobotanically relevant plants, such as *Thalictrum wangii* B. Boivin (Ranunculaceae) and *Cryptocarya densiflora* Blume (Lauraceae).[18]

The azafluoranthenes, tropoisoquinolines and proaporphines share a tricyclic cyclopenta[*ij*]isoquinoline framework. We have previously disclosed an electrocyclization-mediated approach to 2-methyltriclisine, an unnatural analogue of the azafluoranthene alkaloid triclisine,[19] as well as modified Pomeranz–Fritsch cyclization-mediated syntheses of the ABC ring system of the related stephaoxocane alkaloids,[20a] and other alternatives affording analogues of the latter.[20b–e]

In pursuit of our efforts towards the preparation of analogues of isoquinoline-type natural products, herein we wish to report a hydroacylation/Pomeranz–Fritsch cyclization approach for the synthesis of the ABC ring system characteristic of the azafluoranthene, tropoisoquinoline, and proaporphine alkaloids. The synthetic sequence was based on the retrosynthetic analysis outlined in Scheme 1.

Initially, triclisine (**1f**), imerubrine (**3d**), and prodensiflorin B (**4a**) were taken as models and structurally simplified, uncovering the tricycle **5** as the target; the latter was then disconnected at the indicated C–C and C–N bonds of the heterocyclic ring, unveiling the indanone **6** as a suitable precursor, under the assumption that the heterocyclic ring could be built through a reductive amination of the ketonic scaffold, followed by a Pomeranz–Fritsch cyclization sequence. A similar indanone was recently employed to build the tricyclic core of the unusual cyclopenta[*de*]isoquinoline alkaloid delavatine A.[21]



Scheme 1 Structural simplification of triclisine (**1f**), pareitropone (**3a**), and prodensiflorin B (**4a**) and retrosynthetic analysis of the resulting cyclopenta[*ij*]isoquinoline **5**

Further analysis that suggested two strategic C–C and C–O bond disconnections of **6**, revealed the *ortho*-allyl benzaldehyde **7** as a key intermediate. This was guided by the conjecture that the indanone motif **6** could be accessed through an atom economic intramolecular olefin hydroacylation.

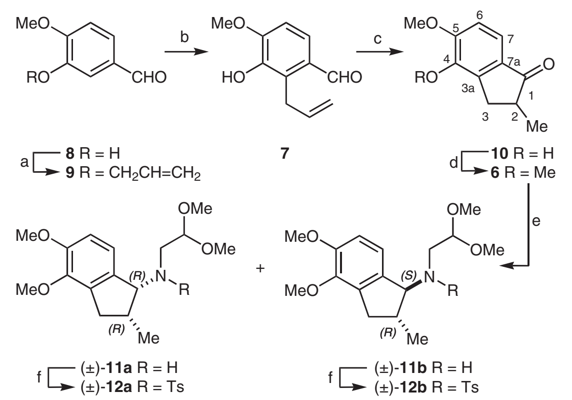
A final C–C bond disconnection of **7** proposed the installation of the allyl substituent through a Claisen rearrangement. This required the inclusion of an *O*-methylation stage and suggested the use of the inexpensive and easily available isovanillin (**8**) as starting material.

As planned, the synthesis commenced with the O-allylation of isovanillin (**8**), followed by Claisen rearrangement of the resulting allyl ether **9**, to afford 89% overall yield of the foreseen intermediate **7** (Scheme 2).

In turn, the proposed intramolecular hydroacylation toward **10** was explored. This kind of reaction has been performed primarily under promotion by transition-metal complexes (mainly derived from expensive, rare elements) and/or comparatively expensive *N*-heterocyclic carbenes.[22]

Fortunately, however, we have found that the use of 40% KF/Al_2O_3 reagent[23] can promote such transformation, in moderate yields, providing that a free phenol is located *ortho* to the allyl moiety.

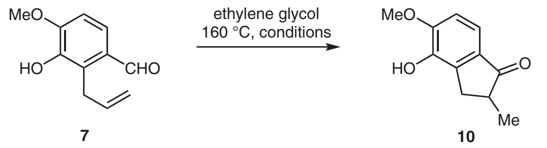
Therefore, 2-allylbenzaldehyde **7** was exposed to 40% *w*/*w* KF/Al_2O_3 and heated in ethylene glycol to 160 °C. Under conventional thermal conditions and a 2:1 ratio (molar relation between the amount of KF in the solid promoter and compound **7**), this afforded 30% yield of **10** after 2.5



Scheme 2 *Reagents and conditions*: (a) $BrCH_2CH{=}CH_2$, K_2CO_3, EtOH, reflux, 3 h; (b) MW (200 °C), 5 min (89% overall); (c) 40% KF/Al_2O_3, ethylene glycol, MW, 160 °C, 30 min (57%); (d) MeI, K_2CO_3, EtOH, reflux, 2 h (82%); (e) 1. $H_2NCH_2CH(OMe)_2$ (6 equiv), AcOH (4.2 equiv), $MgSO_4$, 3 Å MS, EtOH, r.t., 20 h; 2. $NaCNBH_3$, reflux, 24 h (**11a**, 44%; **11b**, 43%); (f) TsCl, $^iPr_2NEt$, $CHCl_3$, reflux (**11a**→**12a**, 48 h, 83%; **11b**→**12b**, 24 h, 95%).

hours (Table 1, entry 1) and no starting material could be recovered. However, better results were obtained upon brief microwave irradiation at the same temperature (entries 2–5), with optimum yields being achieved in 30 minutes (entry 3). The relative amount of the promoter was also optimized (entries 3, 6–9), with a 2:1 ratio (KF/Al_2O_3 to **7**) providing the best reaction performance.

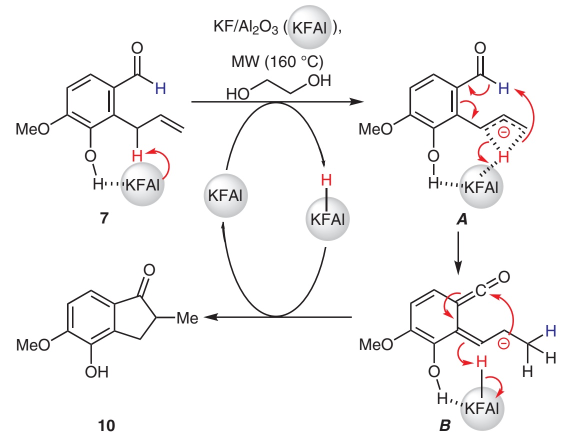
Table 1 Optimization of the Intramolecular Hydroacylation of **7**



Entry	Ratio KF/Al_2O_3 to **7**[a]	Heating[b]	Time (min)	Yield (%) of **10**	Recovery (%) of **7**
1	2:1	Thermal	150	30	0
2	2:1	MW	15	44	0
3	2:1	MW	30	57	0
4	2:1	MW	45	51	0
5	2:1	MW	60	50	0
6	4:1	MW	30	52	0
7	1.5:1	MW	30	38	0
8	1.0:1	MW	30	31	15
9	0.5:1	MW	30	27	28

[a] Molar ratio between the amount of KF and compound **7**. The experiments were carried out at a final concentration of 0.2 mmol of **7** in 1 mL of ethylene glycol.
[b] MW: microwave heating.

