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Synthesis of spongidines A and D: marine metabolites phospholipase A_2 inhibitors

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In memoriam of Professor Rafael Suau

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ABSTRACT

Two different strategies for the synthesis of spongidines A and D are presented. Herein we describe a route based in an amino acid insertion followed by aromatization. Another alternative is the construction of a pyridine derivative followed by N-alkylation. Both methodologies have intermediate **5** as a key compound, which is eventually accessible from methyl isoanticopalate.

1. Introduction

Nature offers a wide variety of nitrogen containing compounds.[1] In particular, pyridine and pyridinium derivatives are among the most important and distributed compounds in natural products.[2] Besides, it is noteworthy the presence of amino acids inserted in those structures.[3]

Diploclidine[4] and lycodine[5] are examples of recently isolated natural products containing the pyridine core and showing very different structures. Pyridine-containing compounds show a wide spectrum of biological activities, which is of special relevance due to its therapeutic use. Pyridine-derived pharmaceuticals include atazanavir[6] and imatinib[7] (Fig. 1).

Many pyridinium alkaloids have a marine origin, as niphatoxin C,[8] purealidin D[9] or daminin[10] (Fig. 2). Among them terpenoids are an important group. Those azaheterocycles have been the focus of intense research throughout decades. In particular, spongidines A, **1**, and D, **2**, are two bioactive pyridinium alkaloids isolated from a Vanuatu sponge of the genus *Spongia*.[11] They have a terpenic framework and a pyridine ring inserted in the structure, which is *N*-alkylated as a glycine chain in spongidine A, **1**, and a taurine residue in spongidine D, **2**. Those compounds proved to be PLA_2 inhibitors. However, they are structurally very different from well-known anti-inflammatory sesterterponolides as manoalide, luffolide or several cacospongiolides,[12] possessing a butenolide ring in their structure. Therefore, the synthesis of spongidines would contribute not only to obtain the final product, but also many analogues that could be tested for SAR studies.

There is a wide range of methodologies for the synthesis of pyridines.[13] Traditionally, many of them rely on condensation of amine and carbonyl compounds. [2+2+1+1] Hantzsch pyridine synthesis or [5+1] condensations using ammonia as the nitrogen source are among the most applied strategies.[14] Bolhmann–Rahtz synthesis[15] allows the generation of substituted pyridines from enamines and ethynylketones. Acetylenes and α,β-unsaturated carbonyls are also appropriate scaffolds for condensation reactions.[16] Modern alternatives include the use of transition-metal catalysts, and ring-closing metathesis or hydroamination reactions.[17] Consequently, the construction of the pyridine core has been the key step in the synthesis of several natural products, as piericidin A1, complanadine A or streptonigrin[18] (Fig. 3).

We focused our attention on the synthesis of spongidines A, **1**, and D, **2**, because of their challenging structure and biological features. To the best of our knowledge, only one attempted synthesis of **1** and **2** has been reported,[19] following a radical-based cascade reaction. Herein we present two different routes to access **1** and **2**, based on the formation of the pyridine ring and starting from sclareol, a natural building block successfully used in our research group for the synthesis of natural products,[20] and which is a direct precursor of methyl isoanticopalate.

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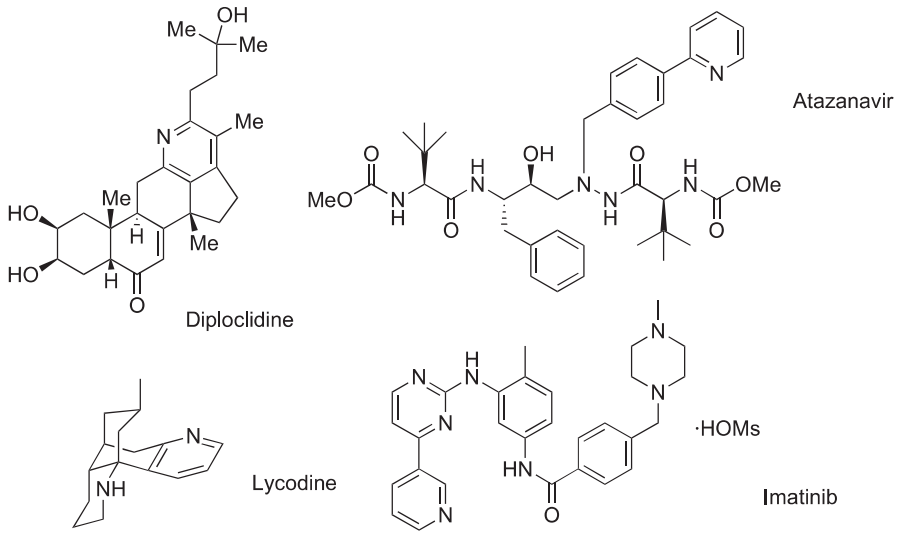


Fig. 1. Several compounds containing a pyridine core, and pyridine-derived pharmaceuticals.

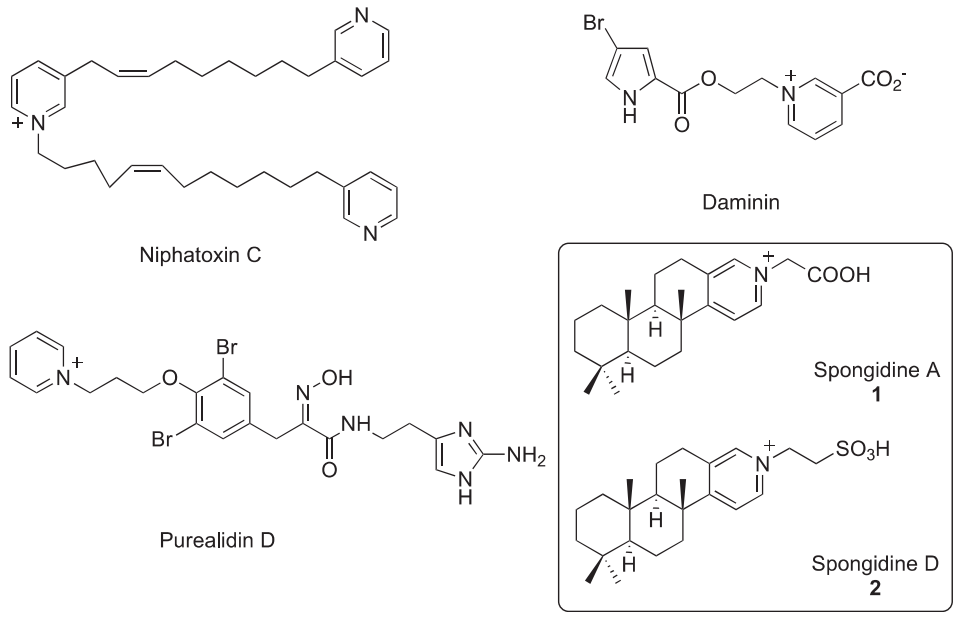


Fig. 2. Several pyridinium alkaloids from marine sources.

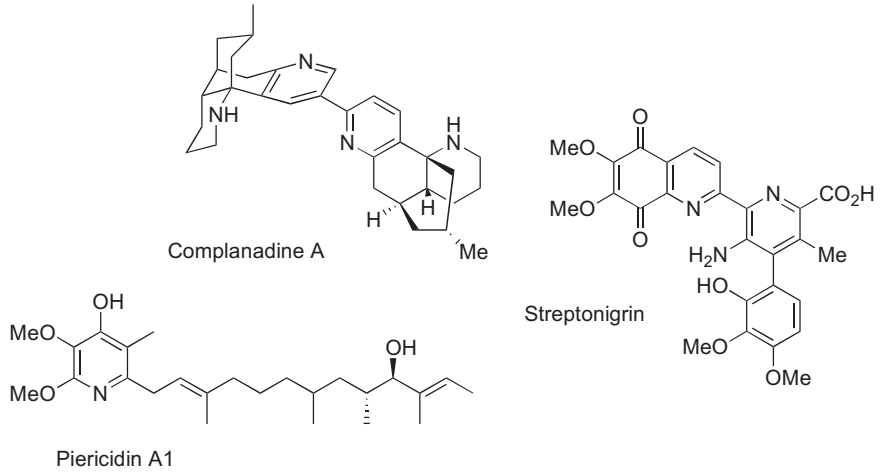
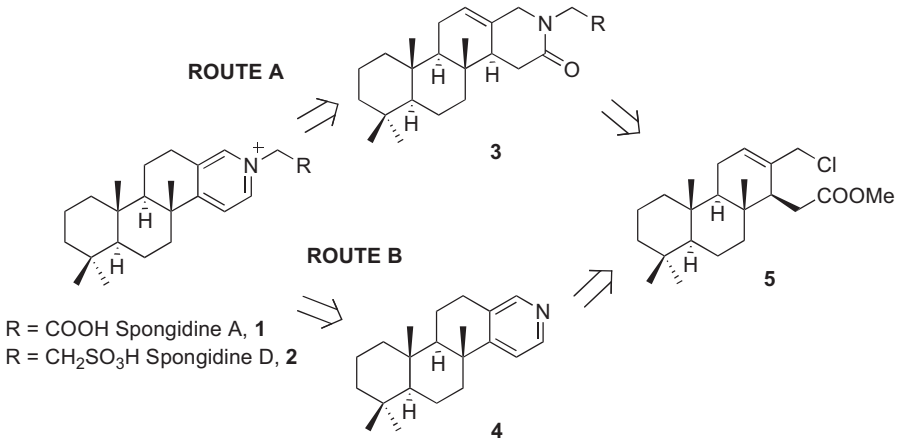


