Tetrahedron 64 (2008) 5236–5245

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A formal total synthesis of the marine alkaloid aaptamine

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ARTICLE INFO

Article history:
Received 6 February 2008
Received in revised form 10 March 2008
Accepted 12 March 2008
Available online 15 March 2008

Keywords:
Formal total synthesis
Aaptamine
Benzo[*de*][1,6]naphthyridine alkaloids
2,3,3a,4,5,6-Hexahydroaaptamine

ABSTRACT

A new strategy for the synthesis of benzo[*de*][1,6]naphthyridine derivative 2,3,3a,4,5,6-hexahydroaaptamine, which involves the construction of the isoquinoline ring after elaboration of the quinoline moiety, is described. Since 2,3,3a,4,5,6-hexahydroaaptamine has been previously synthesized as a key intermediate en route to the marine alkaloid aaptamine, access to this compound represents a formal total synthesis of the natural product.

1. Introduction

The aaptamines[1] are marine alkaloids, which contain a benzo[*de*][1,6]naphthyridine framework;[2] this nucleus was studied theoretically by the group of Efros[3] a few years before being first found in nature by Nakamura and co-workers, in 1982.[1] To date, seven naturally occurring tricyclic members of this family are known (Fig. 1), and all of them have been isolated from marine sponges belonging to the genera *Aaptos*[4a] (Hadromerida, Suberitidae) and *Suberites* (Aplysinellidae, Verongida).[4b]

The aaptamine family includes aaptamine (**1**), first isolated from an Okinawan specimen of *Aaptos aaptos*[1,4a,c] and recently observed in other *Aaptos* sponges,[4d,e] 9-demethylaaptamine (**2**),[4c,f] bisdemethylaaptamine (**3**),[4g] its 9-*O*-sulfate (**4**),[4g] isoaaptamine (**5**),[4d,h–j] 9-demethyloxyaaptamine (**6**),[4c,h,k] and 4-*N*-methylaaptamine (**7**).[4l] Characterization of compound **8** has also been reported, but this ketal is assumed to be an isolation artifact.[4c,i] These sponges also produce alkaloids carrying rearranged 5,8-diazabenzo[*cd*]azulene skeletons.[2a]

The aaptamines were once considered as taxonomic markers for the Hadromerida order within the sub-class of Tetractinomorpha and also of the Suberitidae family of sponges.[5] However, since Brazilian specimens of *Aaptos* were found to be devoid of aaptamines,[5c] and due to the facts that isoaaptamine was isolated from a *Hymeniacidon* sp. (Halichondrida) sponge in the coasts of Singapore[4i] and aaptamine itself was reported from *Luffariella* sp. (Dictyoceratida),[4m] while modified aaptamines **9**–**12** have been isolated from *Xestospongia* sp. (Haplosclerida, sub-class Ceractinomorpha)[6a,b] and other sponges,[6c] including *Aaptos suberitoides* (Hadromerida, Tethyidae),[6d,e] this hypothesis is no longer assumed as valid.

Interestingly, the 1*H*-benzo[*de*][1,6]naphthyridine framework is embedded in other structurally or biologically interesting natural products of marine origin. Examples of this are a pyridoacridine alkaloid isolated from the Indonesian sponge *Biemna fortis*, which proved to cause neurite outgrowth on the murine neuroblastoma cell line Neuro 2A,[2b] and a series of complex cytotoxic compounds, which have been recently reported from crimson *Suberea* sponges (Aplysinellidae, Verongida) native to the Coral Sea.[2c]

However, the occurrence of this heterocyclic skeleton is not restricted to natural products from marine sponges, as the necatorones, which are fungal alkaloids, also display the related 1*H*-benzo[*de*,*h*][1,6]naphthyridine backbone.[2d,e] In addition, tricyclic azakynurenic acids carrying a functionalized 1*H*-benzo[*de*][1,6]-naphthyridine system have been recently synthesized as analogs of the quinolone-type kynurenic acids and NMDA-glycine antagonists.[2f]

The aaptamines display many interesting biological activities. Due to their antagonistic effects on β-adrenergic receptors, a cardiac activity has been described for **1**,[4c,7] suggesting that it could be a competitive antagonist of β-adrenoreceptors in vascular smooth muscles.

Aaptamine and related natural products have also important antineoplastic effects[4h,j,8a–c] on different tumor cell lines such as

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doi:10.1016/j.tet.2008.03.036

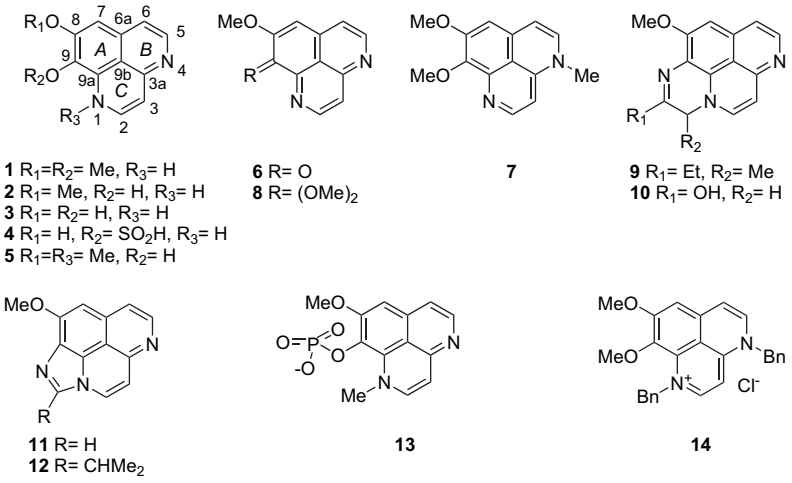


Figure 1. Chemical structures of the aaptamines **1**–**7**, ketal **8**, modified aaptamines **9**–**12**, and two of their semisynthetic derivatives (**13** and **14**).

murine leukemia P388 (**1** and **5**), KB16 cells (**1**, **5**, and **6**),[8d] Ehrlich tumor cells (**2** and **4**),[4b,8d] HeLa,[4j] A549, and HT29 transfected human osteosarcoma MG63 cells (**1**).[6d,9] However, it has been reported that **6** and **7** are not toxic to Vero cells at a concentration of 20 μg/mL.[4l] Recently, aaptamine was launched in the chemical–pharmaceutical market as a potent anti-tumor agent by A.G. Scientific, Inc. and other companies.[8d]

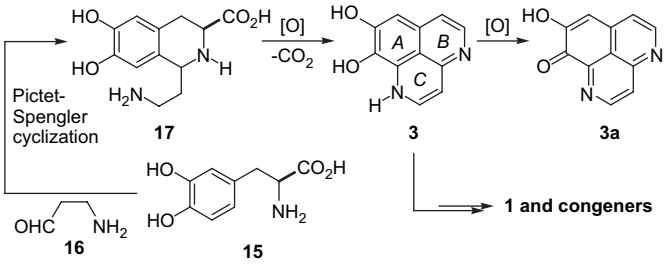
In addition, aaptamine and its congeners have demonstrated to display several other pharmacological activities, including antimicrobial effects[4i] toward Gram-(+) bacteria exemplified by *Staphylococcus aureus* as well as against Gram-(−) microorganisms, such as *Escherichia coli* and *Vibrio anguillarum* bacterial strains, and to have anti-fungal properties, tested against the yeast *Candida tropicalis*.[6a]

Compounds **1** and **5** also behave as potent inhibitors of protein kinase C (PKC) in a cell adherence assay, as claimed in a patent;[10a,b] aaptamine is also a glutamine-fructose-6-phosphate amidotransferase (GFAT)[4d,g] and monoaminooxidase A (MAO A)[10c] inhibitor, and these heterocycles also demonstrated to behave as sortase inhibitors.[10d] The natural product **1** has also shown to have in vitro antioxidant effects[11a] and antidepressant-like activity in the forced swim test.[11b]

Some antiviral activities of the naturally occurring aaptamines have been recently reported. These include anti-HIV-1 properties for **1**, **5**, and **6**,[1,4c,12a] and the ability to act as an agent impairing herpes simplex virus type 1 skin penetration, for **7**.[12b] Also, synthetic and semisynthetic derivatives of isoaaptamine demonstrated to possess interesting antileishmania, antineoplastic, and antimalarial properties, as well as activity against *Mycobacterium intracellulare*.[12c,d] In addition, isoaaptamine (**5**) and aaptamine (**1**) have been chemically converted by the group of Pettit into the cytotoxic prodrug Hystatin 1 (**13**) and the cancer cell growth inhibitor Hystatin 2 (**14**), respectively.[13]

From the biosynthetic point of view, the aaptamine skeleton has been assumed to be derived from the biochemical Pictet–Spengler condensation of L-DOPA (**15**) with a biosynthetic equivalent of β-alanine aldehyde (**16**)[14a] to form the (tetrahydro)isoquinoline skeleton (**17**) followed by oxidative closure to form the piperidine ring *C*, as depicted in Scheme 1.

Subsequent decarboxylation and dehydrogenation would then afford bisdemethylaaptamine (**3**), from which **1** and its congeners could be formed by means of biochemical methylation and oxidation reactions. Interestingly, a biomimetic approach yielding compound **3** and the related bisdemethyl(oxy)aaptamine (**3a**), not yet isolated, has been recently published.[14b]



Scheme 1. Proposed biosynthetic pathway for aaptamine.[14b]

So far, a handful of other synthetic approaches to these unique alkaloids have been published.[15a] Isoaaptamine (**5**),[4f,12d] demethyl(oxy)aaptamine (**6**),[15b] and other derivatives have also been synthesized, an unsuccessful attempt of synthesizing aaptamine has been informed,[15c] and the conversion of **1** into isoaaptamine **5** and other aaptamine derivatives has been disclosed by the group of Pettit.[4f] Therefore, a synthesis of aaptamine constitutes an indirect entry to some of its most important related natural products.