Increasing the amount of promoter to a 4:1 ratio caused diminished yields (Table 1, entry 6), and lowering the ratio (1:1 or lower) also resulted in recovery of the starting material after 30 min. Under the optimized conditions, 57% yield of the 5-*exo-trig* cyclized product **10** was achieved (entry 3). No evidence of the *endo* cyclization isomer was observed by NMR analysis of the crude reaction product. Although the precise details of the reaction mechanism leading to indanone **10** remain unknown, a mechanistic picture like that shown in Scheme 3 can be drawn on the basis of literature precedents. It can be proposed that the reagent can abstract a benzylic proton, generating the allyl anion intermediate **A**. In turn, the latter can abstract the formyl hydrogen and trigger the formation of the ketene derived anionic intermediate **B**. Next, an intramolecular attack of the allyl carbanion onto the carbonyl carbon of the ketene moiety, with capture of a proton from the reagent would result in formation of the observed product **10**. Notably, it has been reported that the presence of ethylene glycol somehow protects allylphenols exposed to KF/Al_2O_3 from heat-mediated deterioration.[24]



Scheme 3 Proposed mechanism for the KF/Al_2O_3-promoted intramolecular hydroacylation of *ortho*-allylbenzaldehyde **7** into indanone derivative **10**

Conventional alkylation of phenol **10** with MeI and K_2CO_3 as base in refluxing EtOH furnished **6** in 82% yield. Interestingly, this compound has been prepared in an alternate way in the context of examining the activity of E2020 (currently marketed as donepezil) and its analogues,[25] as potential candidates for treatment of mild to moderate cognitive disorders of Alzheimer's disease and related dementias.

The indanone was then subjected to a reductive amination with aminoacetaldehyde dimethyl acetal, in the presence of anhydrous $MgSO_4$ and 3Å molecular sieves, as water scavengers. Acetic acid was added to promote condensation toward the intermediate imine and cause further iminium ion formation. The latter was selectively reduced with

NaCNBH$_3$ in refluxing EtOH,[26] affording 87% of the expected amine **11**, as a *ca.* 1:1 mixture of diastereomers, which were chromatographically separated, to provide 44% yield of (±)-**11a** and 43% (±)-**11b** (87% combined yield).

The relative stereochemistry of the amines (±)-**11a**,**b** could not be deduced unambiguously from their ^{1}H and ^{13}C NMR spectra; therefore, it was investigated with the aid of nuclear Overhauser effect (NOE) experiments. As shown in Figure 2, these suggested that compound (±)-**11a**, which displayed H-2 and H-3 signal enhancements but lacked signal increase of H-1 upon irradiation of Me-2, should be the 1,2-*cis* diastereomer. This was unequivocally confirmed by examination of the amine (±)-**11b**, to which the 1,2-*trans* stereochemistry should be attributed, after exhibiting signal enhancements of H-1, H-2 and H-3 upon irradiation of Me-2.

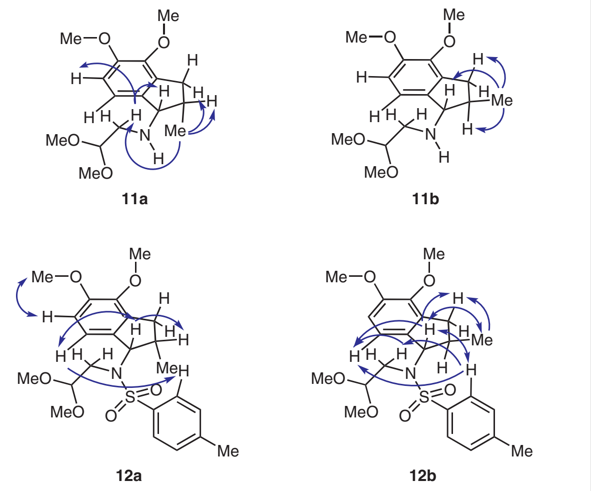
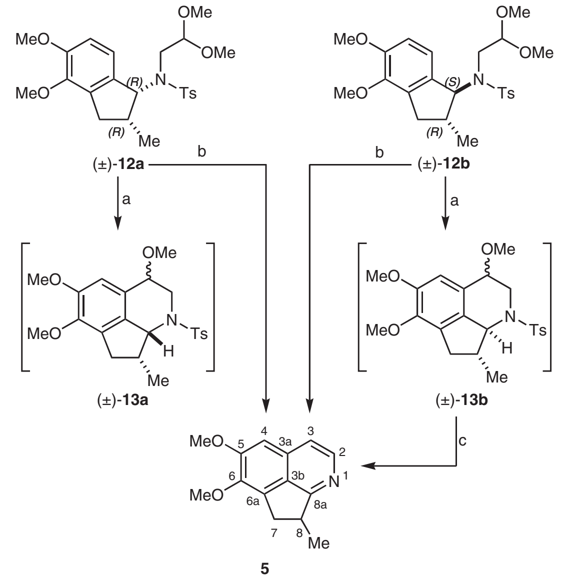


Figure 2 Nuclear Overhauser effect (NOE) signal enhancements observed in compounds **11a**,**b** and **12a**,**b**

The amines **11a**,**b** were individually submitted to a reaction with tosyl chloride in refluxing chloroform, employing DIPEA as HCl scavenger. This resulted in the acquisition of **12a** and **12b** in 83% and 95% yield, respectively. Analysis of the NOE spectra of these sulfonamides confirmed previous stereochemical assignments of their precursors. Irradiation of H-1 of **12a** resulted only in signal intensification of H-2, whereas irradiation of H-1 of **12b** augmented the signals of Me-2 and H-3.

Subsequent exposure of the sulfonamidoacetals to cyclization under the conventional conditions of the Jackson modification of the Pomeranz–Fritsch cyclization (6 N HCl, dioxane, reflux)[27] met with failure. This outcome was not unexpected, probably being a result of the improper activation of the aromatic ring toward cyclization, due to the *ortho*-disubstituted condition of the methyl ether located in the *para* position with regards to the cyclization site.[26b,28]

Therefore, after screening different conditions, and in light of our success with this alternative, the use of Lewis acid promotion was examined (Scheme 4). Thus, (±)-**12a** was exposed to SnCl$_4$ in anhydrous CH$_2$Cl$_2$ at –60 °C. This resulted in a series of unidentified products, along with (±)-**13a**, which was obtained in 35% yield, as an inseparable mixture of diastereomers,[25b] as stemmed from the characteristic signals of the 4-OMe groups (δ = 3.33 and 3.45 ppm, singlets) and the aromatic proton (δ = 6.58 and 6.75 ppm, singlets) in the ^{1}H NMR spectrum.



Scheme 4 *Reagents and conditions*: (a) SnCl$_4$, CH$_2$Cl$_2$, –60 °C, 1 h (**12a**→**13a**, 35%; **12b**→**13b**, 62%); (b) AlCl$_3$, MeNO$_2$, r.t., overnight (**12a**→**5**, 15%; **12b**→**5**, 3%) or 20% TFA in dioxane, 100 °C, 1.5 h (**12a**→**5**, 45%); (c) KO^{t}Bu, pyridine, 100 °C, 30 min (63%).