Fig. 3. Several natural products whose synthesis is based on the construction of a pyridine ring.

2. Results and discussion

The key features of our retro-synthetic plan for preparing Spongidine A, **1**, and D, **2**, is shown in Scheme 1. We planned two different alternatives to achieve our goal, both featuring chloroderivative **5** as the key intermediate. The first route is based on the coupling of an amino acid with a halogen ester in a one-pot fashion, which would lead to an intermediate **3**, followed by aromatization. On the other hand we planned to synthesize a pyridine derivative, like **4**, to perform an N-alkylation. Those two main ideas would allow us to get to the desired spongidines using directly an amino acid (Route A) and to synthesize the spongidines as well as other derivatives just by modifying the chain used in the alkylation (Route B). Therefore we focused on these two strategies: amino acid coupling followed by aromatization and pyridine preparation followed by N-alkylation.

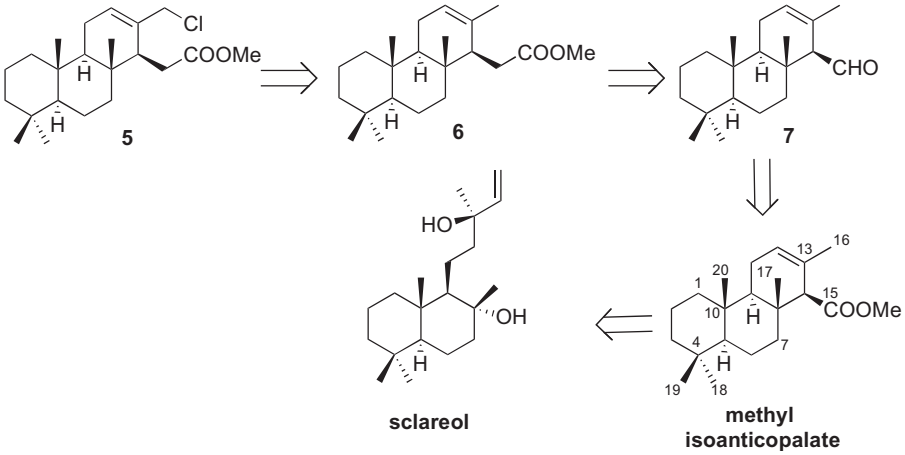


Scheme 1. Retro-synthetic analysis of spongidines A and D.

Intermediate **5** can be synthesized from aldehyde **7** by elongation on C-15 to afford ester **6** and installation of a halogen in C-16 (Scheme 2). Aldehyde **7** is a compound already synthesized in our research group from sclareol,[21] a natural building block successfully used in the synthesis of several natural products. Compound **7** has also been prepared from methyl isoanticopalate.[22]

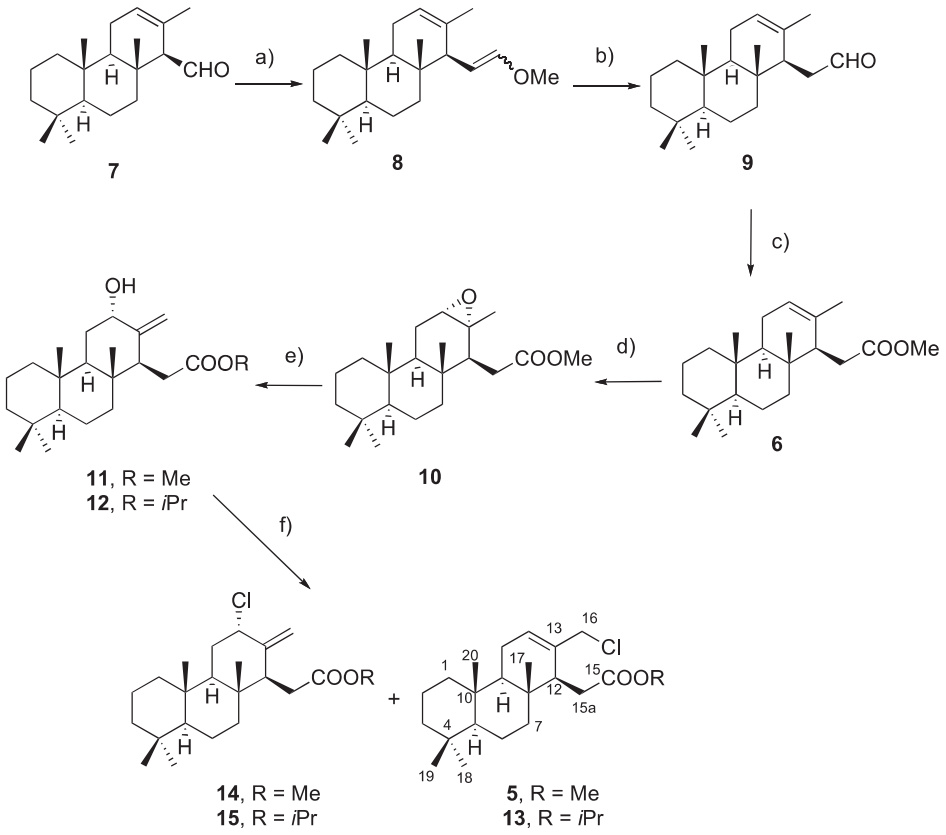
hydrolysis afforded the homologated aldehyde **9** quantitatively. Oxidation and direct esterification of this aldehyde allowed us to get ester **6**, which was then epoxidised diastereoselectively in 98% yield to obtain **10**. With compound **10** in our hands we used a strategy of ring opening followed by an allylic rearrangement to install the chloride atom in the desired position. Epoxide opening was achieved with $Al(^iPrO)_3$[23] yielding the expected allylic alcohol **11** and the unexpected compound **12**, as a result of transesterification. Allylic rearrangement of **11** and **12** was optimized as shown in Table 1.[24] Reaction of **11** in C_6H_6 with a large excess of $SOCl_2$ at 0 °C led to mixture of compounds **5**, result of the expected rearrangement, and **14**, product of direct S_N1 (entry 1). Under the same conditions **12** led to **13** and **15** (entry 2). Nevertheless, we were able to synthesize **5** and **13** in good yield and as the only product when using Et_2O as the solvent, less equivalents of $SOCl_2$ and with a longer reaction time (entries 3 and 4). As compounds **5** and **13** only differentiate in the ester group the strategy does not change and we followed our synthesis with compound **13**.

Once we obtained **13** in good yields we focused on Route A (Scheme 4). We first planned to carry out the strategy developed for the synthesis of decarboxyspongolactmas,[25] optimized in our group. Coupling of an amine with a chloro-ester compound led to



Scheme 2. Retro-synthetic plan of intermediate **5**.