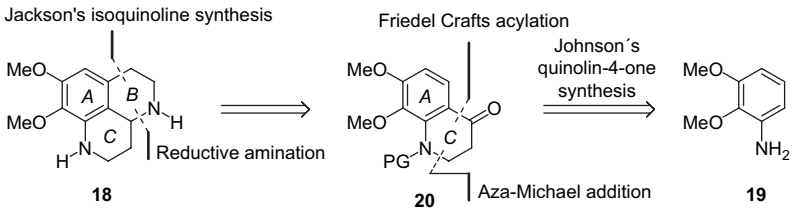
The published syntheses of aaptamine use either the isoquinoline (*AB*) or quinoline (*AC*) components of the benzo[*de*][1,6]-naphthyridine ring as the nucleus onto which the third ring is constructed. Syntheses starting from isoquinoline derivatives (*AB*→*C*) include the routes developed by Cava,[16a] Yamanaka,[16b] Tollari,[16c] Molina,[16d–f] and Joule.[16g,h] On the other hand, the syntheses by Kelly,[16i] Raphael,[16j] and Sato[16k] proceed through quinoline-type intermediates (*AC*→*B*).

Interestingly, the syntheses employing quinolin-4-one derivatives as key intermediates suffer from different drawbacks, including the use of uncommon reagents or special reaction conditions, low yielding steps, or the production of unwanted side products.[16i–k]

Here, we wish to report the synthesis of 2,3,3a,4,5,6-hexahydroaaptamine (**18**), through an *AC*→*B* approach. Taking into account that **18** was the penultimate intermediate of Pelletier and Cava's synthesis of aaptamine,[16a] this constitutes a formal total synthesis of aaptamine. Noteworthy, the published access to **18** employed an isoquinoline derivative as starting material, thus involving an *AB*→*C* sequence.

2. Results and discussion

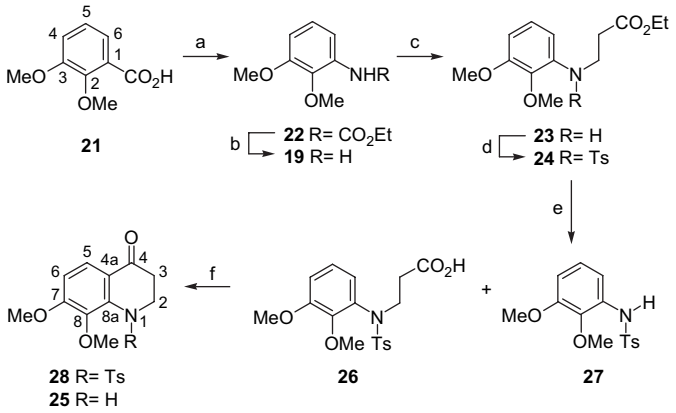
Our synthetic plan toward **18** was based on the retrosynthetic analysis shown in Scheme 2, which entails the successive formation



Scheme 2. Retrosynthetic analysis of 2,3,3a,4,5,6-hexahydroaaptamine (**18**).

of rings *C* and *B* from the known aniline derivative **19**,[17] through the intermediacy of protected quinolin-4-one derivative **20**; in turn, this could be formed by a Johnson (Elderfield–Johnson) synthetic sequence,[18] entailing an aza-Michael addition of **19** to an acrylate ester, followed by a Friedel–Crafts-type acylation.

The synthesis commenced with the preparation of aniline **19**, which was achieved in 87% yield through the Curtius–Yamada rearrangement[19] of commercially available 2,3-dimethoxybenzoic acid (**21**) with diphenylphosphoryl azide in refluxing EtOH, followed by basic hydrolysis of the intermediate ethyl carbamate **22** (Scheme 3).



Scheme 3. (a) $(PhO)_2P(O)N_3$, EtOH, Et_3N, THF, 65 °C, 2 h (90%); (b) KOH, EtOH, reflux, overnight (97%); (c) $H_2C{=}CHCO_2Et$, AcOH (cat.), reflux, 24 h (84%); (d) TsCl, $^iPr_2NEt$, $CHCl_3$, reflux, 14 h (92%); (e) (1) 10% LiOH, EtOH–H_2O, reflux 24 h; (2) HCl, pH=3 (**26**, 74%; **27**, 20%); (f) PPA, 90 °C, overnight (**25**, 20%+**26**, 48%), PPE, PhMe, 55 °C, 2 h (**28**, 95%).

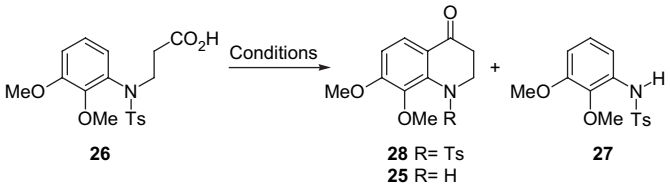
Next, **19** was submitted to an aza-Michael addition by reaction with refluxing ethyl acrylate under acetic acid promotion; this furnished an optimized 84% yield of β-aminoester **23** when 1.3 equiv of AcOH and a 20-fold excess of ethyl acrylate were employed.

Compound **23** was uneventfully converted (92% yield) into the related sulfonamido derivative **24** by reaction with tosyl chloride and DIPEA in refluxing chloroform. However, attempts to cyclize the sulfonamido ester [$SnCl_4$, polyphosphoric ester (PPE), PPA][20] met with failure, leading to decomposition products, such as the known detosylated compound **25**,[21a] which was isolated in 20% yield when PPA was employed as cyclizing agent.[20d] Therefore, the ester was subjected to basic hydrolysis to obtain sulfonamido acid **26**. Not unexpectedly, important quantities of the known sulfonamide **27**,[21b] the retro-Michael side-product of **25**, were isolated irrespective of the nature of the base employed; however, the use of LiOH in THF–H_2O furnished **26** in 76% yield, accompanied by only 20% of **27**.

The cyclization of acid **26** was next studied. Unfortunately, when Lewis acid-mediated cyclization of the acid chloride was attempted (PCl_5, benzene, reflux, followed by $AlCl_3$ at 0 °C or $SOCl_2$ in 1,2-dichloroethane under reflux, followed by $SnCl_4$, at 0 °C), compound **25**[21] was isolated as the major product in up to 70% yield accompanied with only 10–15% of **28** (Table 1). On the other hand, cyclization with $POCl_3$ in refluxing toluene furnished only 21% of the desired quinolin-4-one **28** and reaction with P_2O_5 lead to recovery of the previously observed retro-Michael product **27** in 45% yield and the isolation of 23% of the expected quinolin-4-one derivative **28**. However, when acid **26** was subjected to reaction with excess PPE in toluene at 55 °C, a smooth and clean cyclization took place, allowing the isolation of **28** in 95% yield after 2 h.

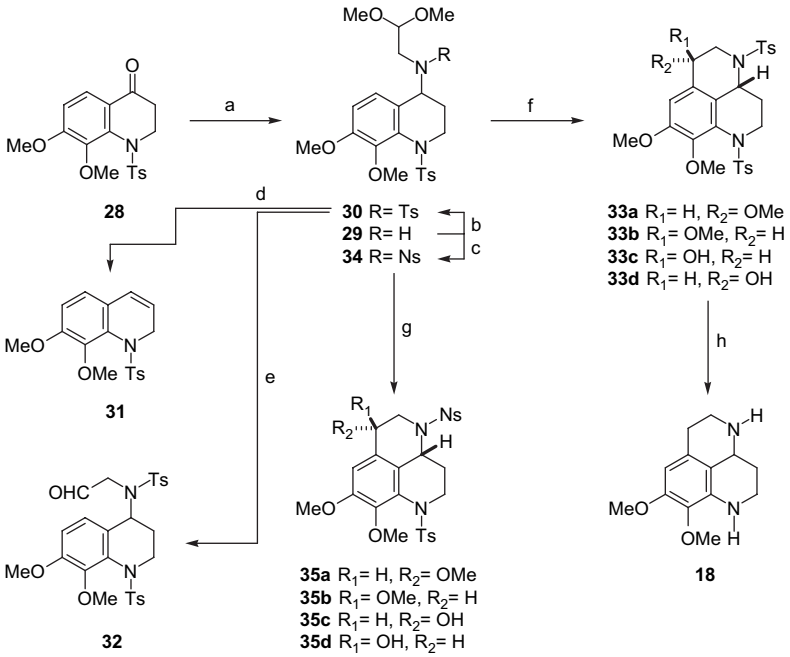
Having secured the access to key intermediate **28**, formation of the third ring was undertaken, as shown in Scheme 4. To that end, the quinolin-4-one was subjected to a reductive amination with aminoacetal and sodium cyanoborohydride as selective reducing agent,[20] with disappointing initial results.

Table 1
Optimization of the cyclization of acid **26**



Reagent	Equiv	Solvent	Temp (°C)	**28** (%)	**25** (%)	Other (%)
1. PCl_5	1.2					
2. $AlCl_3$	2.1	Benzene	Reflux	15	23	
1. $SOCl_2$	33	1,2-DCE	Reflux			
2. $SnCl_4$	2		0	10	70	—
1. $SOCl_2$	5	$CHCl_3$	Reflux			**26** (60)
2. $SnCl_4$	2	Benzene	0	10	10	
P_2O_5	2	Xylene	Reflux	23	—	**27** (45)
$POCl_3$	5	Toluene	Reflux	21	—	—
PPE	20[a]	Toluene	Reflux	Decomposition		
PPE	20[a]	Toluene	55	95	—	—

[a] Expressed as mg PPE/mg substrate.



Scheme 4. (a) (1) $H_2NCH_2CH(OMe)_2$, AcOH, $MgSO_4$, 4 Å MS, EtOH, overnight; (2) $NaCNBH_3$, reflux, 24 h (87%); (b) TsCl, $^iPr_2NEt$, $CHCl_3$, reflux, 14 h (64%); (c) NsCl, $^iPr_2NEt$, $CHCl_3$, reflux, 14 h (20%); (d) 6 N HCl (6 equiv), dioxane, EtOH, reflux, 2 h (94%) or $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 12 h (47%); (e) ZnI_2, CH_2Cl_2,)), rt, 24 h (54%); (f) $SnCl_4$, CH_2Cl_2, −78 °C, 1.5 h, −60 °C overnight (**31**, 23%; **32** (4%); **33a**, 9%; **33b**, 24%; **33c**, 9%); (g) $SnCl_4$, CH_2Cl_2, −78 °C, 1.5 h, −60 °C overnight (**35a**, 18%; **35b**, 18%; **35c**, 16%; **35d**, 22%); (h) (1) Na, NH_3, −33 °C; (2) NH_4Cl (83%).