On the other hand, the reaction of (±)-**12a** with AlCl$_3$ in nitromethane at room temperature proceeded smoothly to give **5**, which was isolated in 15% yield, through the one-pot cyclization-aromatizing desulfonylation.[29] Better performance was achieved with 20% trifluoroacetic acid (TFA) in refluxing dioxane, which gave compound **5** in 45% isolated yield.[30]

Similar results were obtained with the 2,3-*trans*-substituted sulfonamidoacetal (±)-**12b**, which afforded 62% yield of (±)-**13b** as a mixture of diastereomers when submitted to reaction with SnCl$_4$. Its characteristic signals in the ^{1}H NMR spectrum were singlets at δ = 3.32 and 3.38 ppm (4-OMe) and signals of the aromatic proton as singlets at δ = 6.58 and 6.71 ppm. These results indicate that the relative stereochemistry of the substituents on the five-membered ring have no significant impact on the outcome of the cyclization stage. Without purification, (±)-**13b** was exposed to K^{t}BuO in refluxing pyridine, resulting in the isolation of **5** in 63% yield. This result contrasted markedly with those of an attempt at cyclization with $AlCl_3$ in nitromethane, which gave only 3% yield of **5**.

In conclusion, we have developed convenient syntheses of two polysubstituted cyclopenta[*ij*]isoquinoline derivatives, which embody the ABC-ring system of the azafluoranthene, tropoisoquinoline, and proaporphine alkaloids. The synthetic sequence toward **5** proceeded in seven steps and 6.8% overall yield, from the easily available isovanillin. The synthesis was executed without the use of rare transition-metal derivatives and did not require protecting groups, and took place through the novel use of 40% KF/Al_2O_3 as promoter of a key microwave-assisted intramolecular hydroacylation to access an indanone key intermediate, embodying the AC-ring system of the natural products. This transformation was associated with a reductive amination, followed by different modifications of the Pomeranz–Fritsch isoquinoline synthesis protocol (TFA/dioxane, $SnCl_4$-K^tBuO, $AlCl_3/MeNO_2$), for the formation of the remaining heterocyclic B-ring.

All the reactions were carried out under anhydrous argon atmosphere, using oven-dried glassware and freshly distilled anhydrous solvents. Anhydrous EtOH was obtained by reaction of the AR reagent with magnesium turnings and a crystal of iodine, followed by distillation of the solvent from the so formed magnesium ethoxide. Anhydrous chloroform was obtained by a 4 h reflux of the AR product over P_2O_5 and further distillation of the product. Anhydrous CH_2Cl_2 was obtained from an M. Braun solvent purification and dispenser system. Anhydrous 1,2-dichlorobenzene was prepared by refluxing the solvent over CaH_2 for 4 h, followed by distillation. The anhydrous solvents were transferred by using a cannula and stored in dry Young ampoules containing activated molecular sieves. All of the other solvents and reagents were used as received.

The reactions were monitored by TLC, using silica gel GF_{254} plates supported on aluminum and run in different hexane–EtOAc solvent mixtures. The chromatographic spots were detected by exposure to 254 nm UV light, and by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent, 0.1% ninhydrin in EtOH or Dragendorff reagent, followed by careful heating to improve selectivity. Flash column chromatography was performed with silica gel 60 H (particle size < 55 µm), eluting with hexane–EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques.

Melting points were measured with an Ernst Leitz Wetzlar model 350 hot-stage microscope and are uncorrected. FTIR spectra were acquired with a Shimadzu Prestige 21 spectrophotometer, with the samples prepared as solid dispersions in KBr disks or as thin films held between NaCl cells. Nuclear magnetic resonance spectra were recorded with a Bruker Avance 300 NMR spectrometer, at 300.13 (^1H) and 75.48 (^{13}C) MHz. $CDCl_3$ was used as solvent, unless otherwise noted, and the chemical shifts are reported in parts per million in the δ scale. TMS was used as the internal standard (resonances of $CHCl_3$ in $CDCl_3$: δ = 7.26 and 77.0 ppm for ^1H and ^{13}C NMR, respectively). Coupling constants (*J*) are given in Hertz. Pairs of signals marked with asterisk (*) indicate that their assignments may be exchanged. Some 2D NMR experiments (COSY, HSQC, HMBC) were performed concomitantly to aid unambiguous signal assignment. High-resolution mass spectra were obtained from ICYTAC (Córdoba, Argentina) and UMYMFOR (Buenos Aires, Argentina) with Bruker MicroTOF-Q II instruments. Detection of the ions was performed in electrospray ionization, positive ion mode. Microwave-assisted reactions were carried out in a CEM-Discover microwave reactor system.

Preparation of 40% *w*/*w* KF/Al_2O_3[23]

Al_2O_3 (7.5 g) was suspended in deionized water (38 mL) and magnetically stirred for 5 minutes (pH of the liquid phase: 7.6). The mixture was then treated with a solution of KF (5 g) in deionized water (38 mL, pH of the solution: 6.5). The resulting suspension was continuously stirred until the pH of the liquid phase was 11.5–11.7. Most of the water was then removed from the system by rotatory evaporation, and the resulting wet solid mass was dried at 140–150 °C for 6 h under reduced pressure (200 mbar). The so obtained solid mass was ground in a mortar into a fine homogeneous powder.

2-Allyl-3-hydroxy-4-methoxybenzaldehyde (7)[20a]

A suspension of isovanillin (**8**, 500 mg, 3.3 mmol), allyl bromide (0.363 mL, 4.2 mmol) and anhydrous K_2CO_3 (635 mg, 4.6 mmol) in absolute EtOH (5 mL) was heated at reflux for 3 h. After completion of the reaction, the solvent was evaporated, brine (5 mL) was added to the residue, and the product was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. A small sample of the resulting 3-allyloxy-4-methoxybenzaldehyde (**9**) was analyzed spectroscopically.

IR (film): 2934, 2841, 1686, 1585, 1436, 1397, 1268, 1134, 1018, 932, 811, 757, 641 cm^{-1}.

^1H NMR: δ = 3.96 (s, 3 H, OMe), 4.67 (dt, *J* = 1.3, 5.3 Hz, 2 H, $O\mathit{CH}_2CH{=}CH_2$), 5.32 (dd, *J* = 1.3, 10.5 Hz, 1 H, $OCH_2CH{=}C\mathit{H}_{2cis}$), 5.44 (dd, *J* = 1.3, 17.3 Hz, 1 H, $OCH_2CH{=}C\mathit{H}_{2trans}$), 6.10 (dddd, *J* = 5.3, 10.5, 17.3 Hz, 1 H, $OCH_2C\mathit{H}{=}CH_2$), 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).

^{13}C NMR: δ = 56.1 (OMe), 69.6 ($O\mathit{C}H_2CH{=}CH_2$), 110.6 (C-5),* 110.8 (C-2),* 118.5 ($OCH_2CH{=}\mathit{C}H_2$), 126.7 (C-6), 129.9 (C-1), 132.4 ($OCH_2\mathit{C}H{=}CH_2$), 148.4 (C-3), 154.7 (C-4), 190.7 (CHO).

Without additional purification, the oily residue was transferred to a microwave reaction tube, argon was bubbled to create a suitable atmosphere and the oil was irradiated in the microwave reactor (200 °C, ca. 50 W, 5 min). After cooling, the resulting thick oil was purified by silica gel column chromatography, furnishing **7**.