Scheme 3 describes the synthesis of chloroderivative **5**, which started with aldehyde **7**. Wittig reaction of **7** using methoxymethylentriphenylphosphonium chloride led to the corresponding enol ether **8** as a mixture of isomers *E*/*Z* and their subsequent the formation of a pyrrolidinone ring in a single step. However, our first attempts to use glycine or taurine were unsuccessful, due to their insolubility in organic solvents. Therefore we decided to use a derivative, as glycine methyl ester hydrochloride. Reaction of the

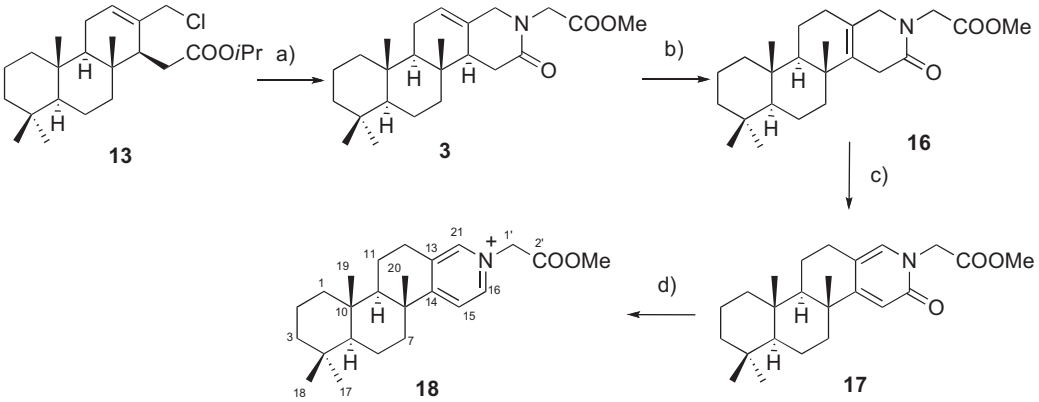


Scheme 3. Reagents and conditions. (a) $MeOCH_2PPh_3Cl$, THF, NaHMDS, −78 °C, 1 h, (80%); (b) *p*-TsOH, acetone, rt, 2 h, (99%); (c) (1) ^tBuOH, 2-methyl-2-butene, NaH_2PO_4, $NaClO_2$, rt, 3 h; (2) $TMSCHN_2$, C_6H_6/MeOH 1:1, 0 °C, 10 min, (85% over two steps); (d) *m*-CPBA, DCM, 0 °C→rt, 2 h, (98%); (e) $Al(^iPrO)_3$, toluene, 150 °C, 16 h, (12% **11**, 50% **12**); (f) See Table 1.

Table 1
Optimization of the allylic rearrangement to get chloroderivatives **5** and **13**

Entry	Compound	Solvent	$SOCl_2$ (equiv)	M	T	Time	Results
1	**11**	C_6H_6	69	0.4	0 °C	10 min	**5** (71%), **14** (24%)
2	**12**	C_6H_6	69	0.4	0 °C	10 min	**13** (69%), **15** (15%)
3	**11**	Et_2O	15	0.02	0 °C	3 h	**5** (80%)
4	**12**	Et_2O	15	0.02	0 °C→rt	3 h	**13** (89%)

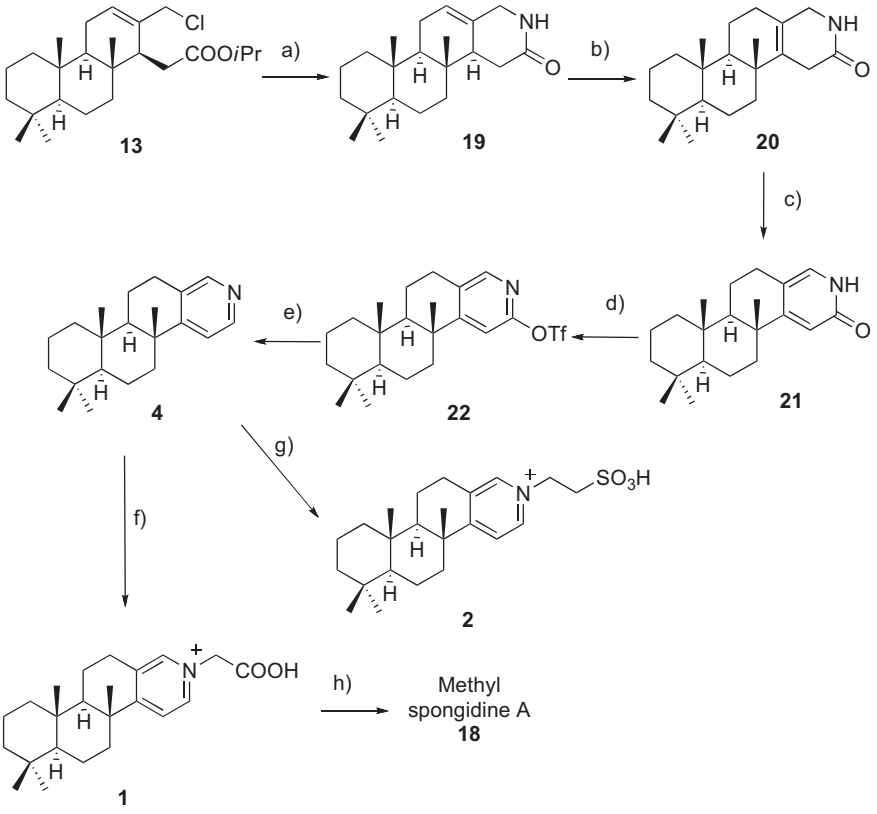
amide[27] (BH_3, 9-BBN, $NaBH_4$ or DIBAL) followed by aromatization did not succeed. However, treatment of **16** with Pd/C[28] in xylene afforded pyridone **17** in moderate yield and recovering starting material. Eventually, aromatization was achieved through a known one-spot strategy.[29] Conversion of pyridone **17** in its chloropyridine derivative followed by reduction with activated Zn yielded the desired methyl ester of the natural compound, spongidine A, **18**. The signals in the pyridine ring appear at 8.61 (s), 8.58 (d) and 7.99



Scheme 4. Reagents and conditions. (a) HCl H_2NCH_2COOMe, Et_3N, MeOH, 50 °C, 16 h, (80%); (b) HI, C_6H_6, 80 °C, 6 h, (91%); (c) Pd/C, xylene, 175 °C, 2 h, (62% **16**, 36% **17**); (d) (1) $POCl_3$, 120 °C, 40 min; (2) Zn, AcOH, 130 °C, 45 min, (75% over two steps).

latter with **13** in MeOH and using Et_3N to neutralize the hydrochloride, led to **3**. The mechanism could be understood by amide formation and S_N2 displacement of the allylic chloride. Isomerization of **3** in acid media led quantitatively to **16**, meanwhile in basic media produced decomposition products. At this point any attempt of aromatization with DDQ[26] failed. Likewise, reduction of the (d) ppm in the ^1H NMR spectrum and the HMBC experiment shows the coupling of H-1′ with C-21 and C-16. Due to problems with the hydrolysis of **18**, we decided to start a new route.

The alternative route from **13** to spongidine A and D is outlined in Scheme 5. Introduction of the nitrogen moiety is performed with NH_4OH,[30] similar to the insertion of the glycine moiety, affording



Scheme 5. Reagents and conditions. (a) NH_4OH, EtOH, 50 °C, 7 h, (73%); (b) HI, C_6H_6, 80 °C, 5 h, (99%); (c) LDA, THF, −78 °C→45 °C, 5 h, (91%); (d) Tf_2O, DCM, pyridine, −78 °C→rt, 2 h, (66%); (e) DMF, Et_3N, $Pd(OAc)_2$, dppf, NH_4O_2CH, 60 °C, 3 h, (67%); (f) $BrCH_2CO_2H$, C_6H_5Br, 85 °C, 24 h, (56%); (g) $BrCH_2CH_2SO_3Na$, DMF, 100 °C, 15 h, (49%); (h) $TMSCHN_2$, C_6H_6/MeOH 1:1, 0 °C, 15 min, (85%).