It is known that aromatic ketones bearing activating substituents in the *ortho*/*para* positions react sluggishly with amines to form the corresponding imines, thus furnishing poor yields of the reductive amination products.[22] However, it was observed that yields increased when the carbonyl compound was left to react overnight with the amine in the presence of activated 4 Å molecular sieves before adding the reducing agent, this strategy furnished secondary amine **29** in an optimized 87% yield.

Amine **29** was then submitted to sulfonamidation with tosyl chloride and DIPEA under forcing conditions, yielding sulfonamidoacetal **30** in 64% yield and setting the stage for the cyclization step. The moderate yield attained is perhaps due to steric hindrance, which in related cases has forced to change the strategy for the introduction of the sulfonamidoacetal moiety.[23a,b] Reaction of **30** under modified Jackson[24a] conditions (6 N HCl, dioxane, EtOH, reflux)[23] did not afford the expected tricyclic product, cleanly furnishing instead an almost quantitative yield of 1,2-dihydroquinoline derivative **31**, resulting from the acid promoted elimination of the sulfonamidoacetal side chain. Analogously, 47% of **31** together with 48% of aldehyde **32** were isolated when cyclization of **30** was attempted under $BF_3{\cdot}Et_2O$ promotion.

This unwanted but not fully unexpected outcome could be the result of the improper activation of the aromatic ring, due to the *ortho*-disubstituted nature of the methoxy group located *para* to the ring closure position. These steric effects are reflected in an out-of-plane preferred conformation of the 8-methoxy group of acetal **30**, which was evident in its ^{13}C NMR spectrum, when compared with the chemical shift of the neighboring 8-methoxy moiety (δ_C OMe-7=55.91; δ_C OMe-8=59.58). ZnI_2 catalysis did not afford better results, being the aldehyde **32** isolated as the major product, in 54% yield. Fortunately, however, use of $SnCl_4$ at −60 °C provided a mixture of methyl ethers **33a**,**b** and alcohols **33c**,**d** in 42% combined yield, accompanied by 23% of compound **31** and 4% of aldehyde **32**.[25] Although pure samples of **33d** could not been obtained, some of its most distinctive signals were observed in the ^1H NMR spectrum of its mixture with **33c**. These included a singlet at δ 6.99 and a doublet of doublets resonating at δ 4.42 (H-3a). The results of the optimization of the cyclization conditions of **30** are shown in Table 2.

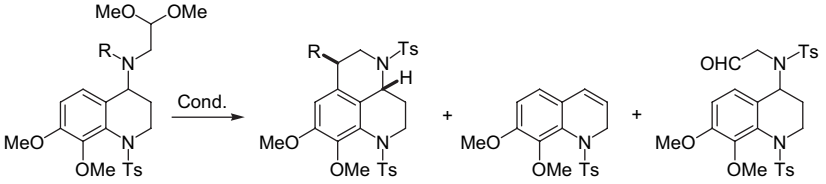
Complete and unequivocal attribution of the proton and carbon atoms of **33a**–**c** was performed with the aid of 2D NMR experiments, while the coupling constants of H-6 allowed assignment of the relative stereochemistry of the alcohol and ether moieties attached to C-6.

In these cyclizations, it has been recognized that the stabilizing effect of the sulfonamido group[24] is due to its electron-withdrawing characteristics. Therefore, in view of the meager yields of the cyclization, the performance of the nosyl protecting group was explored.[23b] Thus, amine **29** was submitted to reaction with nosyl chloride and DIPEA in refluxing chloroform; unexpectedly, however, the reaction did not proceed to completion even after prolonged reflux, furnishing only 20% of nosylamide **34**. However, when nosylamide **34** was submitted to cyclization with $SnCl_4$, cyclized products **35a**–**d** were isolated in 74% combined yield.

Structural elucidation of the tricyclic sulfonamides **35** was carried out through a combination of NMR experiments and comparisons with the spectra of **33a**–**c**. Encouraged by the better performance of **34** in the critical cyclization step, alternative conditions for the introduction of the 4-nitrosulfonamide moiety were explored; however, these resulted unsuccessful, favoring the tosylamide route as a strategy toward the target. Therefore, taking into account the use of sodium in liquid ammonia for the removal of benzyl and tosyl protecting groups,[26] the mixture of tricyclic compounds **33** was subjected to reductive desulfonylation with concomitant deoxygenation of the benzylic position with this reagent combination, furnishing the expected 2,3,3a,4,5,6-hexahydroaaptamine **18** in 83% yield.

In conclusion, a formal total synthesis of the marine alkaloid aaptamine (**1**) was achieved through the development of a new strategy to obtain the previously known 2,3,3a,4,5,6-hexahydroaaptamine (**18**). This alternative access of **18** was accomplished in eight steps and 11% overall yield from aniline derivative **19**, employing an *AC*→*B* ring forming strategy, with quinolin-4-one **28** as key intermediate.

Table 2
Optimization of the cyclization of sulfonamidoacetal **30**



29 R= H
30 R= Ts

33a R= α-OMe
33b R= β-OMe
33c R= β-OH

31

32

Reagent (equiv)	Solvent	Temp (°C)	Time (h)	**33a–c** (%)	**31** (%)	**32** (%)
6 N HCl (6), EtOH (10)	Dioxane	Reflux	2	0	94	0
$BF_3 \cdot Et_2O$ (3)	CH_2Cl_2	rt	12	0	47	48
PPA, PPE (10)[a]	CH_2Cl_2	rt	12	0	56	0
ZnI_2 (2)	CH_2Cl_2	rt,)))	24	<5	0	54
$TiCl_4$ (2)	CH_2Cl_2	−78	12	<10	ND	ND
TMSOTf (2)	CH_2Cl_2	−78	12	<10	ND	ND
HCl (excess)	6 N HCl	rt	24	<10[b]	—	0
$SnCl_4$ (2)	CH_2Cl_2	−40	12	30[c]	<10	<10
$SnCl_4$ (2)	CH_2Cl_2	−78[d]	12	42[c,e]	23	4

ND=Not determined.
[a] Water (1 equiv) was added to PPE.
[b] Bobbitt reaction with aminoacetal **29**.[22b]
[c] As a mixture of diastereomeric alcohols and methyl ethers.
[d] 1.5 h at −78 °C and then overnight at −60 °C.
[e] Overall yield; a mixture of **33a** (9%), **33b** (24%), and **33c** (9%) was isolated.

3. Experimental

3.1. General conditions

Melting points were taken on an Ernst Leitz Wetzlar model 350 hot-stage microscope apparatus and are informed uncorrected. FTIR spectra were determined with a Shimadzu Prestige 21 spectrophotometer as thin films held between NaCl cells or as solid dispersions in KBr disks. The ^1H and ^{13}C NMR spectra were acquired in $CDCl_3$ employing TMS as internal standard, with a Bruker Avance 300 apparatus (300.13 and 75.48 MHz, for ^1H and ^{13}C, respectively).

The chemical shifts are consigned in parts per million downfield from TMS, as the internal standard. DEPT 135 and DEPT 90 aided the interpretation and assignment of the fully decoupled ^{13}C NMR spectra. In special cases, 2D NMR experiments (COSY, HSQC, HMBC, NOE, and ROESY) were also employed. Symbols such as asterisk (*) and number sign (#) indicate that assignments may be exchanged among each set of marked resonances. Pairs of diastereotopic protons designated as 'uf' and 'df' mean the most upfield (shielded) and downfield (deshielded) signal, respectively, by extension of the nomenclature employed in these cases by Culvenor and coworkers.[27] Proton and carbon signals belonging to tosyl/nosyl groups are designated as 'ArH' and 'TsC/NsC', respectively. High-resolution mass spectral data were obtained from the Laboratory of Glycochemistry and Asymmetric Synthesis (LGSA) of EPFL, Lausanne, Switzerland and Kent Electronics, Kent, UK. The reactions were carried out under positive pressure of dry Nitrogen or Argon, employing oven-dried glassware.

The standard work-up procedure, depending of the reaction medium, consisted in diluting the reaction with brine (5–20 mL) and extracting the reaction products with EtOAc or CH_2Cl_2 (3×20–40 mL); the combined organic extracts were washed once with brine (5–10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The respective residues were flash chromatographed.

Flash column chromatographies were carried out with silica gel 60 H. Samples were pre-adsorbed on coarse grain silica gel and loaded as free flowing powders. For the separation of all compounds, elution was carried out in the gradient of solvent polarity mode, with different mixtures of hexane–EtOAc, followed by EtOAc–EtOH, employing 0.75–1 atm of compressed air in order to accelerate the eluting flow. All new compounds gave single spots on TLC plates run in different hexane–EtOAc and CH_2Cl_2–toluene solvent systems. Chromatographic spots were detected by exposure to UV light (254 nm) followed by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent and careful heating of the plates for better selectivity.