Yield: 564 mg (89% overall yield from **8**); solid; mp 51–53 °C.

IR (KBr): 3425, 2954, 2850, 1679, 1600, 1575, 1492, 1345, 1279, 1165, 1084, 915, 804, 785, 656 cm^{-1}.

^1H NMR: δ = 3.88 (dt, *J* = 1.7, 6.0 Hz, 2 H, $ArCH_2CH{=}CH_2$), 3.97 (s, 3 H, OMe), 4.99 (ddt, *J* = 1.7, 1.7, 17.1 Hz, 1 H, $ArCH_2CH{=}C\mathit{H}_{2trans}$), 5.01 (ddt, *J* = 1. 7, 1.7, 10.7 Hz, 1 H, $ArCH_2CH{=}C\mathit{H}_{2cis}$), 5.79 (s, 1 H, OH), 6.03 (ddt, *J* = 6.0, 10.7, 17.1 Hz, 1 H, $ArCH_2C\mathit{H}{=}CH_2$), 6.88 (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).

^{13}C NMR: δ = 28.3 ($ArCH_2CH{=}CH_2$), 55.0 (OMe), 108.0 (C-5), 115.2 ($ArCH_2CH{=}CH_2$), 125.3 (C-6), 127.5 (C-1), 128.2 (C-2), 136.1 ($ArCH_2\mathit{C}H{=}CH_2$), 143.7 (C-3), 150.7 (C-4), 191.3 (CHO).

4-Hydroxy-5-methoxy-2-methyl-2,3-dihydro-1*H*-inden-1-one (10)

A stirred mixture of **7** (100 mg, 0.52 mmol) and 40% KF/Al_2O_3 (64 mg) in anhydrous ethylene glycol (2.6 mL), was placed in a microwave vial and degassed under vacuum for 20 min. The suspension was then irradiated in a microwave oven at 160 °C for 30 min. After cooling, glacial acetic acid (2 mL) was added to the reaction mixture and the system was stirred for 45 min. Brine (5 mL) was added and the organic products were extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with water (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give indanone **10**.

Yield: 57 mg (57%); yellow solid; mp 135–138 °C.

IR (KBr): 3550–3040, 2967, 2930, 2880, 2849, 1694, 1607, 1501, 1439, 1364, 1279, 1184, 1078, 905, 820, 773, 669 cm^{-1}.

^{1}H NMR: δ = 1.29 (d, *J* = 7.3 Hz, 1 H, Me-2), 2.63 (dd, *J* = 3.8, 16.9 Hz, 1 H, H-3), 2.71 (ddq, *J* = 3.8, 7.3, 7.5 Hz, 1 H, H-2), 3.34 (dd, *J* = 7.5, 16.9 Hz, 1 H, H-3), 3.95 (s, 3 H, OMe), 5.85 (br s, OH), 6.91 (d, *J* = 8.2 Hz, 1 H, H-6), 7.34 (d, *J* = 8.2 Hz, 1 H, H-7).

^{13}C NMR: δ = 16.7 (Me-2), 31.1 (C-3), 42.3 (C-2), 56.5 (OMe), 110.6 (C-6), 116.5 (C-7), 130.8 (C-7a), 138.9 (C-3a), 142.2 (C-4), 151.1 (C-5), 208.5 (C-1).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{12}NaO_3$: 215.0684; found: 215.0681.

4,5-Dimethoxy-2-methyl-2,3-dihydro-1*H*-inden-1-one (6)

A mixture of indanone **10** (216 mg, 1.1 mmol) and K_2CO_3 (304 mg, 2.2 mmol) in absolute EtOH (5 mL) was stirred for 10 min under argon. MeI (0.205 mL, 3.3 mmol) was then added, and the resulting suspension was heated at reflux for 2 h. After completion of the reaction, the solvent was removed under reduced pressure, brine (5 mL) was added to the residue, and the products were extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford compound **6**.

Yield: 180 mg (82%); yellow solid; mp 72–75 °C.

IR (KBr): 2968, 2934, 2872, 2848, 1699, 1599, 1497, 1339, 1279, 1177, 1069, 978, 822, 775, 610 cm^{-1}.

^{1}H NMR: δ = 1.29 (d, *J* = 7.2 Hz, 3 H, Me-2), 2.67 (dd, *J* = 4.0, 15.6 Hz, 1 H, H-3), 2.70 (ddq, *J* = 4.0, 7.2, 8.8 Hz, 1 H, H-2), 3.39 (dd, *J* = 8.8, 18.3 Hz, 1 H, H-3), 3.91 (s, 3 H, OMe-4), 3.94 (s, 3 H, OMe-3), 6.97 (d, *J* = 8.3 Hz, 1 H, H-6), 7.52 (d, *J* = 8.3 Hz, 1 H, H-7).

^{13}C NMR: δ = 16.6 (Me-2), 31.7 (C-3), 42.3 (C-2), 56.3 (OMe-5), 60.5 (OMe-4), 112.5 (C-6), 120.6 (C-7), 130.5 (C-7a), 145.5 (C-3a), 146.3 (C-4), 157.7 (C-5), 208.0 (C-1).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{14}NaO_3$: 229.0841; found: 229.0837.

(1*R**,2*R**)-*N*-(2,2-Dimethoxyethyl)-4,5-dimethoxy-2-methyl-2,3-dihydro-1*H*-inden-1-amine [(±)-11a] and (1*S**,2*R**)-*N*-(2,2-Dimethoxyethyl)-4,5-dimethoxy-2-methyl-2,3-dihydro-1*H*-inden-1-amine [(±)-11b]

Aminoacetaldehyde dimethylacetal (0.549 mL, 5 mmol) and glacial acetic acid (0.192 mL, 3.36 mmol) were successively added to a suspension containing the indanone **6** (175 mg, 0.84 mmol), $MgSO_4$ (50 mg), and activated 4 Å molecular sieves (50 mg) in absolute EtOH (6 mL). The mixture was stirred for 20 h at r.t., then $NaCNBH_3$ (63 mg, 1 mmol) was carefully added. The resulting slurry was heated at reflux for 24 h, then cooled to r.t. and the volatiles were removed in vacuum. The resulting residue was purified by column chromatography to furnish the expected amine (±)-**11a**.

Compound (±)-11a

Yield: 111 mg (44%); yellow oil.

IR (NaCl): 3300–3650, 3339, 2953, 2936, 2870, 2832, 1611, 1487, 1373, 1271, 1132, 1078, 968, 812, 721 cm^{-1}.

^{1}H NMR: δ = 0.98 (d, *J* = 6.8 Hz, 3 H, Me-2), 1.47 (br s, $w_{1/2}$ = 11.5 Hz, 1 H, NH), 2.56–2.69 (m, 1 H, H-2), 2.66 (dd, *J* = 5.2, 16.4 Hz, 1 H, H-3), 2.81 (d, *J* = 5.5 Hz, 2 H, N*CH*$_2$-), 2.94 (dd, *J* = 8.4, 17.0 Hz, 1 H, H-3), 3.38 (s, 3 H, OMe, acetal), 3.40 (s, 3 H, OMe, acetal), 3.83 (s, 3 H, OMe-4), 3.84 (s, 3 H, OMe-5), 3.99 (d, *J* = 5.8 Hz, 1 H, H-1), 4.50 (t, *J* = 5.5 Hz, 1 H, NCH_2*CH*<), 6.74 (d, *J* = 8.1 Hz, 1 H, H-6), 6.98 (d, *J* = 8.1 Hz, 1 H, H-7).