19. Isomerization of **19** to **20** proceeds quantitatively with HI as before. For the conversion of **20** to **21** several procedures were tried but best results were achieved when **20** was deprotonated with LDA and subsequent air oxidation during reflux (Table 2).[31] Surprisingly, all attempts for the direct transformation of **21** in the pyridine derivative **4**, following same procedure as with **17**, were unsuccessful. Therefore we followed the two steps strategy described by Fischer and Sarpong.[32] Treatment of **21** with Tf_2O led to triflate **22**, which was submitted to a Pd mediated reduction to afford the key compound **4**. Eventually, N-alkylation[33] of **4** with bromoacetic acid and sodium bromoethylensulfonate yielded spongidine A and D, **1** and **2**, respectively, in good yields. Besides, **1** was converted into **18** by esterification, which confirms the structure of these compounds. Spectroscopic data and optical rotation of spongidine A, **1**, and D, **2**, are coincident with those found in literature. ^{1}H NMR signal for C-1′ in **2** is hidden under the solvent signal, but HMBC correlations proved its presence.

Table 2
Optimization of the transformation of **20** in **21**

Entry	Solvent	Base	T	Time (h)	Results
1	Xylene, 0.1 M	10% Pd/C, 125%weight	175 °C	3	**20** (41%), **21** (46%)
2	THF, 0.03 M	NaH, 6 equiv	60 °C	6.5	**20** (48%), **21** (48%)
3	THF, 0.08 M	LDA, 10 equiv	−78→45 °C	5	**21** (91%)

3. Conclusions

First synthesis of spongidine A, **1**, and D, **2**, has been accomplished, from a common pyridine derivative **4**. The structure of these natural compounds has been corroborated and the absolute configuration has been established, since the absolute configuration of the starting compound, sclareol, is known.

We have developed two different alternatives to obtain the peculiar nitrogenated structures. Compound **13** is a key intermediate in our synthesis and an important building block for the preparation of many analogues to carry out SAR studies.

Spongidine A, **1**, and D, **2**, have proven their biological activity as inhibitors of phospholipase A_2, therefore future work will be focused in SAR studies.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BONEM FT MB-100 or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (J) are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as m/z (% rel int.). HRMS was recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

4.2. Wittig reaction of 7

To a suspension of methoxymethyltriphenylphosphonium chloride ($MeOCH_2PPh_3Cl$) (1.08 g, 3.15 mmol) in THF (1.6 mL) at −78 °C under argon atmosphere, 0.6 M in toluene NaHMDS (2.63 mL, 1.58 mmol) was added dropwise and the solution was stirred for 20 min. A solution of aldehyde **7** (229 mg, 0.79 mmol) in THF (0.97 mL) was added via cannula and dropwise and the mixture was stirred for 1 h. It was allowed to warm to room temperature, quenched with aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. After removal of the solvent the residue was purified by column chromatography (Hex/AcOEt 95:5) to afford a mixture of **8a**/**8b** *E*/*Z* 6:4 (202 mg, 0.64 mmol, 80%).

*4.2.1. 15-Methoxy-15a-homo-isoanticopal-12,15-diene (**8**).* IR. (film): 2930, 2848, 1648, 1460, 1387, 1207, 1154, 1043, 939 cm^{-1}; HRMS (EI): calcd for $C_{22}H_{36}O$ (M^+): 316.2563, found 316.0483. *E-isomer*: ^1H NMR (200 MHz) δ: 6.20 (1H, d, *J*=12.4 Hz), 5.44 (1H, br s), 4.54 (1H, dd, *J*=12.4, 10.6 Hz), 3.56 (3H, s), 3.01 (1H, d, *J*=10.6 Hz), 2.10–1.00 (14H, m), 1.53 (3H, s), 0.89 (3H, s), 0.86 (3H, s), 0.82 (3H, s), 0.77 (3H, s); ^{13}C NMR (50 MHz) δ: 148.4, 134.2, 121.9, 106.5, 59.6, 56.8, 55.8, 55.1, 42.2, 41.4, 40.1, 37.6, 36.7, 33.7, 33.4, 23.0, 22.3, 22.0, 19.0, 18.8, 15.9, 15.4; *Z-isomer*: ^1H NMR (200 MHz) δ: 6.04 (1H, d, *J*=6.4 Hz), 5.44 (1H, br s), 4.54 (1H, dd, *J*=10.4, 6.4 Hz), 3.54 (3H, s), 2.21 (1H, d, *J*=10.4 Hz), 2.10–1.00 (14H, m), 1.53 (3H, s), 0.89 (3H, s), 0.86 (3H, s), 0.82 (3H, s), 0.77 (3H, s); ^{13}C NMR (50 MHz) δ: 147.7, 134.1, 121.3, 102.2, 56.6, 56.3, 55.0, 50.7, 42.2, 41.4, 40.1, 37.5, 36.2, 33.7, 33.4, 23.0, 22.3, 22.0, 19.0, 18.8, 15.9, 15.0.

4.3. Hydrolysis of 8

To a solution of **8a**/**8b** (606 mg, 1.92 mmol) in acetone (12.9 mL) *p*-TsOH (330 mg, 1.71 mmol) was added. The reaction mixture was stirred at room temperature and after 2 h the reaction had finished according to TLC. Water was added and it was extracted with EtOAc. The combined organics were washed with 10% $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting crude was purified by column chromatography (Hex/EtOAc 9:1), leading to aldehyde **9** (576 mg, 1.90 mmol, 99%).

*4.3.1. 15a-Homo-isoanticopal-12-en-15-al (**9**).* $[\alpha]_D^{22}$ −9.2 (*c* 0.06, $CHCl_3$); IR. (film): 2931, 2867, 1726, 1458, 1386, 1039, 971 cm^{-1}; ^1H NMR (200 MHz) δ: 9.83 (1H, t, *J*=1.8 Hz), 5.43 (1H, t, *J*=1.21 Hz), 2.52 (1H, s), 2.40 (1H, dd, *J*=6.4, 1.8Hz), 2.38 (1H, dd, *J*=1.8, 6.4 Hz), 2.00–1.05 (14H, m), 1.50 (3H, s), 0.87 (3H, s), 0.84 (3H, s), 0.80 (3H, s), 0.74 (3H, s); ^{13}C NMR (50 MHz) δ: 203.7, 132.9, 123.4, 56.3, 55.0, 49.3, 42.5, 42.1, 41.3, 40.1, 37.4, 36.3, 33.6, 33.3, 23.1, 22.9, 21.9, 19.0, 18.7, 15.8, 15.2; HRMS (EI): calcd for $C_{21}H_{34}O$ (M^+): 302.2610, found 302.2614.

4.4. Oxidation and esterification of 9

To a solution of **9** (285 mg, 0.94 mmol) in ^{t}BuOH (11.3 mL) and 2-methyl-2-butene (3.0 mL), a solution of monobasic sodium phosphate (NaH_2PO_4, 668 mg) in water (4.6 mL) and 25% $NaClO_2$ (2.8 mL, 9.36 mmol) were added. The reaction mixture was stirred for 3 h. Then, water and 2 M HCl were added. It was extracted with EtOAc and the organic layer was washed with water until neutral pH was reached. It was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The obtained acid was directly esterified: the crude was dissolved in C_6H_6/MeOH 1:1 (2.3 mL) and cooled to 0 °C. Under argon atmosphere $TMSCHN_2$ 2.0 M/Et_2O (0.7 mL, 1.4 mmol) was added. After 10 min the solvent was removed under reduced pressure and the resulting crude was purified by column chromatography (Hex/EtOAc 9:1), affording **6** (265 mg, 0.80 mmol, 85%).

*4.4.1. Methyl 15a-homo-isoanticopal-12-en-15-oate (**6**).* $[\alpha]_D^{22}$ −21.0 (*c* 0.19, $CHCl_3$); IR. (film): 2931, 2847, 1740, 1458, 1386, 1252, 1159 cm^{-1}; ^1H NMR (200 MHz) δ: 5.38 (1H, s), 3.67 (3H, s), 2.55–1.05 (14H, m), 2.37 (1H, dd, *J*=16.4, 2.8 Hz), 2.17 (1H, dd, *J*=16.4, 9.8 Hz), 1.77 (1H, t, *J*=2.8 Hz), 1.54 (3H, s), 0.87 (3H, s), 0.85 (3H, s), 0.81 (3H, s), 0.72 (3H, s); ^{13}C NMR (50 MHz) δ: 175.5, 133.6, 122.8, 56.2, 54.9, 51.9, 51.3, 42.1, 40.8, 40.1, 37.4, 36.2, 33.6, 33.3, 32.4, 22.9, 21.9, 21.4, 19.0, 18.7, 15.7, 15.0; HRMS (ESI): calcd for $C_{22}H_{36}O_2Na$ ($M+Na)^+$: 355.2607, found 355.2602.