3.2. 2,3-Dimethoxyphenylamine 19

To a solution of 2,3-dimethoxybenzoic acid (**21**, 1000 mg, 5.49 mmol) in dry THF (20 mL) were added diphenylphosphoryl azide (1586 mg, 5.76 mmol), absolute ethanol (3.2 mL, 55 mmol), and anhydrous Et_3N (0.92 mL, 6.58 mmol). The mixture was stirred at 65 °C for 2 h, being observed a strong evolution of gas. After cooling to room temperature, the reaction was concentrated under reduced pressure in order to remove most of the ethanol, and then it was diluted with EtOAc (20 mL); the organic phase was successively washed with saturated aqueous $NaHCO_3$ solution, water, brine, dried over anhydrous sodium sulfate, and concentrated in vacuum. The concentrate was purified by flash chromatography to give **22** (1113 mg, 90%), as an oil.[17a,b] IR (film, ν): 3372, 2978, 1735, 1608, 1535, 1478, 1300, 1258, 1169, 1050, 998, and 782 cm^{-1}; ^1H NMR (δ): 1.32 (t, 3H, J=7.1 Hz, OCH_2Me), 3.85 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.23 (q, 2H, J=7.1 Hz, OCH_2Me), 6.61 (dd, 1H, J=1.3, 8.3 Hz, H-4), 7.02 (t, 1H, J=8.3 Hz, H-5), 7.26 (br s, 1H, $w_{1/2}$=7 Hz, NH), and 7.73 (dd, 1H, J=1.3, 8.3 Hz, H-6); ^{13}C NMR (δ): 14.5 (CH_2Me), 55.8 (OMe-3), 60.6 (OMe-2), 61.2 (CH_2Me), 106.5 (C-4), 110.9 (C-6), 124.2 (C-5), 132.3 (C-1), 137.0 (C-2), 152.1 (C=O)*, and 153.5 (C-3)*. To a solution of ethyl carbamate **22** (1.236 g, 5.49 mmol) in ethanol (10 mL), was added a freshly prepared solution of potassium hydroxide (3250 mg, 58 mmol) in ethanol (20 mL). The mixture was refluxed overnight, and after assessment (by TLC) of absence of starting material, it was cooled to room temperature and concentrated under reduced pressure. The resulting oily residue was diluted with EtOAc, washed with brine,

dried over Na_2SO_4, and concentrated under vacuum. The dark brownish oil so obtained was purified by flash chromatography giving 2,3-dimethoxyaniline **19** (812 mg, 97%), as an orange oil. IR (film, ν): 3447, 3371, 2937, 1612, 1477, 1321, 1264, 1131, 1087, and 732 cm^{-1}; ^1H NMR (δ): 2.90–3.93 (br s, 2H, NH_2), 3.82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.34 (dd, 1H, J=1.4, 8.1 Hz, H-6), 6.39 (dd, 1H, J=1.4, 8.1 Hz, H-4), and 6.84 (t, 1H, J=8.1 Hz, H-5); ^{13}C NMR (δ): 55.7 (OMe-3), 59.8 (OMe-2), 102.3 (C-4), 108.8 (C-6), 124.2 (C-5), 136.0 (C-1), 140.7 (C-2), and 153.1 (C-3). These data were in agreement with the literature.[17]

3.3. 3-[(2,3-Dimethoxyphenyl)-(toluene-4-sulfonyl)-amino]-propionic acid ethyl ester 24

Acetic acid (50 μL) was added to 2,3-dimethoxyaniline (**19**, 100 mg, 0.63 mmol) in ethyl acrylate (2 mL) and the mixture was refluxed 24 h. The resulting red solution was carefully evaporated under reduced pressure and the residue was flash chromatographed, furnishing **23** (165 mg, 84%), as an oil. IR (film, ν): 3405, 2967, 1731, 1602, 1513, 1481, 1263, 1130, and 1005 cm^{-1}; ^1H NMR (δ): 1.26 (t, 2H, J=7.1 Hz, CH_2Me), 2.61 (t, 2H, J=6.5 Hz, CH_2CO_2Et), 3.47 (t, 2H, J=6.5 Hz, NCH_2), 3.78 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.15 (q, 2H, J=7.1 Hz, OCH_2Me), 4.59 (br s, 1H, $w_{1/2}$=30 Hz, NH), 6.32 (dd, 1H, J=1.2, 8.2 Hz, H-6)*, 6.34 (dd, 1H, J=1.2, 8.2 Hz, H-4)*, and 6.92 (t, 1H, J=8.2 Hz, H-5); ^{13}C NMR (δ): 14.2 (OCH_2Me), 34.3 (CH_2CO_2Et), 39.3 ($ArNCH_2$), 55.7 (OMe-3), 59.8 (OMe-2), 60.6 (OCH_2Me), 101.5 (C-4), 104.24 (C-6), 124.4 (C-5), 135.7 (C-1), 141.8 (C-2), 152.6 (C-3), and 172.2 (C=O). To a stirred solution of amine **23** (144 mg, 0.57 mmol) in dry chloroform (3 mL) at 0 °C, were added DIPEA (0.15 mL, 0.86 mmol) and tosyl chloride (135 mg, 0.71 mmol). The mixture was allowed to reach room temperature after 15 min and then refluxed until consumption of the starting amine (by TLC, 14–20 h). The reaction was allowed to attain room temperature, concentrated in vacuum, and the residue was chromatographed, rendering sulfonamide **24** (213 mg, 92%), as an oil. IR (film, ν): 2943, 1734, 1587, 1474, 1347, 1270, 1160, and 1096 cm^{-1}; ^1H NMR (δ): 1.17 (t, 3H, J=7.1 Hz, CH_2Me), 2.42 (s, 3H, Ar*Me* of Ts), 2.54 (t, 2H, J=7.5 Hz, CH_2CO_2Et), 3.70 (s, 3H, OMe-2), 3.84 (s, 3H, OMe-3), 3.85 (t, 2H, J=7.5 Hz, NCH_2), 4.01 (q, 2H, J=7.1 Hz, OCH_2Me), 6.63 (dd, 1H, J=2.1, 8.3 Hz, H-6), 6.89 (dd, 1H, J=2.1, 8.3 Hz, H-4), 6.94 (t, 1H, J=8.3 Hz, H-5), 7.28 (d, 2H, J=8.4 Hz, ArH-3 and ArH-5 of Ts), and 7.68 (d, 2H, J=8.4 Hz, ArH-2 and ArH-6 of Ts); ^{13}C NMR (δ): 14.1 (OCH_2Me), 21.5 (Ar*Me* of Ts), 34.1 (CH_2CO_2Et), 46.8 ($ArNCH_2$), 55.9 (OMe-3), 60.5 (OCH_2Me), 60.8 (OMe-2), 113.0 (C-4), 122.9 (C-5)*, 123.0 (C-6)*, 127.7 (2C, TsC-2 and TsC-6), 129.5 (2C, TsC-3 and TsC-5), 131.9 (C-1), 137.4 (TsC-1), 143.2 (TsC-4), 147.6 (C-2), 153.5 (C-3), and 171.2 (C=O); HRMS (TOF MS ESI+ion mode) calcd for $C_{13}H_{20}NO_4$: 254.1392; found: 254.1393.

3.4. 3-[(2,3-Dimethoxyphenyl)-(toluene-4-sulfonyl)-amino]-propionic acid 26

To a suspension of ester **24** (978 mg, 2.4 mmol) in an EtOH–H_2O mixture (3:1, 5 mL), was carefully added a 10% solution of LiOH (1.8 mL) and the system was heated at reflux for 24 h. Then, the reaction was cooled to room temperature acidified to pH=3–4 with 1 M HCl; the ethanol was cautiously removed under reduced pressure and the remaining aqueous suspension was extracted with EtOAc (4×10 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure, leaving a residue, which was purified by column chromatography. The side-product **27** was isolated (154 mg, 20%), as a colorless solid, mp 155–157 °C (hexane–EtOAc) or 108–110 °C (EtOH; lit.[21b] 109 °C, EtOH). IR (film, ν): 3422, 3262, 2917, 2849, 1599, 1443, 1384, 1297, 1118, 1043, 965, 814, 745, and 665 cm^{-1}; ^1H NMR (δ): 2.36 (s, 3H, Ar*Me* of Ts), 3.57 (s, 3H, OMe-2), 3.80 (s, 3H, OMe-3), 6.62 (dd, 1H, J=1.2, 8.4 Hz, H-6), 6.96 (t, 1H, J=8.4 Hz, H-5), 7.14 (br s, 1H, $w_{1/2}$=7 Hz, N*H*), 7.19 (dd, 1H, J=1.2, 8.4 Hz, H-4), 7.21 (d, 2H, J=8.2 Hz, ArH-3 and ArH-5 of Ts), and 7.69 (d, 2H, J=8.2 Hz, ArH-2 and ArH-6 of Ts); ^{13}C NMR (δ): 21.7 (Ar*Me* of Ts), 56.0 (OMe-2), 60.6 (OMe-3), 114.9 (C-4), 122.6 (C-6), 124.2 (C-5), 127.7 (C-1), 129.1 (2C, TsC-2 and TsC-6)*, 129.3 (2C, TsC-3 and TsC-5)*, 137.1 (TsC-1), 144.7 (TsC-4), 148.5 (C-2), and 153.4 (C-3); CIMS, m/z (%): 308 (MH^+, 16), 307 (M^+, 9), 278 (MH^+-H_2CO, 5), 153 (MH^+–Ts, 84), 137 (M^+–Ts–Me, 50), 123 (MH^+–Ts–H_2CO, 100), 110 (19), and 91 ($PhMe^+$, 85). Increasing solvent polarity furnished acid **26** (694 mg, 76%), as a white solid, mp 143–144 °C (hexane–EtOAc). IR (KBr, ν): 3600–2600, 3430, 2949, 1718, 1584, 1432, 1339, 1262, 1161, 1038, 995, and 746 cm^{-1}; ^1H NMR (δ): 2.42 (s, 3H, Ar*Me* of Ts), 2.58 (t, 2H, J=7.6 Hz, CH_2CO_2H), 3.72 (s, 3H, OMe-2), 3.84 (t, 2H, J=7.6 Hz, NCH_2), 3.85 (s, 3H, OMe-3), 6.27 (br s, $w_{1/2}$=9 Hz, OH), 6.62 (dd, 1H, J=2.0, 8.3 Hz, H-6), 6.90 (dd, 1H, J=2.0, 8.3 Hz, H-4), 6.95 (t, 1H, J=8.3 Hz, H-5), 7.28 (d, 2H, J=8.2 Hz, ArH-3 and ArH-5 of Ts), and 7.68 (d, 2H, J=8.2 Hz, ArH-2 and ArH-6 of Ts); ^{13}C NMR (δ): 21.5 (Ar*Me* of Ts), 33.6 (CH_2CO_2H), 46.5 ($ArNCH_2$), 55.9 (OMe-3), 60.8 (OMe-2), 113.1 (C-4), 122.7 (C-5)*, 123.2 (C-6)*, 127.7 (2C, TsC-2 and TsC-6), 129.5 (2C, TsC-3 and TsC-5), 131.8 (C-1), 137.2 (TsC-1), 143.4 (TsC-4), 147.6 (C-2), 153.5 (C-3), and 176.2 (C=O); HRMS (TOF MS ESI+ion mode) calcd for $C_{18}H_{21}NO_6SNa$: 402.0988 $(M+Na)^+$; found: 402.0988.