^{13}C NMR: δ = 13.8 (Me-2), 35.5 (C-3), 38.4 (C-2), 49.4 (NCH_2-), 54.1 (OMe, acetal), 54.2 (OMe, acetal), 56.2 (OMe-5), 60.4 (OMe-4), 65.1 (C-1), 104.5 (NCH_2*CH*<), 110.8 (C-6), 119.6 (C-7), 135.4 (C-3a), 138.8 (C-7a), 145.7 (C-5), 151.8 (C-4).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{25}NNaO_4$: 318.1681; found: 318.1675.

Compound (±)-11b

Increasing solvent polarity furnished (±)-**11b**.

Yield: 110 mg (43%); greenish yellow oil.

IR (NaCl): 2949, 2936, 2866, 2832, 1609, 1489, 1271, 1221, 1128, 1076, 964, 810 cm^{-1}.

^{1}H NMR: δ = 1.15 (d, *J* = 6.8 Hz, 3 H, Me-2), 1.51 (br s, $w_{1/2}$ = 14.5 Hz, 1 H, NH), 2.23–2.37 (m, 1 H, H-2), 2.44 (dd, *J* = 6.2, 16.0 Hz, 1 H, H-3), 2.80 (dd, *J* = 5.5, 12.0 Hz, 1 H, -N*CH*$_2$-), 2.84 (dd, *J* = 5.5, 12.0 Hz, 1 H, N*CH*$_2$-), 3.20 (dd, *J* = 7.5, 16.0 Hz, 1 H, H-3), 3.38 (s, 6 H, 2 × OMe, acetal), 3.73 (d, *J* = 5.5 Hz, 1 H, H-1), 3.83 (s, 3 H, OMe-4), 3.84 (s, 3 H, OMe-5), 4.48 (t, *J* = 5.5 Hz, 1 H, NCH_2*CH*<), 6.76 (d, *J* = 8.1 Hz, 1 H, H-6), 6.97 (d, *J* = 8.1 Hz, 1 H, H-7).

^{13}C NMR: δ = 19.7 (Me-2), 35.7 (C-3), 41.3 (C-2), 48.3 (NCH_2-), 54.0 (OMe, acetal), 54.2 (OMe, acetal), 56.3 (OMe-5), 60.3 (OMe-4), 70.1 (C-1), 104.6 (NCH_2*CH*<), 111.3 (C-6), 119.5 (C-7), 135.7 (C-3a), 138.6 (C-7a), 145.5 (C-5), 151.9 (C-4).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{25}NNaO_4$: 318.1681; found: 318.1684.

N-((1*R**,2*R**)-4,5-Dimethoxy-2-methyl-2,3-dihydro-1*H*-inden-1-yl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide [(±)-12a]

To a stirred solution of amine (±)-**11a** (100 mg, 0.34 mmol) in anhydrous $CHCl_3$ (5 mL) were successively added DIPEA (0.119 mL, 0.68 mmol) and tosyl chloride (117 mg, 0.61 mmol). The mixture was heated under reflux for 48 h, when it was cooled to r.t., and most of the organic solvent was removed under reduced pressure. The resulting residue was purified chromatographically to furnish the tosylamide (±)-**12a**.

Yield: 127 mg (83%); pale-yellow solid; mp 84–87 °C.

IR (KBr): 2955, 2934, 2872, 2835, 1611, 1595, 1491, 1341, 1269, 1125, 1061, 970, 800, 791, 673 cm^{-1}.

^{1}H NMR: δ = 1.16 (d, *J* = 6.6 Hz, 3 H, Me-2), 2.33 (dd, *J* = 9.3, 15.6 Hz, 1 H, H-3), 2.46 (s, 3 H, ArMe of Ts), 2.50–2.68 (m, 1 H, H-2), 2.82 (dd, *J* = 7.6, 15.4 Hz, 1 H, N*CH*$_2$-), 3.11 (dd, *J* = 8.1, 15.6 Hz, 1 H, H-3), 3.28 (dd, *J* = 3.0, 15.4 Hz, 1 H, N*CH*$_2$-), 3.33 (s, 3 H, OMe, acetal), 3.46 (s, 3 H, OMe, acetal), 3.76 (s, 3 H, OMe-5), 3.78 (s, 3 H, OMe-4), 4.66 (dd, *J* = 3.0, 7.6 Hz, 1 H, NCH_2*CH*<), 4.83 (d, *J* = 8.8 Hz, 1 H, H-1), 5.77 (d, *J* = 8.0 Hz, 1 H, H-6), 6.47 (d, *J* = 8.0 Hz, 1 H, H-7), 7.33 (d, *J* = 8.0 Hz, 2 H, H-3 and H-5 of Ts), 7.82 (d, *J* = 8.0 Hz, 2 H, H-2 and H-6 of Ts).

^{13}C NMR: δ = 17.6 (Me-2), 21.7 (Ar-Me of tosyl), 34.7 (C-3), 40.3 (C-2), 47.5 (NCH$_2$-), 54.9 (OMe, acetal), 56.2 (OMe-5), 57.0 (OMe-acetal), 60.4 (OMe-4), 70.5 (C-1), 105.4 (NCH$_2$*C*H<), 111.2 (C-7), 119.1 (C-6), 127.6 (Ar-2 and Ar-6 of tosyl), 129.9 (Ar-3 and Ar-5 of tosyl), 133.7 (C-3a), 135.8 (C-7a), 137.6 (Ar-1 of tosyl), 143.6 (Ar-4 of tosyl), 145.3 (C-4), 152.0 (C-5).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{31}NNaO_6S$: 472.1770; found: 472.1777.

N-((1*S**,2*R**)-4,5-Dimethoxy-2-methyl-2,3-dihydro-1*H*-inden-1-yl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide [(±)-12b]

By following the procedure employed for the preparation of (±)-**12a**, amine (±)-**11b** (100 mg, 0.34 mmol) was dissolved in anhydrous CHCl$_3$ (5 mL) and treated with DIPEA (0.119 mL, 0.68 mmol) and tosyl chloride (117 mg, 0.61 mmol), under reflux for 24 h, giving (±)-**12b**.

Yield: 145 mg (95%); white solid; mp 125–128 °C.

IR (KBr): 2961, 2936, 2886, 2837, 1603, 1489, 1339, 1273, 1161, 1074, 970, 822, 798, 675 cm^{-1}.