4.5. Epoxidation of 6

Compound **6** (260 mg, 0.78 mmol) was dissolved in DCM (8.7 mL), cooled to 0 °C and *m*-CPBA (242 mg, 1.40 mmol) was added. The solution was stirred for 14 h and after this time the mixture was diluted with EtOAc. It was washed with 10% Na_2SO_3, 6% $NaHCO_3$ and water until neutral pH. It was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude was purified by column chromatography (Hex/EtOAc 9:1), leading to the epoxide **10** (267 mg, 0.77 mmol, 98%).

*4.5.1. Methyl 12α-13-epoxy-15a-homo-isoanticopal-15-oate (**10**).* $[\alpha]_D^{22}$ −17.0 (*c* 0.10, $CHCl_3$); IR. (film): 2935, 2850, 1733, 1437, 1386, 1235, 1170, 856 cm^{-1}; ^1H NMR (400 MHz) δ: 3.71 (3H, s), 2.97 (1H, dd, *J*=2.8, 1.2 Hz), 2.43 (1H, dd, *J*=16.8, 3.1 Hz), 2.29 (1H, dd, *J*=16.8, 10.8 Hz), 2.07 (1H, dd, *J*=10.8, 3.1 Hz), 1.75–0.90 (14H, m), 1.19 (3H, s), 0.86 (3H, s), 0.82 (3H, s), 0.78 (3H, s), 0.74 (3H, s); ^{13}C NMR (100 MHz) δ: 174.1, 61.0, 58.0, 55.7, 51.9, 51.0, 50.3, 41.6, 40.4, 39.3, 37.1, 35.2, 33.3, 33.0, 31.4, 22.2, 21.7, 21.6, 18.6, 18.4, 15.6, 15.3; HRMS (ESI): calcd for $C_{22}H_{36}O_3Na$ ($M+Na)^+$: 371.2557, found 371.2556.

4.6. Epoxide opening with Al(^{i}PrO)$_3$

To a solution of **10** (285 mg, 0.80 mmol) in toluene (25 mL) Al(^{i}PrO)$_3$ (145 mg, 0.70 mmol) was added. The reaction mixture was stirred at 150 °C under argon atmosphere for 12 h. Then, it was allowed to reach room temperature and it was diluted with Et_2O. The organic mixture was washed with 10% $NaHCO_3$ and saturated NaCl, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude was purified by column chromatography (Hex/EtOAc 8:2), leading to a colourless oil **11**, methyl allylic alcohol (35 mg, 0.10 mmol, 12%) and the transesterified isopropyl allylic alcohol **12** (150 mg, 0.40 mmol, 50%).

*4.6.1. Methyl 12-hydroxy-15a-homo-isoanticopal-13(16)-en-15-oate (**11**).* IR. (film): 3494, 2933, 2847, 1738, 1441, 1386, 1261, 1161, 1043, 970 cm^{-1}; ^1H NMR (200 MHz) δ: 4.97 (1H, s), 4.62 (1H, s), 4.36 (1H, t, *J*=2.8 Hz), 3.64 (3H, s), 2.87 (1H, d, *J*=11.0 Hz), 2.51 (1H, dd, *J*=15.8, 4.0 Hz), 2.34 (1H, dd, *J*=15.8, 11.0 Hz), 1.87 (1H, dt, *J*=13.2, 2.8 Hz), 1.80–1.10 (13H, m), 0.89 (3H, s), 0.80 (3H, s), 0.80 (3H, s), 0.66 (3H, s), −O*H* no visible; ^{13}C NMR (50 MHz) δ: 174.0, 150.6, 109.3, 73.9, 56.6, 52.2, 51.6, 47.8, 42.2, 40.6, 40.1, 39.6, 37.5, 33.4, 33.4, 30.4, 29.7, 21.6, 19.3, 18.8, 16.2, 14.5; HRMS (ESI): calcd for $C_{22}H_{36}O_3Na$ ($M+Na)^+$: 371.2557, found 371.2538.

*4.6.2. Isopropyl 12-hydroxy-15a-homo-isoanticopal-13(16)-en-15-oate (**12**).* $[\alpha]_D^{22}$ +34.4 (*c* 0.45, $CHCl_3$); IR. (film): 3466, 2933, 2870, 1724, 1458, 1386, 1110, 1044, 901 cm^{-1}; ^1H NMR (200 MHz) δ: 5.01 (1H, m), 4.98 (1H, s), 4.61 (1H, s), 4.34 (1H, br s), 2.85 (1H, d, *J*=11.0 Hz), 2.48 (1H, dd, *J*=15.8, 4.0 Hz), 2.30 (1H, dd, *J*=15.8, 11.0 Hz), 1.90–1.10 (14H, m), 1.21 (3H, s), 1.18 (3H, s), 0.85 (3H, s), 0.80 (6H, s), 0.66 (3H, s), −O*H* not visible; ^{13}C NMR (50 MHz) δ: 173.3, 109.5, 105.5, 73.9, 67.6, 56.5, 52.1, 47.6, 42.2, 40.5, 40.0, 39.5,

37.4, 33.5 (×2), 31.0, 29.5, 22.0 (×2), 21.6, 19.2, 18.8, 16.3, 14.6; HRMS (ESI): calcd for $C_{24}H_{40}O_3Na$ $(M+Na)^+$: 399.2870, found 399.2875.

4.7. Allylic rearrangement of 11

Method A: To a solution of **11** (73 mg, 0.21 mmol) in C_6H_6 (0.52 mL) and cooled to 0 °C, $SOCl_2$ (1.06 mL, 14.50 mmol) was added. The reaction mixture was stirred in anhydrous atmosphere for 10 min. Then, ice was added and it was extracted with Et_2O. The combined organics were washed with 10% $NaHCO_3$ and brine and dried over Na_2SO_4. It was concentrated under reduced pressure and the resulting crude was purified by column chromatography (Hex/EtOAc 8:2). Chloroderivative **5** (55 mg, 0.15 mmol, 71%) and chloroderivative **14** (18 mg, 0.05 mmol, 24%) were obtained.

Method B: 65 mg (0.19 mmol) of **11** were dissolved in ether (9.5 mL) and cooled to 0 °C, $SOCl_2$ (0.22 mL, 2.89 mmol) was added and the reaction mixture was stirred at room temperature. After 3 h the reaction had finished according to TLC. $NaHCO_3$ (10%) was added and it was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (Hex/EtOAc 9:1) affording the chloroderivative **5** (55 mg, 0.15 mmol, 80%).

*4.7.1. Methyl 16-chloro-15a-homo-isoanticopal-12-en-15-oate (**5**).* IR. (film): 2932, 2868, 2847, 1738, 1461, 1435, 1387, 1261, 1160, 1030 cm^{-1}; ^1H NMR (200 MHz) δ: 5.89 (1H, s), 4.16 (1H, d, J=11.2 Hz), 3.96 (1H, d, J=11.2 Hz), 3.70 (3H, s), 3.05–2.90 (1H, m), 2.70–2.20 (2H, m), 2.10–1.10 (14H, m), 0.91 (3H, s), 0.88 (3H, s), 0.84 (3H, s), 0.81 (3H, s); ^{13}C NMR (50 MHz) δ: 175.0, 134.7, 130.6, 56.1, 54.4, 52.1, 49.1, 48.9, 42.0, 40.5, 39.9, 37.4, 36.5, 33.6, 33.5, 31.7, 23.2, 21.9, 18.9, 18.7, 15.8, 14.9; HRMS (ESI): calcd for $C_{22}H_{35}O_2NaCl$ $(M+Na)^+$: 389.2218, found 389.2212.