3.5. 7,8-Dimethoxy-2,3-dihydro-1*H*-quinolin-4-one 25

A mixture of **26** (20 mg, 0.049 mmol) and PPA (400 mg, 20 equiv) was heated overnight at 90 °C; the reddish mixture was then treated with 10% $NaHCO_3$ (2 mL) and the organic products were extracted with EtOAc (4×15 mL) the combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed. Starting material **26** (9.6 mg, 48%) was recovered. Increasing solvent polarity furnished **25** (2 mg, 20%), as a solid, mp 90–92 °C (hexane–EtOAc; lit.[21] 92 °C). ^1H NMR (δ): 2.67 (t, 2H, J=6.9 Hz, H-3), 3.57 (t, 2H, J=6.9 Hz, H-2), 3.83 (s, 3H, OMe-8), 3.90 (s, 3H, OMe-7), 4.91 (br s, 1H, $w_{1/2}$=8 Hz, N*H*), 6.39 (d, 1H, J=8.8 Hz, H-6), and 7.64 (d, 1H, J=8.8 Hz, H-5); ^{13}C NMR (δ): 37.9 (C-3), 42.1 (C-2), 55.9 (OMe-7), 60.1 (OMe-8), 102.5 (C-6), 114.8 (C-5), 124.1 (C-4a), 134.2 (C-8a), 146.8 (C-8), 156.7 (C-7), and 192.7 (C-4).

3.6. 7,8-Dimethoxy-1-(toluene-4-sulfonyl)-2,3-dihydro-1*H*-quinolin-4-one 28

To a solution of acid **26** (96 mg, 0.25 mmol) in toluene (6 mL) was added recently prepared PPE[28] (1.4 mL), and the resulting homogeneous mixture was heated at 55 °C for 2 h. Crushed ice (10 g) was then carefully added, and extraction of the products was carried out with EtOAc (4×10 mL). The organic phase was washed with brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed to afford quinolin-4-one **28** (70 mg, 95%), as a white solid, mp 128–129 °C (hexane–EtOAc). IR (KBr, ν): 2966, 2848, 1682, 1593, 1458, 1359, 1207, 1181, 1090, 963, 801, 706, and 668 cm^{-1}; ^1H NMR (δ): 2.45 (s, 3H, Ar*Me* of Ts), 2.81 (t, 2H, J=6.3 Hz, H-3), 3.48 (s, 3H, OMe-8), 3.93 (s, 3H, OMe-7), 4.09 (t, 2H, J=6.3 Hz, H-2), 6.88 (d, 1H, J=8.9 Hz, H-6), 7.32 (d, 2H, J=8.0 Hz, ArH-3 and ArH-5 of Ts), 7.79 (d, 1H, J=8.9 Hz, H-5), and 7.86 (d, 2H, J=8.0 Hz, ArH-2 and ArH-6 of Ts); ^{13}C NMR (δ): 21.6 (Ar*Me* of Ts), 38.5 (C-3), 47.7 (C-2), 56.1 (OMe-7), 60.1 (OMe-8), 110.1 (C-6), 122.6 (C-5), 123.9 (C-4a), 127.2 (2C, TsC-2 and TsC-6), 129.5 (2C, TsC-3 and TsC-5), 136.5 (TsC-1), 141.1 (C-8), 143.6 (TsC-4)*, 143.9 (C-8a)*, 158.3 (C-7), and 192.7 (C-4); HRMS (TOF MS ESI+ion mode) calcd for $C_{18}H_{19}NO_5SNa$: 384.0882 $(M+Na)^+$; found: 384.0886.

3.7. (2,2-Dimethoxyethyl)-[7,8-dimethoxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl]-amine 29

Aminoacetaldehyde dimethylacetal (360 μL, 3.5 mmol) and glacial acetic acid (110 μL, 2.44 mmol) were successively added to a suspension of quinolin-4-one **28** (233 mg, 0.65 mmol), $MgSO_4$ (300 mg), and activated 4 Å molecular sieves (300 mg) in absolute EtOH (10 mL). The mixture was stirred overnight at room temperature, then $NaCNBH_3$ (53 mg, 0.84 mmol) was carefully added. The resulting slurry was refluxed for 24 h, then cooled to room temperature and after removal of the volatiles in vacuum, the remaining solid was directly purified by column chromatography, furnishing the expected amine **29** (254 mg, 87%), as an oil. IR (film, ν): 2934, 2835, 1601, 1495, 1335, 1157, 1094, and 760 cm^{-1}; ^1H NMR (δ): 2.15–2.40 (m, 1H, H-3uf), 2.44 (s, 3H, Ar*Me* of Ts), 2.80 (dd, 1H, J=5.3, 12.0 Hz, CH_2CH(OMe)$_2$), 2.87 (dd, 1H, J=5.0, 12.0 Hz, CH_2CH(OMe)$_2$), 3.40 (s, 6H, 2×acetal-OMe), 3.47 (s, 3H, OMe-8), 3.45–3.65 (m, 1H, H-3df), 3.70–3.85 (m, 1H, H-2uf), 3.86 (s, 3H, OMe-7), 3.97–4.17 (m, 2H, H-2df and H-4), 3.98 (br s, $w_{1/2}$=9 Hz, NH), 4.52 (dd, 1H, J=5.0, 5.3 Hz, CH(OMe)$_2$), 6.85 (d, 1H, J=8.5 Hz, H-6), 7.10 (d, 1H, J=8.5 Hz, H-5), 7.33 (d, 2H, J=8.5 Hz, ArH-3 and ArH-5 of Ts), and 7.90 (d, 2H, J=8.5 Hz, ArH-2 and ArH-6 of Ts); ^{13}C NMR (δ): 21.6 (Ar*Me* of Ts), 29.9 (C-3), 44.2 (C-2), 47.7 (NCH_2), 53.2 (C-4)*, 54.5 (acetal-OMe)*, 54.6 (acetal-OMe)*, 56.0 (OMe-7), 60.1 (OMe-8), 102.7 (acetal), 110.7 (C-6), 123.4 (C-5), 123.5 (C-4a), 127.4 (2C, TsC-2 and TsC-6), 129.4 (2C, TsC-3 and TsC-5), 131.3 (C-8a), 137.8 (TsC-1), 143.5 (TsC-4)#, 144.5 (C-8)#, and 153.1 (C-7); HRMS (TOF MS ESI+ion mode) calcd for $C_{22}H_{31}N_2O_6S$: 451.1903 $(M+1)^+$; found: 451.1901.

3.8. *N*-(2,2-Dimethoxyethyl)-*N*-[7,8-dimethoxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl]-4-methyl-benzenesulfonamide 30

To a cooled solution of amine **29** (96 mg, 0.21 mmol) in anhydrous $CHCl_3$ (5 mL) were successively added DIPEA (74 μL, 0.43 mmol) and tosyl chloride (52 mg, 0.38 mmol). The suspension was heated under reflux overnight until consumption of the starting material (by TLC). The flask was cooled to room temperature and most of the organic solvent was removed in the rotary evaporator, leaving an oily residue, which was purified by chromatography to afford the tosylamide **30** (82 mg, 64%), as a solid, mp 169–170 °C (hexane–EtOAc). IR (KBr, ν): 2926, 2854, 1600, 1496, 1338, 1292, 1157, and 668 cm^{-1}; ^1H NMR (δ): 1.97–2.10 (m, 1H, H-3uf), 2.28–2.42 (m, 1H, H-3df), 2.42 (s, 3H, Ar*Me* of 1-Ts), 2.45 (s, 3H, Ar*Me* of 4-NTs), 3.17 (s, 3H, acetal-OMe), 3.19 (s, 3H, OMe-8), 3.20 (dd, 1H, J=5.9, 15.1 Hz, CH_2CH(OMe)$_2$), 3.24 (s, 3H, acetal-OMe), 3.29 (dd, 1H, J=4.7, 15.1 Hz, CH_2CH(OMe)$_2$), 3.45–3.57 (m, 1H, H-2uf), 3.81 (s, 3H, OMe-7), 3.93 (dt, 1H, J=4.5, 13.9 Hz, H-2df), 4.44 (dd, 1H, J=4.7, 5.9 Hz, CH(OMe)$_2$), 5.12 (t, 1H, J=8.5 Hz, H-4), 6.70 (d, 1H, J=8.9 Hz, H-6), 6.87 (d, 1H, J=8.9 Hz, H-5), 7.29 (d, 2H, J=8.5 Hz, ArH-3 and ArH-5 of 1-Ts), 7.32 (d, 2H, J=8.5 Hz, ArH-3 and ArH-5 of 4-NTs), 7.77 (d, 2H, J=8.5 Hz, ArH-2 and ArH-6 of 4-NTs), and 7.82 (d, 2H, J=8.5 Hz, ArH-2 and ArH-6 of 1-Ts); ^{13}C NMR (δ): 21.5 (Ar*Me* of Ts), 21.6 (Ar*Me* of Ts), 28.9 (C-3), 46.7 (NCH_2), 46.9 (C-2), 53.5 (C-4), 54.0 (acetal-OMe), 54.8 (acetal-OMe), 55.9 (OMe-7), 59.6 (OMe-8), 103.0 (acetal), 110.1 (C-6), 122.7 (C-5), 124.3 (C-4a), 126.8 (2C, 1-TsC-2 and TsC-6), 127.3 (2C, 4-NTsC-2 and 4-NTsC-6), 129.1 (2C, 1-NTsC-3 and 1-NTsC-5), 129.7 (2C, 4-NTsC-3 and 4-NTsC-5), 133.2 (C-8a), 137.8 (4-NTsC-1), 139.4 (1-TsC-1), 142.7 (1-TsC-4), 143.3 (4-NTsC-4)*, 143.5 (C-8)*, and 152.3 (C-7); HRMS (TOF MS ESI+ion mode) calcd for $C_{29}H_{36}N_2O_8S_2Na$: 627.1811 $(M+Na)^+$; found: 627.1813.