^{1}H NMR: δ = 1.28 (d, *J* = 7.0 Hz, 3 H, Me-2), 2.48 (s, 3 H, ArMe of Ts), 2.54–2.67 (m, 1 H, H-2), 2.68–2.92 (m, 3 H, NC*H*$_2$- and H-3), 3.00 (dd, *J* = 8.1, 16.1 Hz, 1 H, H-3), 3.18 (s, 3 H, OMe, acetal), 3.24 (s, 3 H, OMe, acetal), 3.78 (s, 3 H, OMe-5), 3.80 (s, 3 H, OMe-4), 4.21 (dd, *J* = 3.0, 6.6 Hz, 1 H, NCH$_2$*CH*<), 5.17 (d, *J* = 7.7 Hz, 1 H, H-1), 5.93 (d, *J* = 8.2 Hz, 1 H, H-6), 6.55 (d, *J* = 8.2 Hz, 1 H, H-7), 7.35 (d, *J* = 8.1 Hz, 2 H, H-3 and H-5 of Ts), 7.83 (br d, *J* = 7.2 Hz, 2 H, H-2 and H-6 of Ts).

^{13}C NMR: δ = 14.3 (Me-2), 21.7 (Ar-Me of tosyl), 36.2 (C-3), 38.8 (C-2), 48.6 (NCH$_2$-), 54.3 (OMe, acetal), 54.7 (OMe-5), 56.2 (OMe-acetal), 60.3 (OMe-4), 65.7 (C-1), 104.9 (NCH$_2$*C*H<), 111.6 (C-7), 120.7 (C-6), 127.7 (Ar-2 and Ar-6 of tosyl), 129.7 (Ar-3 and Ar-5 of tosyl), 133.9 (C-3a), 138.0 (C-7a), 138.5 (Ar-1 of tosyl), 143.3 (Ar-4 of tosyl), 145.2 (C-4), 152.6 (C-5).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{31}NNaO_6S$: 472.1770; found: 472.1766.

5,6-Dimethoxy-8-methyl-7,8-dihydrocyclopenta[*ij*]isoquinoline (5) from (±)-12a

The tosylacetal (±)-**12a** (32 mg, 0.07 mmol) was dissolved in dioxane (1 mL), the resulting solution was treated with trifluoroacetic acid (0.250 mL) and the mixture was heated at 105 °C for 1.5 h. The reaction was then allowed to cool to r.t., 10 % NaHCO$_3$ (3 mL) was added and the organic products were extracted with EtOAc (2 × 80 mL). The organic extracts were combined, dried over MgSO$_4$, concentrated under reduced pressure, and purified by chromatography, to give isoquinoline **5**.

Yield: 7.2 mg (45%); pale-yellowish thick oil.

IR (NaCl): 3053, 2926, 2852, 2835, 1722, 1620, 1558, 1469, 1334, 1222, 1159, 1095, 963, 846, 736, 665 cm^{-1}.

^{1}H NMR: δ = 1.52 (d, *J* = 7.1 Hz, 3 H, Me-8), 3.08 (dd, *J* = 3.2, 16.8 Hz, 1 H, H-7), 3.67 (ddq, *J* = 3.2, 7.1, 7.8 Hz, 1 H, H-8), 3.80 (dd, *J* = 7.9, 16.8 Hz, 1 H, H-7), 3.99 (s, 3 H, OMe-6), 4.07 (s, 3 H, OMe-5), 6.94 (s, 1 H, H-4), 7.25 (d, *J* = 5.9 Hz, 1 H, H-3), 8.32 (d, *J* = 5.9 Hz, 1 H, H-2).

^{13}C NMR: δ = 19.9 (Me-8), 36.3 (C-7), 39.9 (C-8), 56.5 (OMe-6), 59.8 (OMe-5), 101.9 (C-4), 115.0 (C-3), 128.3 (C-3a),130.5 (C-3b), 131.2 (C-6a), 144.6 (C-2), 145.2 (C-5), 157.6 (C-6), 171.1 (C-8a).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_2$: 230.1181; found: 230.1178.

5,6-Dimethoxy-8-methyl-7,8-dihydrocyclopenta[*ij*]isoquinoline (5) from (±)-12b

A stirred solution of tosylacetal (±)-**12b** (58 mg, 0.13 mmol) in CH$_2$Cl$_2$ (4 mL) was cooled to –78 °C, and treated dropwise with a freshly prepared solution of SnCl$_4$ in CH$_2$Cl$_2$ (0.370 mL, 0.26 mmol). After 1 h at –78 °C, the reaction temperature was increased to –60 °C and the resulting yellow mixture was further stirred for 2.5 h. The deep-red mixture was slowly warmed to r.t., then the reaction was quenched with saturated K$_2$CO$_3$ solution (1 mL). After 10 min stirring, brine (4 mL) was added and the organic products were extracted with EtOAc (2 × 80 mL). The organic extracts were combined, dried over MgSO$_4$, concentrated under reduced pressure, and purified by chromatography, furnishing the 1,2,3,4-tetrahydroisoquinolines (±)-**13b** (34 mg, 62%), as a diastereomeric mixture. Without further purification, (±)-**13b** (32 mg, 0.07 mmol) was dissolved in freshly distilled pyridine (1 mL), potassium *tert*-butoxide (86 mg, 0.77 mmol) was added, and the stirred reaction was heated to 100 °C for 30 min. Then, 10% NaOH solution (1 mL) and brine (2 mL) were successively added, and the organic products were extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford compound **5** (9.6 mg, 63%), as a pale-yellowish oil with the same spectroscopic characteristics as the compound obtained from (±)-**12a**.

Cyclization of Tosylacetals (±)-12a and (±)-12b with AlCl$_3$

To a solution of AlCl$_3$ (59 mg, 0.44 mmol) in MeNO$_2$ (2 mL) at 0 °C was added tosylacetal (±)-**12a** (50 mg, 0.11 mmol) in MeNO$_2$ (1.5 mL) dropwise. The resulting solution was stirred under argon at r.t. overnight. The mixture was cooled to 0 °C, and the reaction was quenched with saturated NaHCO$_3$ solution (5 mL), and the mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). Combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The crude residue was then purified by flash column chromatography to afford **5** (3.8 mg, 15%). Employing the same procedure on (±)-**12b** (59 mg, 0.44 mmol) gave **5** (0.8 mg, 3%). The spectroscopic data of the heterocycles obtained from both tosylacetals were in full agreement with those of the compound obtained by TFA-assisted cyclization of (±)-**12a**.

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Supporting Information

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References

(1) (a) Wu, Z. Y. *Xinhua Bencao Gangyao (Essentials of the New China Materia Medica)*; Shanghai Science & Technology Press: Shanghai, **1988**, 174. (b) Röder, E. T.; Wiedenfeld, H. *Pharmazie* **2013**, *68*, 83. (c) Tantisewie, B.; Ruchirawat, S. *Alkaloids from the Plants of Thailand*, In *The Alkaloids: Chemistry and Pharmacology, Vol. 41*; Brossi, A., Ed.; Academic Press: New York, **1992**, 1–40. (d) Daniel, M. *Medicinal Plants: Chemistry and Properties*; Science Publishers: Enfield (NH, USA), **2006**. (e) Wangkheirakpam, S. *Traditional and Folk Medicine as a Target for Drug Discovery*, In *Natural Products and Drug Discovery*; Mandal, S. C.; Mandal, V.; Konishi, T., Ed.; Elsevier: Amsterdam, The Netherlands, **2018**, 29–56. (f) Roumy, V.; García-Pizango, G.; Gutierrez-Choquevilca, A.-L.; Ruiz, L.; Jullian, V.; Winterton, P.; Fabre, N.; Moulis, C.; Valentin, A. *J. Ethnopharmacol.* **2007**, *112*, 482.