*4.7.2. Methyl 12-chloro-15a-homo-isoanticopal-13(16)-en-15-oate (**14**).* IR. (film): 2932, 2868, 2847, 1738, 1461, 1435, 1387, 1261, 1160, 1030 cm^{-1}; ^1H NMR (200 MHz) δ: 5.06 (1H, d, J=1.2 Hz), 4.83 (1H, s), 4.70 (1H, d, J=1.8 Hz), 3.69 (3H, s), 2.98 (1H, d, J=10.2 Hz), 2.50 (1H, dd, J=15.8, 4.2 Hz), 2.34 (1H, dd, J=15.8, 10.2 Hz), 2.05–1.05 (14H, m), 0.96 (3H, s), 0.81 (3H, s), 0.81 (3H, s), 0.68 (3H, s); ^{13}C NMR (50 MHz) δ: 173.8, 147.8, 110.7, 63.8, 56.4, 52.4 (×2), 51.9, 42.0, 40.2, 39.8, 39.6, 37.4, 33.5 (×2), 30.5, 29.9, 21.6, 18.7, 18.5, 15.6, 15.0; HRMS (ESI): calcd for $C_{22}H_{35}O_2NaCl$ $(M+Na)^+$: 389.2218, found 389.2212.

4.8. Allylic rearrangement of 12

Method A: To a solution of **12** (86 mg, 0.23 mmol) in C_6H_6 (0.57 mL) and cooled to 0 °C, $SOCl_2$ (1.21 mL, 15.9 mmol) was added. The reaction mixture was stirred in anhydrous atmosphere for 10 min. Then, ice was added and it was extracted with Et_2O. The combined organics were washed with 10% $NaHCO_3$ and brine and dried over Na_2SO_4. It was concentrated under reduced pressure and the resulting crude was purified by column chromatography (Hex/EtOAc 8:2). Chloroderivative **13** (63 mg, 0.16 mmol, 69%) and chloroderivative **15** (14 mg, 0.03 mmol, 15%) were obtained.

Method B: 115 mg (0.30 mmol) of **12** were dissolved in 15 mL ether and cooled to 0 °C, $SOCl_2$ (0.35 mL, 4.57 mmol) was added and the reaction mixture was stirred at room temperature until the reaction had finished according to TLC. Then 10% $NaHCO_3$ was added and it was extracted with EtOAc. The organic layer was washed with brine until neutral pH was reached. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (Hex/EtOAc 9:1) affording the chloroderivative **13** (105 mg, 0.25 mmol, 89%).

*4.8.1. Isopropyl 16-chloro-15a-homo-isoanticopal-12-en-15-oate (**13**).* $[\alpha]_D^{22}$ +12.5 (c 0.06, $CHCl_3$); IR. (film): 2963, 2929, 2850, 1725, 1372, 1262, 1110, 1024, 801 cm^{-1}; ^1H NMR (200 MHz) 5.89 (1H, t, J=2.4 Hz), 5.02 (1H, m), 4.15 (1H, d, J=11.4 Hz), 3.97 (1H, d, J=11.4 Hz), 2.66 (1H, br s), 2.43 (1H, dd, J=16.0, 4.0 Hz), 2.33 (1H, dd, J=16.0, 10.0 Hz), 2.10–1.10 (14H, m), 1.26 (3H, d, J=1.6 Hz), 1.23 (3H, d, J=1.6 Hz), 0.88 (3H, s), 0.85 (3H, s), 0.81 (3H, s), 0.73 (3H, s); ^{13}C NMR (50 MHz) δ: 174.0, 134.8, 130.5, 68.2, 56.1, 54.4, 49.0, 48.8, 42.0, 40.6, 39.9, 37.4, 36.5, 33.6 (×2), 32.2, 23.2, 22.0 (×2), 21.9, 18.9, 18.7, 15.8, 15.0; HRMS (ESI): calcd for $C_{24}H_{39}O_2NaCl$ $(M+Na)^+$: 417.2531, found 417.2527.

*4.8.2. Isopropyl 12-chloro-15a-homo-isoanticopal-13(16)-en-15-oate (**15**).* IR. (film): 2932, 2848, 1729, 1387, 1260, 1162, 1110, 909 cm^{-1}; ^1H NMR (200 MHz) 5.06 (1H, s), 4.99 (1H, m), 4.83 (1H, s), 4.73 (1H, s), 2.96 (1H, d, J=11.0 Hz), 2.50 (1H, dd, J=15.6, 4.0 Hz), 2.28 (1H, dd, J=15.6, 11.0 Hz), 2.08–1.20 (14H, m), 1.21 (3H, d, J=4.6 Hz), 1.18 (3H, d, J=4.6 Hz), 0.87 (3H, s), 0.81 (6H, s, Me-18), 0.67 (3H, s); ^{13}C NMR (50 MHz) δ: 172.8, 147.7, 110.7, 67.8, 65.6, 56.4, 52.4, 47.6, 42.0, 40.3, 39.8, 39.5, 37.4, 33.5 (×2), 31.7, 31.2, 22.0, 21.9, 21.6, 19.2, 18.7, 16.6, 15.0; HRMS (ESI): calcd for $C_{24}H_{39}O_2NaCl$ $(M+Na)^+$: 417.2531, found 417.2538.

4.9. Reaction of 13 to yield 3

Glycine methyl ester hydrochloride (484 mg, 3.86 mmol) was dissolved in MeOH (1.4 mL) and Et_3N (0.54 mL, 3.86 mmol) was added. To this colourless solution chloroderivative **5** (138 mg, 0.34 mmol) in DCM/MeOH 8:2 was added via cannula. The reaction mixture was heated at 50 °C under inert atmosphere and the reaction progress was controlled by TLC. After 16 h the solvent was evaporated and the residue was re-dissolved in water. It was extracted with EtOAc and the combined organics were washed with 2M HCl, 10% $NaHCO_3$ and brine. It was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by column chromatography (Hex/EtOAc 7:3), leading to **3** (106 mg, 0.26 mmol, 80%).

*4.9.1. Methyl 2-(spongid-12-en-16-one) acetate (**3**).* $[\alpha]_D^{22}$ −100.0 (c 0.06, $CHCl_3$); IR (film): 2930, 2847, 1752, 1666, 1478, 1438, 1210, 1180, 1005 cm^{-1}; ^1H NMR (400 MHz) δ: 5.53 (1H, t, J=2.1 Hz), 4.28 (1H, d, J=17.4 Hz), 4.06 (1H, dd, J=15.2, 2.1 Hz), 3.99 (1H, d, J=17.4 Hz), 3.80 (1H, d, J=15.2 Hz), 3.72 (3H, s), 2.44 (1H, dd, J=14.2, 4.4 Hz), 2.30–1.10 (15H, m), 2.16 (1H, dd, J=14.2, 12.0 Hz), 0.90 (3H, s), 0.86 (3H, s), 0.82 (3H, s), 0.76 (3H, s); ^{13}C NMR (100 MHz) δ: 173.1, 169.7, 130.1, 120.6, 56.3, 54.4, 52.3, 52.1, 48.5, 47.8, 41.8, 40.2, 39.7, 37.2, 35.1, 33.4, 33.1, 31.5, 22.6, 21.6, 18.5, 18.4, 15.5, 14.2; HRMS (ESI): calcd for $C_{24}H_{37}NO_3Na$ $(M+Na)^+$: 420.2666, found 410.2653.

4.10. Isomerization of 3 with HI

To a solution of **3** (92 mg, 0.24 mmol) in C_6H_6 (8.0 mL), HI 57% (0.30 mL, 1.44 mmol) was added. The reaction mixture was stirred at 80 °C under argon atmosphere for 6 h. Then, it was allowed to reach room temperature and water was added. It was extracted with EtOAc and the organic layer was washed with 10% $NaHSO_3$, 10% $NaHCO_3$ and brine. It was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude was purified by column chromatography (Hex/EtOAc 7:3), to afford **16** (84 mg, 0.22 mmol, 91%).

*4.10.1. Methyl 2-(spongid-13-en-16-one) acetate (**16**).* $[\alpha]_D^{22}$ −25.1 (c 0.35, $CHCl_3$); IR. (film): 2928, 2848, 1753, 1658, 1462, 1368, 1208, 1180 cm^{-1}; ^1H NMR (400 MHz) δ: 4.20 (1H, d, J=17.2 Hz), 4.13 (1H, d, J=17.2 Hz), 3.82–3.62 (2H, m), 3.73 (3H, s), 2.92 (2H, s), 1.94 (2H, d, J=7.6 Hz), 1.55–1.05 (14H, m), 0.99 (3H, s), 0.85 (3H, s), 0.84 (3H, s), 0.81 (3H, s); ^{13}C NMR (100 MHz) δ: 169.4, 169.4, 134.6, 120.5,

56.4, 55.8, 53.6, 52.1, 47.4, 42.0, 39.6, 37.7, 37.4, 37.2, 33.2 (×2), 30.9, 29.0, 22.6, 20.4, 18.6, 18.5, 17.1, 16.4; HRMS (ESI): calcd for $C_{24}H_{37}NO_3Na$ $(M+Na)^+$: 420.2666, found 410.2676.