3.9. *N*-(2,2-Dimethoxyethyl)-*N*-[7,8-dimethoxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl]-4-nitro-benzenesulfonamide 34

To a cooled solution of amine **29** (57 mg, 0.12 mmol) in anhydrous $CHCl_3$ (2 mL) were successively added DIPEA (46 μL, 0.36 mmol) and nosyl chloride (42 mg, 0.19 mmol). The suspension was heated under reflux until consumption of the starting material (by TLC). The flask was cooled to room temperature and most of the organic solvent was removed in the rotary evaporator, leaving an oily residue, which was purified by chromatography to afford the nosylamide **34** (15 mg, 20%). IR (film, ν): 2926, 2855, 1604, 1530, 1496, 1350, 1294, 1158, 1088, 953, and 735 cm^{-1}; ^1H NMR (δ): 2.05–2.15 (m, 1H, H-3uf), 2.40–2.51 (m, 1H, H-3df), 2.42 (s, 3H, Ar*Me* of Ts), 3.19 (s, 3H, acetal-OMe)*, 3.20 (s, 3H, acetal-OMe)*, 3.21 (s, 3H, OMe-8)*, 3.29 (dd, 1H, J=5.4, 15.2 Hz, CH_2CH(OMe)$_2$), 3.43 (dd, 1H, J=4.9, 15.2 Hz, CH_2CH(OMe)$_2$), 3.40–3.52 (m, 1H, H-2uf), 3.81 (s, 3H, OMe-7), 3.99 (dt, 1H, J=4.1, 13.8 Hz, H-2df), 4.32 (dd, 1H, J=4.9, 5.4 Hz, CH(OMe)$_2$), 5.24 (t, 1H, J=8.8 Hz, H-4), 6.69 (d, 1H, J=8.8 Hz, H-6), 6.77 (d, 1H, J=8.8 Hz, H-5), 7.30 (d, 2H, J=8.5 Hz, ArH-3 and ArH-5 of Ts), 7.84 (d, 2H, J=8.5 Hz, ArH-2 and ArH-6 of Ts), 8.09 (d, 2H, J=8.8 Hz, ArH-2 and ArH-6 of Ns), and 8.37 (d, 2H, J=8.8 Hz, ArH-3 and ArH-5 of Ns); ^{13}C NMR (δ): 21.5 (Ar*Me* of Ts), 29.3 (C-3), 47.0 (C-2)#, 47.1 (NCH_2)#, 54.2 (C-4)*, 54.3 (acetal-OMe)*, 54.8 (acetal-OMe)*, 56.0 (OMe-7), 59.6 (OMe-8), 102.6 (acetal), 110.1 (C-6), 121.8 (C-5), 123.9 (C-4a), 124.2 (2C, NsC-3 and NsC-5), 126.8 (2C, TsC-2 and TsC-6), 128.6 (2C, NsC-2 and NsC-6), 129.2 (2C, TsC-3 and TsC-5), 133.2 (C-8a), 139.2 (TsC-1), 143.0 (NsC-1), 143.6 (C-8), 146.9 (TsC-4), 149.9 (NsC-4), and 152.6 (C-7); HRMS (TOF MS ESI+ion mode) calcd for $C_{28}H_{33}N_3O_{10}S_2Na$: 658.1505 $(M+Na)^+$; found: 658.1512.

3.10. Attempt of cyclization of tosylacetal 30 under modified Jackson conditions. Isolation of 7,8-dimethoxy-1-(toluene-4-sulfonyl)-1,2-dihydroquinoline 31

EtOH (0.22 mL) and 6 N HCl (0.23 mL) were successively added to a cold solution of tosylacetal **30** (121 mg, 0.20 mmol) in dioxane (1 mL) and the resulting solution submitted to reflux until complete disappearance of the starting material (30 min). The reaction was then diluted with EtOAc (25 mL) and successively washed with brine (5 mL) containing 10% Na_2CO_3 (0.5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed, furnishing **31** (65 mg, 94%), as an oil. IR (film, ν): 2923, 2853, 1597, 1491, 1350, 1266, 1160, 1090, 809, and 674 cm^{-1}; ^1H NMR (δ): 2.39 (s, 3H, Ar*Me* of Ts), 3.87 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.26 (br s, 2H, H-2), 5.51 (dt, 1H, J=4.0, 9.7 Hz, H-3), 6.05 (dt, 1H, J=1.5, 9.7 Hz, H-4), 6.67 (d, 1H, J=8.2 Hz, H-6), 6.78 (d, 1H, J=8.2 Hz, H-5), 7.16 (d, 2H, J=8.5 Hz, ArH-3 and ArH-5 of Ts), and 7.53 (d, 2H, J=8.5 Hz, ArH-2 and ArH-6 of Ts); ^{13}C NMR (δ): 21.6 (Ar*Me* of Ts), 45.7 (C-2), 56.1 (OMe-7), 60.5 (OMe-8), 110.9 (C-6), 120.7 (C-5), 123.0 (C-4), 124.8 (C-4a), 126.1 (C-3), 127.8 (2C, TsC-2 and TsC-6), 129.0 (2C, TsC-3 and TsC-5), 137.3 (C-8a), 143.2 (2C, C-8 and TsC-1), 145.8 (TsC-4), and 152.9 (C-7); HRMS (TOF MS ESI+ion mode) calcd for $C_{18}H_{19}NO_4SNa$: 368.0933 $(M+Na)^+$; found: 368.0933. An increase in solvent polarity furnished aldehyde **32** (8 mg, 45%).

3.11. Attempted cyclization of tosylacetal 30 with $BF_3 \cdot Et_2O$

A solution of $BF_3 \cdot Et_2O$ (0.215 mL, 0.092 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise to a solution of tosylacetal **30** (18 mg, 0.031 mmol) in CH_2Cl_2 at −40 °C. After 12 h at room temperature, the reaction was quenched with brine (5 mL) and the products were extracted with EtOAc (4×10 mL). Drying (Na_2SO_4) and

concentration of the extracts under reduced pressure, followed by chromatography afforded **31** (6 mg, 47%) and **32** (8 mg, 48%).

3.12. Attempted cyclization of 30. Isolation of *N*-[7,8-dimethoxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl]-4-methyl-*N*-(2-oxoethyl)-benzenesulfonamide 32

Anhydrous ZnI_2 (21 mg, 0.064 mmol) was added to sulfonamidoacetal **30** (19 mg, 0.032 mmol) dissolved in CH_2Cl_2 (1 mL) and the resulting suspension was submitted to sonication for 24 h. The mixture was then chromatographed, furnishing aldehyde **32** (11, mg, 54%), as an oil. IR (film, ν): 2925, 1854, 1739, 1733, 1599, 1495, 1339, 1156, 816, and 672 cm^{-1}; ^1H NMR (δ): 2.01 (dt, 1H, J=6.4, 8.8 Hz, H-3uf), 2.42 (s, 3H, Ar*Me* of Ts), 2.47 (s, 3H, Ar*Me* of Ts), 3.21 (dt, 1H, J=8.8, 9.0 Hz, H-3df), 3.21 (s, 3H, OMe-8), 3.36 (ddd, 1H, J=6.4, 8.4, 14.3 Hz, H-2uf), 3.74 (d, 2H, J=1.4 Hz, NCH_2), 3.82 (OMe-7), 3.88 (dt, 1H, J=9.0, 14.3 Hz, H-2df), 5.23 (dd, 1H, J=8.4, 9.0 Hz, H-4), 6.76 (d, 1H, J=8.9 Hz, H-6), 7.11 (d, 1H, J=8.9 Hz, H-5), 7.29 (d, 2H, J=8.4 Hz, ArH-3 and ArH-5 of Ts), 7.36 (d, 2H, J=8.4 Hz, ArH-3 and ArH-5 of Ts), 7.80 (d, 4H, J=8.4 Hz, 2×ArH-2 and ArH-6 of Ts), and 9.47 (t, 1H, J=1.4 Hz, CHO); ^{13}C NMR (δ): 21.5 (Ar*Me* of Ts), 21.6 (Ar*Me* of Ts), 28.3 (C-3), 47.2 (C-2), 53.0 (NCH$_2$CHO), 53.7 (C-4), 55.9 (OMe-7), 59.6 (OMe-8), 110.7 (C-6), 121.8 (C-4a), 124.1 (C-5), 126.9 (2C, TsC-2 and TsC-6), 127.6 (2C, TsC-2 and TsC-6), 129.2 (2C, TsC-3 and TsC-5), 130.0 (2C, TsC-3 and TsC-5), 133.7 (C-8a), 136.6 (TsC-1), 138.9 (TsC-1), 143.1 (TsC-4), 143.6 (TsC-4), 144.2 (C-8), 152.8 (C-7), and 197.4 (CHO); HRMS (TOF MS ESI+ion mode) calcd for $C_{27}H_{31}N_2O_7S_2$: 559.1573 $(M+1)^+$; found: 559.1578.