(2) (a) Boye, O.; Brossi, A. *Tropolonic Colchicum Alkaloids and Allo Congeners*, In *The Alkaloids: Chemistry and Pharmacology, Vol. 41*; Brossi, A., Ed.; Academic Press: New York, **1992**, 125–176. (b) Semwal, D. K.; Semwal, R. B.; Vermaak, I.; Viljoen, A. *J. Ethnopharmacol.* **2014**, *155*, 1011.

(3) (a) Menachery, M. D.; Mandell, H. M.; DeSaw, S. A.; De Antonio, N. A.; Freyer, A. J.; Killmer, L. B. *J. Nat. Prod.* **1997**, *60*, 1328. (b) Menachery, M. D.; Edgren, D. L. *J. Nat. Prod.* **1988**, *51*, 1283. (c) Menachery, M. D.; Cava, M. P. *J. Nat. Prod.* **1981**, *44*, 320. (d) Morita, H.; Matsumoto, K.; Takeya, K.; Itokawa, H. *Chem. Pharm. Bull.* **1993**, *41*, 1307.

(4) (a) Yan, M.-H.; Cheng, P.; Jiang, Z.-Y.; Ma, Y.-B.; Zhang, X.-M.; Zhang, F.-X.; Yang, L.-M.; Zheng, Y.-T.; Chen, J.-J. *J. Nat. Prod.* **2008**, *71*, 760. (b) Cava, M. P.; Buck, K. T.; Noguchi, I.; Srinivasan, M.; Rao, M. G.; da Rocha, A. I. *Tetrahedron* **1975**, *31*, 1667. (c) Tang, L.-J.; Guan, H.-Y.; Zhang, Y.-H.; He, L.; Yang, X.-S.; Hao, X.-J. *Zhong Yao Cai* **2010**, *33*, 1881.

(5) (a) Cava, M. P.; Buck, K. T.; da Rocha, A. I. *J. Am. Chem. Soc.* **1972**, *94*, 5931. (b) Huls, R.; Gaspers, J.; Warin, R. *Bull. Soc. R. Sci. Liege* **1976**, *45*, 40.

(6) (a) Tong, X.-G.; Qiu, B.; Luo, G.-F.; Zhang, X.-F.; Cheng, Y.-X. *J. Asian Nat. Prod. Res.* **2010**, *12*, 438. (b) Chen, L.; Jiang, Z.; Ma, H.; Ning, L.; Chen, H.; Li, L.; Qi, H. *Sci. Rep.* **2016**, *6*, 21148. (c) Li, J.; Liu, Q. R.; Zhao, J. P.; Gao, J. Y.; Chen, Y. Y.; Li, S. X. *J. Chin. Med. Mater.* **2014**, *37*, 1587. (d) Feng, X. L.; Li, H. B.; Gao, H.; Huang, Y.; Zhou, W.-X.; Yu, Y.; Yao, X.-S. *Magn. Reson. Chem.* **2016**, *54*, 396.

(7) Ma, Y.; Jia, Q.; Wang, P.; Cheng, X.; Kang, Y. *Chem. Biodivers.* **2015**, *12*, 284.

(8) (a) Swaffar, D. S.; Holley, C. J.; Fitch, R. W.; Elkin, K. R.; Zhang, C.; Sturgill, J. P.; Menachery, M. D. *Planta Med.* **2012**, *78*, 230. (b) Yan, M. H.; Cheng, P.; Jiang, Z. Y.; Ma, Y. B.; Zhang, X. M.; Zhang, F. X.; Yang, L. M.; Zheng, Y. T.; Chen, J. J. *J. Nat. Prod.* **2008**, *71*, 760. (c) Lewis, W. H.; Stonard, R. J.; Porras-Reyes, B.; Mustoe, T. A. US Patent 5156847, **1992**; *Chem. Abstr.* **1992**, *117*, 245630t (d) Schwan, T. J. US Patent 3971788, **1976**; *Chem. Abstr.* **1976**, *85*, 192589y

(9) (a) Srivastava, A. K.; Pandey, A. K.; Jain, S.; Misra, N. *Spectrochim. Acta, Part A* **2015**, *136*, 682. (b) Roesch, E. S. *Isoquinolines*, In *RSC Drug Discovery Series No. 50 – Privileged Scaffolds in Medicinal Chemistry Design, Synthesis, Evaluation*; Bräse, S., Ed.; RSC: London, **2016**, Chap. 7, 147–213.

(10) (a) Ramana, M. M. V.; Sharma, R. H.; Parihar, J. A. *Tetrahedron Lett.* **2005**, *46*, 4385. (b) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050. (c) Banwell, M. G.; Hamel, E.; Ireland, N. K.; Mackay, M. F.; Serelis, A. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1905. (d) Menachery, M. D.; Cava, M. P.; Buck, K. T.; Prinz, W. J. *Heterocycles* **1982**, *19*, 2255. (e) Párraga, J.; Galán, A.; Sanz, M. J.; Cabedo, N.; Cortes, D. *Eur. J. Med. Chem.* **2015**, *90*, 101.

(11) (a) Zhao, B.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 5277. (b) Molina, P.; García-Zafra, S.; Fresneda, P. M. *Synlett* **1995**, 43. (c) Menachery, M. D.; Muthler, C. D.; Buck, K. T. *J. Nat. Prod.* **1987**, *50*, 726. (d) Ponnala, S.; Harding, W. W. *Eur. J. Org. Chem.* **2013**, 1107. (e) Khunnawutmanotham, N.; Sahakitpichan, V.; Chimnoi, N.; Techasakul, S. *Eur. J. Org. Chem.* **2015**, 6324.

(12) (a) Chen, H.-Y.; Preston, M. R. *Environ. Sci. Technol.* **1998**, *32*, 577. (b) Hua, R.-J.; Liu, H.-X.; Zhang, R.-S.; Xue, C.-X.; Yao, X.-J.; Liu, M.-C.; Hu, Z.-D.; Fan, B.-T. *Talanta* **2005**, *68*, 31. (c) Barron, M. G.; Heintz, R.; Rice, S. D. *Mar. Environ. Res.* **2004**, *58*, 95. (d) Fent, K. *Toxicol. in vitro* **2001**, *15*, 477.

(13) (a) Gasiorski, P.; Danel, K. S.; Matusiewicz, M.; Uchacz, T.; Vlokh, R.; Kityk, A. V. *J. Fluoresc.* **2011**, *21*, 443. (b) Gasiorski, P.; Danel, K. S.; Matusiewicz, M.; Uchacz, T.; Kuznik, W.; Kityk, A. V. *J. Fluoresc.* **2012**, *22*, 81. (c) Calus, S.; Danel, K. S.; Uchacz, T.; Kityk, A. V. *Mater. Chem. Phys.* **2010**, *121*, 477. (d) Scherowsky, G.; Frackowiak, E.; Adam, D. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1997**, *53*, 5.

(14) Buck, K. T. *Azafluoranthene and Tropoloisoquinoline Alkaloids*, In *The Alkaloids: Chemistry and Pharmacology, Vol. 23*; Brossi, A., Ed.; Academic Press: New York, **1984**, 301–325.