4.11. Reaction of 16 to yield 17

To a solution of **16** (20 mg, 0.05 mmol) in xylene (0.4 mL) 10% Pd/C (25 mg) was added. The reaction mixture was stirred under argon atmosphere at 175 °C for 2 h. Then it was allowed to reach room temperature and it was diluted with EtOAc. The mixture was filtered over Celite® eluting with EtOAc. The solvent was evaporated and crude was purified by chromatography (Hex/EtOAc: 7:3 and 4:6). Remaining starting product was recovered **16** (12 mg, 0.031 mmol, 62%), and the desired product **17** (7 mg, 0.018 mmol, 36%) was obtained.

*4.11.1. Methyl 2-(spongida-13(21),14-dien-16-one) acetate (**17**).* $[\alpha]_D^{22}$ −62.5 (*c* 0.04, $CHCl_3$); IR. (film): 2925, 2852, 1752, 1664, 1587, 1457, 1261, 1026, 800 cm^{-1}; ^1H NMR (200 MHz) δ: 6.88 (1H, s), 6.46 (1H, s), 4.64 (1H, d, *J*=16.7 Hz), 4.55 (1H, d, *J*=16.7 Hz), 3.78 (3H, s), 2.73 (1H, ddd, *J*=16.2, 6.9, 2.8 Hz), 2.54 (1H, ddd, *J*=16.2, 8.4, 1.6 Hz), 2.50–1.10 (14H, m), 1.18 (3H, s), 0.91 (3H, s), 0.88 (3H, s), 0.84 (3H, s); ^{13}C NMR (50 MHz) δ: 168.5, 165.9, 162.5, 134.2, 115.1, 114.4, 56.0, 53.7, 52.6, 49.8, 41.8, 39.7, 39.6, 38.6, 37.9, 33.3, 33.2, 25.9, 25.0, 21.4, 18.8, 18.5, 17.6, 16.2; HRMS (ESI): calcd for $C_{24}H_{35}NO_3Na$ $(M+Na)^+$: 408.2509, found 408.2513.

4.12. Aromatization of 17 to yield 18

Pyridone **17** (7 mg, 0.018 mmol) was dissolved in $POCl_3$ (0.12 mL, 1.3 mmol) and the reaction mixture was stirred under argon atmosphere at 120 °C. After 40 min the solvent was evaporated affording a brownish residue, which was dissolved in acetic acid (0.39 mL) and activated Zn (12 mg, 0.18 mmol) was added. The reaction mixture was stirred under argon atmosphere at 130 °C for 45 min. Then, it was allowed to reach room temperature and the mixture was filtered over Celite®, eluting with EtOAc. The solvent was removed under reduced pressure and the crude was purified by column chromatography (DCM/MeOH 8:2).

*4.12.1. Methyl spongidine A (**18**).* $[\alpha]_D^{22}$ −20.7 (*c* 0.13, $CHCl_3$); IR. (film): 3518, 3448, 2927, 2867, 2867, 1754, 1627, 1463, 1441, 1237, 735 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 8.61 (1H, s), 8.58 (1H, d, *J*=6.7 Hz), 7.99 (1H, d, *J*=6.7 Hz), 5.46 (2H, d, *J*=5.7 Hz), 3.85 (3H, s), 3.16 (1H, dd, *J*=18.1, 6.1 Hz), 2.98 (1H, ddd, *J*=18.1, 9.4, 3.5 Hz), 2.60–2.45 (1H, m), 2.10–1.10 (13H, m), 1.31 (3H, s), 1.01 (3H, s), 0.92 (3H, s), 0.91 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 171.8, 168.0, 146.6, 143.7, 138.1, 125.0, 60.7, 57.0, 54.3, 53.8, 42.9, 40.9, 40.6, 40.0, 39.0, 34.1, 33.6, 28.4, 25.4, 21.7, 19.7, 19.4, 17.6, 16.8; HRMS (EI): calcd for $C_{24}H_{36}NO_2$ (M^+): 370.2741, found 370.2749.

4.13. Reaction of 13 to yield 19

To a solution of chloroderivative **13** (168 mg, 0.42 mmol) in EtOH (6 mL), NH_4OH 28% (1.8 mL) was added and the reaction mixture was stirred at 50 °C for 7 h. Then the solvent was evaporated and the residue was re-dissolved in EtOAc. It was washed with brine and dried over anhydrous Na_2SO_4. It was concentrated under reduced pressure affording a crude, which was purified by column chromatography (Hex/EtOAc 1:1). Compound **19** (96 mg, 0.30 mmol, 73%) was obtained.

*4.13.1. Spongid-12-en-16-one (**19**).* $[\alpha]_D^{22}$ −59.4 (*c* 0.16, $CHCl_3$); IR. (film): 3204, 2921, 2843,1653, 1478, 1436, 1383, 992 cm^{-1}; ^1H NMR (400 MHz) δ: 5.85 (1H, br s), 5.54 (1H, t, *J*=2.2 Hz), 3.88 (1H, d, *J*=16.4 Hz), 3.83 (1H, d, *J*=16.4 Hz), 2.36 (1H, dd, *J*=14.6, 4.8 Hz), 2.09 (1H, dd, *J*=14.6, 11.8 Hz), 2.30–1.05 (15H, m), 0.90 (3H, s), 0.86 (3H, s), 0.82 (3H, s), 0.82 (3H, s); ^{13}C NMR (100 MHz) δ: 175.0, 129.9, 120.8, 56.5, 54.6, 48.4, 45.4, 41.8, 40.2, 39.7, 37.2, 35.3, 33.4, 33.1, 31.1, 22.7, 21.6, 18.5, 18.4, 15.5, 14.2; HRMS (ESI): calcd for $C_{21}H_{33}NONa$ $(M+Na)^+$: 338.2454, found 338.2469.

4.14. Isomerization of 19 with HI

To a solution of **19** (96 mg, 0.30 mmol) in C_6H_6 (9.6 mL), HI 57% (0.32 mL, 1.52 mmol) was added. The reaction mixture was stirred at 80 °C in argon atmosphere for 5 h. Then, it was allowed to reach room temperature and water was added. It was extracted with EtOAc and the organic layer was washed with 10% $NaHSO_3$, 10% $NaHCO_3$ and brine. It was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography (Hex/EtOAc 8:2) to afford **20** (96 mg, 0.30 mmol, 99%).

*4.14.1. Spongid-13-en-16-one (**20**).* $[\alpha]_D^{22}$ −33.7 (*c* 0.30, $CHCl_3$); IR. (film): 3205, 2993, 2922, 2847, 1673, 1630, 1500, 1458, 1382 cm^{-1}; ^1H NMR (200 MHz) δ: 6.15 (1H, br s), 3.75 (1H, d, *J*=18.0 Hz), 3.67 (1H, d, *J*=18.0 Hz), 2.83 (2H, br s), 2.05–1.05 (16H, m), 1.00 (3H, s), 0.86 (3H, s), 0.85 (3H, s), 0.82 (3H, s); ^{13}C NMR (50 MHz) δ: 171.7, 134.4, 120.8, 56.7, 56.2, 47.4, 42.3, 39.9, 38.0, 37.7, 37.6, 33.5, 33.5, 29.7, 29.1, 21.6, 20.5, 18.8, 18.8, 17.4, 16.7; HRMS (ESI): calcd for $C_{21}H_{33}NONa$ $(M+Na)^+$: 338.2456, found 338.2462.

4.15. Reaction of 20 with LDA to yield 21

To 1.38 mL of THF cooled to −78 °C, $^iPr_2NH$ (0.27 mL, 1.89 mmol) and *n*-BuLi 1.6 N in hexane (1.20 mL, 1.89 mmol) were added and the mixture was stirred under argon atmosphere for 10 min. Compound **20** (54 mg, 0.18 mmol) was dissolved in THF (2.25 mL) and solution was cooled to −78 °C. The prepared LDA (2.85 mL, 0.6 M) was added dropwise via cannula to the solution of **20**. The reaction mixture was stirred at −78 °C for 30 min, then it was allowed to reach room temperature and after that it was stirred at 45 °C during 4 h. After this time the reaction mixture reached room temperature again and saturated NH_4Cl was added. It was extracted with EtOAc and the combined organics were washed with brine. It was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude was purified by column chromatography (DCM/MeOH 98:2) to afford pyridone **21** (21 mg, 0.15 mmol, 91%).