3.13. $SnCl_4$-mediated cyclization of tosylacetal 30

To a solution of tosylacetal **30** (121 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) cooled to −78 °C, was added dropwise a CH_2Cl_2 solution of $SnCl_4$ (0.54 mL, 0.40 mmol). After 1.5 h at −78 °C, the reaction temperature was increased to −60 °C and left overnight. The system was slowly heated up to room temperature and 0.2 mL of MeOH was added to quench the Lewis acid. After 10 min of stirring, brine (5 mL) was added and the organic products were extracted with EtOAc (4×20 mL). The organic extracts were combined, successively washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed, furnishing 1,2-dihydroquinoline derivative **31** (16 mg, 23%), aldehyde **32** (5 mg, 4%), followed by **33a** (10 mg, 9%). IR (film, ν): 2954, 2923, 2853, 1598, 1494, 1341, 1158, and 1092 cm^{-1}; ^1H NMR (δ): 1.73 (dddd, 1H, J=6.0, 6.2, 9.9, 11.0 Hz, H-3uf), 2.41 (s, 3H, Ar*Me* of 1-Ts), 2.44 (s, 3H, Ar*Me* of 4-Ts), 2.63–2.76 (m, 1H, H-3df), 2.89 (dd, 1H, J=9.8, 13.3 Hz, H-5uf), 3.08 (ddd, 1H, J=4.1, 9.9, 13.2 Hz, H-2uf), 3.50 (s, 3H, OMe-6), 3.68 (s, 3H, OMe-9), 3.83 (dd, 1H, J=4.8, 9.8 Hz, H-5df), 3.84 (s, 3H, OMe-8), 4.07 (ddd, 1H, J=2.9, 6.2, 13.2 Hz, H-2df), 4.13 (dd, 1H, J=4.8, 13.3 Hz, H-6), 4.50 (dd, 1H, J=6.0, 11.5 Hz, H-3a), 6.93 (s, 1H, H-7), 7.29 (d, 2H, J=8.2 Hz, ArH-3 and ArH-5 of Ts), 7.34 (d, 2H, J=8.3 Hz, ArH-3 and ArH-5 of Ts), 7.69 (d, 2H, J=8.3 Hz, ArH-2 and ArH-6 of Ts), and 7.91 (d, 2H, J=8.2 Hz, ArH-2 and ArH-6 of Ts); ^{13}C NMR (δ): 21.5 (Ar*Me* of Ts), 21.6 (Ar*Me* of Ts), 29.4 (C-3), 42.8 (C-5), 43.0 (C-2), 49.5 (C-3a), 56.0 (OMe-8), 57.5 (OMe-6), 60.4 (OMe-9), 73.0 (C-6), 107.9 (C-7), 124.7 (C-9a), 126.9 (2C, TsC-2 and TsC-6), 127.6 (2C, TsC-2 and TsC-6), 129.6 (2C, TsC-3 and TsC-5), 129.9 (2C, TsC-3 and TsC-5), 130.0 (C-9b)*, 130.3 (C-6a)*, 137.4 (TsC-1), 137.7 (TsC-1), 143.6 (TsC-4), 143.7 (TsC-4), 145.2 (C-9), and 152.6 (C-8); HRMS (TOF MS ESI+ion mode) calcd for $C_{28}H_{32}N_2O_7S_2Na$: 595.1549 $(M+Na)^+$; found: 595.1554. Increasing solvent polarity afforded **33b** (28 mg, 24%), as an oil. IR (film, ν): 2954, 2924, 2853, 1598, 1496, 1337, 1157, and 1092 cm^{-1}; ^1H NMR (δ): 1.71 (dddd, 1H, J=5.4, 8.0, 9.6, 11.9 Hz, H-3uf), 2.39 (s, 3H, Ar*Me* of 1-Ts), 2.43 (s, 3H, Ar*Me* of 4-Ts), 2.75 (dddd, 1H, J=2.8, 3.5, 11.6, 11.9 Hz, H-3df), 3.13 (ddd, 1H, J=3.5, 7.8, 9.6 Hz, H-2uf), 3.13 (s, 3H, OMe-6), 3.20 (d, 1H, J=13.2 Hz, H-5uf), 3.74 (s, 3H, OMe-9), 3.84 (s, 3H, OMe-8), 4.03 (ddd, 1H, J=2.8, 5.7, 7.8 Hz, H-2df), 4.04 (d, 1H, J=3.3 Hz, H-6), 4.07 (dd, 1H, J=3.3, 13.2 Hz, H-5df), 4.38 (dd, 1H, J=5.4, 11.6 Hz, H-3a), 6.70 (s, 1H, H-7), 7.23 (d, 2H, J=8.2 Hz, ArH-3 and ArH-5 of Ts), 7.32 (d, 2H, J=8.3 Hz, ArH-3 and ArH-5 of Ts), 7.70 (d, 2H, J=8.3 Hz, ArH-2 and ArH-6 of Ts), and 7.88 (d, 2H, J=8.2 Hz, ArH-2 and ArH-6 of Ts); ^{13}C NMR (δ): 21.5 (Ar*Me* of Ts), 21.6 (Ar*Me* of Ts), 29.4 (C-3), 42.9 (C-5), 43.0 (C-2), 49.3 (C-3a), 56.2 (2C, OMe-8 and OMe-6), 60.6 (OMe-9), 74.4 (C-6), 112.2 (C-7), 126.4 (C-9b), 127.6 (2C, TsC-2 and TsC-6), 127.8 (2C, TsC-2 and TsC-6), 129.2 (2C, TsC-3 and TsC-5), 129.6 (2C, TsC-3 and TsC-5), 130.0 (C-6a), 136.8 (TsC-1), 137.6 (TsC-1), 143.1 (2C, TsC-4 and C-9a), 143.6 (TsC-4), 146.1 (C-9), and 152.4 (C-8); HRMS (TOF MS ESI+ion mode) calcd for $C_{28}H_{32}N_2O_7S_2Na$: 595.1549 $(M+Na)^+$; found: 595.1552. Further increase in solvent polarity furnished a mixture of diastereomeric alcohols, **33c** being the most abundant one (12 mg, 9%). IR (film, ν): 3482, 2924, 2852, 1598, 1496, 1337, 1266, 1158, 1056, 914, 815, 736, and 666 cm^{-1}; ^1H NMR (δ): 1.60–1.75 (m, 1H, H-3uf), 2.40 (s, 3H, Ar*Me* of 1-Ts), 2.45 (s, 3H, Ar*Me* of 4-Ts), 2.64 (dddd, 1H, J=1.6, 5.2, 10.6, 17.0 Hz, H-3df), 3.02–3.13 (m, 1H, H-2uf), 3.25 (dd, 1H, J=1.9, 14.2 Hz, H-5uf), 3.71 (s, 3H, OMe-9), 3.85 (s, 3H, OMe-8), 4.00 (dd, 1H, J=2.8, 14.2 Hz, H-5df), 4.02–4.13 (m, 1H, H-2df), 4.05 (dd, 1H, J=1.9, 2.8 Hz, H-6), 4.54 (br s, 1H, $w_{1/2}$=7.5 Hz, OH), 4.58 (dd, 1H, J=5.6, 11.7 Hz, H-3a), 6.81 (s, 1H, H-7), 7.29 (d, 2H, J=8.3 Hz, ArH-3 and ArH-5 of 1-Ts), 7.34 (d, 2H, J=8.3 Hz, ArH-3 and ArH-5 of 4-Ts), 7.75 (d, 2H, J=8.3 Hz, ArH-2 and ArH-6 of 1-Ts), and 7.91 (d, 2H, J=8.3 Hz, ArH-2 and ArH-6 of 4-Ts); ^{13}C NMR (δ): 21.5 (Ar*Me* of Ts), 21.6 (Ar*Me* of Ts), 31.3 (C-3), 43.1 (C-2), 46.6 (C-5), 49.0 (C-3a), 56.1 (OMe-8), 60.5 (OMe-9), 66.1 (C-6), 111.6 (C-7), 125.5 (C-9a), 127.0 (C-9b), 127.5 (2C, TsC-2 and TsC-6), 127.6 (2C, TsC-2 and TsC-6), 128.7 (C-6a), 129.6 (2C, TsC-3 and TsC-5), 129.7 (2C, TsC-3 and TsC-5), 136.8 (TsC-1), 137.6 (TsC-1), 143.7 (2C, 2×TsC-4), 146.1 (C-9), and 152.8 (C-8); HRMS (TOF MS ESI+ion mode) calcd for $C_{27}H_{31}N_2O_7S_2$: 559.1573 $(M+1)^+$; found: 559.1578.

3.14. $SnCl_4$-mediated cyclization of nosylacetal 34

To a solution of nosylacetal **34** (28 mg, 0.04 mmol) in CH_2Cl_2 (1.6 mL) cooled to −78 °C, was added dropwise a CH_2Cl_2 solution of $SnCl_4$ (0.155 mL, 0.128 mmol). After 1.5 h at −78 °C, the reaction temperature was increased to −60 °C and left overnight. The system was slowly heated up to room temperature and 0.2 mL of MeOH was added to quench the Lewis acid. After 10 min of stirring, brine (5 mL) was added and the organic products were extracted with EtOAc (4×20 mL). The organic extracts were combined, successively washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed, furnishing **35a** (4.7 mg, 18%), as an oil. ^1H NMR (δ): 1.70–1.84 (m, 1H, H-3uf), 2.45 (s, 3H, Ar*Me* of Ts), 2.71 (dddd, 1H, J=5.7, 6.3, 10.0, 11.4 Hz, H-3df), 2.98 (dd, 1H, J=9.8, 13.5 Hz, H-5uf), 3.04 (ddd, 1H, J=5.7, 9.4, 13.9 Hz, H-2uf), 3.55 (s, 3H, OMe-6), 3.66 (s, 3H, OMe-9), 3.84 (s, 3H, OMe-8), 3.91 (dd, 1H, J=4.7, 9.8 Hz, H-6), 4.06 (ddd, 1H, J=6.1, 10.0, 13.9 Hz, H-2df), 4.25 (dd, 1H, J=4.7, 13.5 Hz, H-5df), 4.69 (dd, 1H, J=6.0, 11.4 Hz, H-3a), 6.94 (s, 1H, H-7), 7.35 (d, 2H, J=8.4 Hz, ArH-3 and ArH-5 of Ts), 7.94 (d, 2H, J=8.4 Hz, ArH-2 and ArH-6 of Ts), 8.04 (d, 2H, J=9.0 Hz, ArH-2 and ArH-6 of Ns), and 8.35 (d, 2H, J=9.0 Hz, ArH-3 and ArH-5 of Ns); HRMS (TOF MS ESI+ion mode) calcd for $C_{27}H_{30}N_3O_9S_2$: 604.1424 $(M+1)^+$; found: 604.1404. This was followed by **35b** (4.7 mg, 18%), as an oil. ^1H NMR (δ): 1.82 (dddd, 1H, J=5.9, 6.7, 9.7, 12.6 Hz, H-3uf), 2.45 (s, 3H, Ar*Me* of Ts), 2.84 (m, 1H, H-3df), 3.05 (s, 3H, OMe-6), 3.06 (ddd, 1H, J=3.9, 9.7, 13.2 Hz, H-2uf), 3.23 (dd, 1H, J=1.7, 14.8 Hz, H-5uf), 3.74 (s, 3H, OMe-9), 3.84 (s, 3H, OMe-8), 4.02 (dd, 1H, J=1.7, 2.4 Hz, H-6), 4.07 (ddd, 1H, J=6.7, 7.1, 13.2 Hz, H-2df), 4.31 (dd, 1H, J=2.4, 14.8 Hz, H-5df), 4.68 (dd, 1H, J=5.9, 11.7 Hz, H-3a), 6.64 (s, 1H, H-7), 7.35 (d, 2H, J=8.4 Hz, ArH-3 and ArH-5 of Ts), 7.96 (d, 2H, J=8.4 Hz,