(15) (a) Sayagh, C.; Long, C.; Moretti, C.; Lavaud, C. *Phytochem. Lett.* **2012**, *5*, 188. (b) Morita, H.; Takeya, K.; Itokawa, H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 597. (c) Menachery, M. D.; Cava, M. P. *Heterocycles* **1980**, *14*, 943. (d) Silverton, J. V.; Kabuto, C.; Buck, K. T.; Cava, M. P. *J. Am. Chem. Soc.* **1977**, *99*, 6708. (e) Morita, H.; Matsumoto, K.; Takeya, K.; Itokawa, H.; Itaka, Y. *Chem. Lett.* **1993**, 339.

(16) (a) Zhao, J. *Curr. Med. Chem.* **2007**, *14*, 2597. (b) Itokawa, H.; Matsumoto, K.; Morita, H.; Takeya, K. *Heterocycles* **1994**, *37*, 1025.

(17) (a) Banwell, M. G.; Hamel, E.; Ireland, N. K.; Mackay, M. F. *Heterocycles* **1994**, *39*, 205. (b) Banwell, M. G.; Ireland, N. K. *J. Chem. Soc., Chem. Commun.* **1994**, 591. (c) Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12452. (d) Feldman, K. S.; Cutarelli, T. D. *J. Am. Chem. Soc.* **2002**, *124*, 11600. (e) Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 3243. (f) Feldman, K. S.; Cutarelli, T. D.; Di Florio, R. *J. Org. Chem.* **2002**, *67*, 8528. (g) Hong, S.-K.; Kim, H.; Seo, Y.; Lee, S. H.; Cha, J. K.; Kim, Y. G. *Org. Lett.* **2010**, *12*, 3954.

(18) (a) Wu, H.; Ding, L.; Shen, J.; Zhu, H.; Zhang, X. *Fitoterapia* **2009**, *80*, 252. (b) Wu, T.-S.; Lin, F.-W. *J. Nat. Prod.* **2001**, *64*, 1404. (c) Mukhtar, M. R.; Aziz, A. N.; Thomas, N. F.; Hadi, A. H. A.; Litaudon, M.; Awang, K. *Molecules* **2009**, *14*, 1227. (d) Othman, W. N. N. W.; Sivasothy, Y.; Liew, S. Y.; Mohamad, J.; Nafiah, M. A.; Ahmad, K.; Litaudon, M.; Awang, K. *Phytochem. Lett.* **2017**, *21*, 230. (e) Mukhtar, M. R.; Hadi, A. H. A.; Rondeau, D.; Richomme, P.; Litaudon, M.; Mustafa, M. R.; Awang, K. *Nat. Prod. Res.* **2008**, *22*, 921.

(19) Silveira, C. C.; Larghi, E. L.; Mendes, S. R.; Bracca, A. B. J.; Rinaldi, F.; Kaufman, T. S. *Eur. J. Org. Chem.* **2009**, 4637.

(20) (a) Bracca, A. B. J.; Kaufman, T. S. *Eur. J. Org. Chem.* **2007**, 5284. (b) Larghi, E. L.; Kaufman, T. S. *Tetrahedron* **2008**, *64*, 9921. (c) Bianchi, D. A.; Cipulli, M. A.; Kaufman, T. S. *Eur. J. Org. Chem.* **2003**, 4731. (d) Kaufman, T. S. *Heterocycles* **2001**, *55*, 323. (e) Bianchi, D. A.; Kaufman, T. S. *ARKIVOC* **2003**, *(x)*, 178.

(21) (a) Zhang, Z.; Yang, F.; Fu, J. J.; Shen, Y.-H.; He, W.; Zhang, W.-D. *RSC Adv.* **2016**, *6*, 65885. (b) Zhang, Z.; Wang, J.; Li, J.; Yang, F.; Liu, G.; Tang, W.; He, W.; Fu, J. J.; Shen, Y. H.; Li, A.; Zhang, W. D. *J. Am. Chem. Soc.* **2017**, *139*, 5558.

(22) For some recent reviews, see: (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (b) Leung, J. C.; Krische, M. J. *Chem. Sci.* **2012**, *3*, 2202. (c) Murphy, S. K.; Dong, V. M. *Chem. Commun.* **2014**, 13645. (d) Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869. (e) González-Rodríguez, C.; Willis, M. C. *Pure Appl. Chem.* **2011**, *83*, 577.

(23) (a) Silveira, C. C.; Bernardi, C. R.; Braga, A. L.; Kaufman, T. S. *Synlett* **2002**, 906. (b) Blass, B. E. *Tetrahedron* **2002**, *58*, 9301.

(24) (a) Radhakrishna, A. S.; Suri, S. K.; Prasad Rao, K. R. K.; Sivaprakash, K.; Singh, B. B. *Synth. Commun.* **1990**, *20*, 345. (b) Luu, T. X. T.; Lam, T. T.; Le, T. N.; Duus, F. *Molecules* **2009**, *14*, 3411.

(25) (a) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316. (b) Cardozo, M. G.; Iimura, Y.; Sugimoto, H.; Yamanishi, Y.; Hopfinger, A. J. *J. Med. Chem.* **1992**, *35*, 584. (c) Fillion, E.; Lou, T.; Liao, E.-T.; Wilsily, A. *Org. Synth.* **2012**, *89*, 115. (d) Kawakami, Y.; Inoue, A.; Kawai, T.; Wakita, M.; Sugimoto, H.; Hopfinger, A. J. *Bioorg. Med. Chem.* **1996**, *4*, 1429.

(26) (a) Heredia, D. A.; Larghi, E. L.; Kaufman, T. S. *Eur. J. Org. Chem.* **2016**, 1397. (b) Larghi, E. L.; Obrist, B. V.; Kaufman, T. S. *Tetrahedron* **2008**, *64*, 5236.

(27) (a) Kaufman, T. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2497. (b) Ponzo, V. L.; Kaufman, T. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3131.

(28) (a) Patel, H. A.; Maclean, D. B. *Can. J. Chem.* **1983**, *61*, 7. (b) Larghi, E. L.; Amongero, M.; Bracca, A. B. J.; Kaufman, T. S. *ARKIVOC* **2005**, *(xii)*, 98.

(29) (a) Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, 5179. (b) Kaniskan, H. U.; Eram, M. S.; Zhao, K.; Szewczyk, M. M.; Yang, X.; Schmidt, K.; Luo, X.; Xiao, S.; Dai, M.; He, F.; Zang, I.; Lin, Y.; Li, F.; Dobrovetsky, E.; Smil, D.; Min, S.-J.; Lin-Jones, J.; Schapira, M.; Atadja, P.; Li, E.; Barsyte-Lovejoy, D.; Arrowsmith, C. H.; Brown, P. J.; Liu, F.; Yu, Z.; Vedadi, M.; Jin, J. *J. Med. Chem.* **2018**, *61*, 1204.

(30) (a) Naciuk, F. F.; Castro, J. A. M.; Serikava, B. K.; Miranda, P. C. M. L. *ChemistrySelect* **2018**, *3*, 436. (b) Sato, N.; Kawai, Y.; Akaba, Y.; Honma, S.; Sakai, N.; Konakahara, T. *Heterocycles* **2016**, *92*, 664.