ArH-2 and ArH-6 of Ts), 8.04 (d, 2H, *J*=8.8 Hz, ArH-2 and ArH-6 of Ns), and 8.27 (d, 2H, *J*=8.8 Hz, ArH-3 and ArH-5 of Ns); ^{13}C NMR (δ): 21.6 (Ar*Me* of Ts), 32.5 (C-3), 42.8 (C-5), 43.9 (C-2), 49.3 (C-3a), 55.9 (OMe-8), 56.2 (OMe-6), 60.6 (OMe-9), 74.2 (C-6), 112.7 (C-7), 123.5 (2C, NsC-3 and NsC-5), 125.6 (C-9a)*, 125.9 (C-9b)*, 127.8 (2C, TsC-2 and TsC-6), 129.2 (2C, NsC-2 and NsC-6), 129.6 (2C, TsC-3 and TsC-5), 130.0 (C-6a), 137.4 (TsC-1), 143.8 (TsC-4), 145.6 (C-9), 146.5 (NsC-1), 149.8 (NsC-4), and 152.4 (C-8); HRMS (TOF MS ESI+ion mode) calcd for $C_{27}H_{30}N_3O_9S_2$: 604.1424 $(M+1)^+$; found: 604.1409. Increasing solvent polarity furnished **35c** (4 mg, 16%), as an oil. ^{1}H NMR (δ): 1.55 (br s, 1H, OH), 1.83 (dddd, 1H, *J*=6.4, 7.0, 9.6, 11.0 Hz, H-3uf), 2.46 (s, 3H, Ar*Me* of Ts), 2.76 (dddd, 1H, *J*=6.1, 6.3, 11.0, 11.5 Hz, H-3df), 3.04 (ddd, 1H, *J*=6.1, 9.6, 14.0 Hz, H-2uf), 3.36 (dd, 1H, *J*=10.1, 14.0 Hz, H-5uf), 3.69 (s, 3H, OMe-9), 3.85 (s, 3H, OMe-8), 4.07 (ddd, 1H, *J*=6.3, 7.0, 14.0 Hz, H-2df), 4.29 (dd, 1H, *J*=4.1, 14.0 Hz, H-5df), 4.67 (dd, 1H, *J*=4.1, 10.1 Hz, H-6), 4.76 (dd, 1H, *J*=6.4, 11.5 Hz, H-3a), 7.02 (s, 1H, H-7), 7.35 (d, 2H, *J*=8.4 Hz, ArH-3 and ArH-5 of Ts), 7.95 (d, 2H, *J*=8.4 Hz, ArH-2 and ArH-6 of Ts), 8.05 (d, 2H, *J*=8.8 Hz, ArH-2 and ArH-6 of Ns), and 8.35 (d, 2H, *J*=8.8 Hz, ArH-3 and ArH-5 of Ns); ^{13}C NMR (δ): 21.6 (Ar*Me* of Ts), 32.2 (C-3), 43.0 (C-5), 47.0 (C-2), 49.6 (C-3a), 54.0 (C-6), 56.2 (OMe-8), 60.6 (OMe-9), 111.4 (C-7), 124.0 (2C, NsC-3 and NsC-5), 125.3 (C-9a)*, 126.3 (C-9b)*, 127.8 (2C, TsC-2 and TsC-6), 129.3 (2C, NsC-2 and NsC-6), 129.7 (2C, TsC-3 and TsC-5), 129.9 (C-6a), 137.3 (TsC-1), 143.9 (TsC-4), 145.1 (C-9), 146.8 (NsC-1), 150.1 (NsC-4), and 153.1 (C-8); HRMS (TOF MS ESI+ion mode) calcd for $C_{26}H_{28}N_3O_9S_2$: 590.1267; found: 590.1244. This was followed by **35d** (5.6 mg, 22%), as an oil. ^{1}H NMR (δ): 1.57 (br s, 1H, OH), 1.79 (dddd, 1H, *J*=6.1, 7.0, 9.2, 12.0 Hz, H-3uf), 2.46 (s, 3H, Ar*Me* of Ts), 2.71–2.83 (m, 1H, H-3df), 3.04 (ddd, 1H, *J*=5.7, 7.0, 13.8 Hz, H-2uf), 3.29 (dd, 1H, *J*=1.6, 14.6 Hz, H-5uf), 3.72 (s, 3H, OMe-9), 3.84 (s, 3H, OMe-8), 4.05 (ddd, 1H, *J*=6.0, 6.1, 13.8 Hz, H-2df), 4.22 (dd, 1H, *J*=2.2, 14.6 Hz, H-5df), 4.60 (dd, 1H, *J*=1.6, 2.2 Hz, H-6), 4.77 (dd, 1H, *J*=6.1, 11.6 Hz, H-3a), 6.76 (s, 1H, H-7), 7.36 (d, 2H, *J*=8.6 Hz, ArH-3 and ArH-5 of Ts), 7.97 (d, 2H, *J*=8.6 Hz, ArH-2 and ArH-6 of Ts), 8.10 (d, 2H, *J*=8.8 Hz, ArH-2 and ArH-6 of Ns), and 8.31 (d, 2H, *J*=8.8 Hz, ArH-3 and ArH-5 of Ns); ^{13}C NMR (δ): 21.6 (Ar*Me* of Ts), 31.9 (C-3), 42.9 (C-2), 46.5 (C-5), 49.2 (C-3a), 55.1 (OMe-8), 60.5 (OMe-9), 66.0 (C-6), 111.7 (C-7), 124.0 (2C, NsC-3 and NsC-5), 125.2 (C-9a)*, 127.8 (2C, TsC-2 and TsC-6), 128.1 (C-9b)*, 129.1 (2C, NsC-2 and NsC-6), 129.6 (2C, TsC-3 and TsC-5), 130.1 (C-6a), 136.4 (TsC-1), 143.9 (TsC-4), 145.5 (C-9), 146.3 (NsC-1), 150.0 (NsC-4), and 153.0 (C-8); HRMS (TOF MS ESI+ion mode) calcd for $C_{26}H_{27}N_3NaO_9S_2$: 612.1086; found: 612.1089.

3.15. 8,9-Dimethoxy-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]-[1,6]naphthyridine (2,3,3a,4,5,6-hexahydroaaptamine) 18

A solution of **33a** and **33b** (38 mg, 0.066 mmol) in anhydrous THF (1.5 mL) was added via cannula to freshly condensed, refluxing (−33 °C) ammonia. Metallic sodium was melted under toluene and aspired into a 0.2 mL pipette, where it solidified as a thin wire.[29] The thus prepared sodium wire was carefully placed in contact with the reaction mixture, where a blue-greenish color developed. The sodium wire was introduced each time the color fainted, and this operation was repeated until a deep blue color was observed, which persisted for 5 min, when the remaining wire was finally removed. The reaction was quenched by addition of solid NH_4Cl ($\approx$100 mg). The ammonia was left to evaporate and the remaining reaction products were admixed with silica gel and chromatographed, furnishing **18** (13 mg, 83%), as a solid, mp 105–107 °C (hexane; lit.[16a] 106–108 °C). IR (KBr, ν): 3403, 3250, 2956, 2865, 2510, 1610, 1516, 1464, 1324, 1239, 1155, 1010, and 685 cm^{-1}; ^{1}H NMR (δ): 2.13 (ddd, 1H, *J*=3.9, 11.8, 23.9 Hz, H-3uf), 2.50–2.60 (m, 1H, H-3df), 2.81 (br dd, 1H, *J*=11.1, 20.8 Hz, H-6uf), 3.22 (dd, 1H, *J*=3.6, 11.1 Hz, H-6df), 3.30 (br dd, 1H, *J*=3.6, 20.8 Hz, H-5uf), 3.40 (dt, 1H, *J*=3.9, 12.3 Hz, H-2uf), 3.45–3.55 (m, 1H, H-2df), 3.65 (dd, 1H, *J*=11.1, 20.8 Hz, H-5df), 3.74 (s, 3H, OMe-9), 3.79 (s, 3H, OMe-8), 4.24 (dd, 1H, *J*=4.4, 11.8 Hz, H-3a), 4.43 (br s, 1H, $w_{1/2}$=36 Hz, NH-1), 5.8–7.5 (br s, 1H, NH-4), and 6.00 (s, 1H, H-7); ^{13}C NMR (δ): 25.3 (C-6), 25.5 (C-3), 39.5 (C-2), 42.1 (C-5), 51.4 (C-3a), 55.7 (OMe-8), 59.9 (OMe-9), 100.0 (C-7), 106.2 (C-9b), 126.5 (C-6a), 132.3 (C-9), 137.3 (C-9a), and 152.5 (C-8); HRMS (TOF MS ESI+ion mode) calcd for $C_{13}H_{19}N_2O_2$: 235.1447 $(M+1)^+$; found: 235.1445.

Acknowledgements

The authors gratefully thank UNR, CONICET (PIP No. 5439), and ANPCyT (PICT Nos. 06-12532 and 06-38165) for financial support. E.L.L. thanks CONICET for his fellowship. Ms. Annabelle Gillig (EPFL, Switzerland) is acknowledged for carrying out the high-resolution mass spectral analyses.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.036.

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