*4.15.1. Spongida-13(21),14-dien-16-one (**21**).* $[\alpha]_D^{22}$ −37.8 (*c* 0.09, $CHCl_3$); IR. (film): 2922, 2850, 1668, 1565, 1469, 1377, 1261, 1060, 876 cm^{-1}; ^1H NMR (400 MHz) δ: 7.02 (1H, br s), 6.45 (1H, br s), 2.73 (1H, dd, *J*=16.6, 5.2 Hz), 2.56 (1H, dd, *J*=16.6, 7.8 Hz), 2.40–1.10 (14H, m), 1.17 (3H, s), 0.94 (3H, s), 0.89 (3H, s), 0.84 (3H, s), N*H* not visible; ^{13}C NMR (100 MHz) δ: 167.4, 165.3, 131.8, 115.9, 113.9, 56.2, 54.1, 42.1, 40.0, 39.8, 39.1, 38.2, 33.5 (×2), 26.2, 25.3, 21.7, 19.1, 18.7, 17.9, 16.5; HRMS (ESI): calcd for $C_{21}H_{31}NONa$ $(M+Na)^+$: 336.2298, found 336.2303.

4.16. Triflate formation of 21

To a solution of pyridone **21** (7 mg, 0.022 mmol) in DCM (0.1 mL) under argon atmosphere, pyridine (0.02 mL) was added. The solution was cooled to −78 °C and Tf_2O (0.01 mL, 0.033 mmol) was added. After 15 min it was allowed to reach room temperature and the reaction mixture was further stirred for 1.5 h. Then it was diluted with hexane and directly filtered in column, eluting with hexane, hexane/Et_2O 1:1 and Et_2O. After collection of the fractions the solvent was evaporated, affording triflate **22** (6.5 mg, 0.015 mmol, 66%).

*4.16.1. Spongida-13(21),14,16-trien-16-trifluoromethansulfonate (**22**).* $[\alpha]_D^{22}$ −84.0 (*c* 0.02, $CHCl_3$); IR. (film): 2925, 2853, 1601, 1471, 1421, 1210, 1134, 940 cm^{-1}; ^1H NMR (200 MHz) δ: 8.02 (1H, s), 6.97 (1H, s), 2.97 (1H, dd, *J*=17.0, 6.0 Hz), 2.77 (1H, ddd, *J*=17.0, 10.0, 4.0 Hz), 2.30–1.00 (14H, m), 1.19 (3H, s), 0.93 (3H, s), 0.88 (3H, s), 0.85 (3H, s); ^{13}C NMR (50 MHz) δ: 164.8, 155.0, 148.9, 132.3, 110.8, 109.5, 56.3, 54.2, 42.1, 39.9, 39.8, 38.9, 37.9, 33.5, 32.2, 27.2, 25.8, 21.6, 19.0, 18.7, 17.4, 16.5; HRMS (ESI): calcd for $C_{22}H_{31}NO_3SF_3$ $(M+Na)^+$: 446.2084, found 446.2063.

4.17. Reaction of triflate 22 to yield 4

To a solution of triflate **22** (6.5 mg, 0.015 mmol) in DMF (0.1 mL) and Et_3N (0.01 mL, 0.07 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), dppf (1.5 mg, 0.003 mmol) and NH_4O_2CH (12 mg, 0.19 mmol) were added. The reaction mixture was stirred under argon atmosphere at 60 °C for 3 h. Then, the solvent was evaporated and the residue was directly purified by chromatography eluting with Et_2O. The solvent was removed under reduced pressure to afford pyridine **4** (3 mg, 0.01 mmol, 67%).

*4.17.1. Spongida-13(21),14,16-triene (**4**).* $[\alpha]_D^{22}$ −76.0 (*c* 0.27, $CHCl_3$); IR. (film): 2924, 2852, 1463, 1379, 1261, 1067, 808 cm^{-1}; ^1H NMR (400 MHz) δ: 8.29 (1H, d, *J*=5.0 Hz), 8.26 (1H, s), 7.10 (1H, d, *J*=5.0 Hz), 2.92 (1H, dd, *J*=16.0, 8.0 Hz), 2.76 (1H, ddd, *J*=16.0, 10.0, 4.0 Hz), 2.35–1.10 (14H, m), 1.18 (3H, s), 0.94 (3H, s), 0.88 (3H, s), 0.86 (3H, s); ^{13}C NMR (100 MHz) δ: 158.7, 150.2, 146.7, 135.2, 125.0, 56.2, 54.5, 41.9, 39.7, 39.6, 37.9, 37.7, 33.7, 33.2, 27.6, 25.6, 21.4, 18.8, 18.5, 17.4, 16.3; HRMS (ESI): calcd for $C_{21}H_{32}N$ $(M+H)^+$: 298.2529, found 298.2532.

4.18. N-Alquilation of 4 with bromoacetic acid

The pyridine derivative **4** (6 mg, 0.02 mmol) was dissolved in C_6H_5Br (0.01 mL) and bromoacetic acid (3 mg, 0.02 mmol) was added. The reaction mixture was stirred under argon atmosphere at 85 °C for 24 h. Then, the solvent was removed under reduced pressure to afford spongidine A, **1** (4 mg, 0.01 mmol, 56%).

*4.18.1. Spongidine A (**1**).* $[\alpha]_D^{22}$ −41.3 (*c* 0.15, MeOH), lit: −16.2 (*c* 0.01, MeOH); IR. (film): 3392, 2925, 2852, 1734, 1645, 1458, 1388, 1260 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 8.60 (1H, s), 8.56 (1H, d, *J*=6.8 Hz), 7.97 (1H, d, *J*=6.8 Hz), 5.38 (2H, s), 3.14 (1H, dd, *J*=18.0, 5.3 Hz), 2.97 (1H, ddd, *J*=18.0, 9.2, 4.0 Hz), 2.52 (1H, d, *J*=12.2 Hz), 2.20–1.10 (13H, m), 1.31 (3H, s), 1.01 (3H, s), 0.90 (6H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 171.6, 168.7, 146.7, 143.7, 138.1, 125.1, 60.9, 57.2, 54.8, 43.0, 41.0, 40.7, 40.1, 39.1, 34.2, 33.7, 28.5, 25.6, 21.8, 19.8, 19.5, 17.7, 16.9; HRMS (ESI): calcd for $C_{23}H_{34}NO_2$ $(M+H)^+$: 356.2584, found 356.2581.

4.19. N-Alquilation of 4 with sodium bromoethanesulfonate

The pyridine derivative **4** (6 mg, 0.02 mmol) was dissolved in DMF (0.01 mL) and sodium bromoethanesulfonate (4.5 mg, 0.02 mmol) was added. The reaction mixture was stirred under argon atmosphere at 100 °C for 15 h. Then, the solvent was removed under reduced pressure and 2 N HCl was added to the resulting residue until acid pH was reached. Concentration under vacuum followed by purification by column chromatography (DCM/MeOH 9:1) afforded spongidine D, **2** (4 mg, 0.01 mmol, 49%).

*4.19.1. Spongidine D (**2**).* $[\alpha]_D^{22}$ −10.1 (*c* 0.02, MeOH), lit: −6 (*c* 0.02, MeOH); IR. (film): 3445, 2924, 2859, 1640, 1463, 1195, 1054 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 8.65 (1H, s), 8.62 (1H, d, *J*=6.6 Hz), 7.87 (1H, d, *J*=6.6 Hz), 4.82 (1H, t, *J*=6.2 Hz), 3.39 (1H, t, *J*=6.2 Hz), 3.19 (1H, dd, *J*=19.1, 6.7 Hz), 2.95 (1H, m), 2.10–1.10 (13H, m), 1.28 (3H, s), 1.00 (3H, s), 0.90 (6H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 171.0, 146.0, 142.8, 137.9, 124.9, 58.0, 57.3, 54.8, 51.6, 43.0, 40.7, 40.3, 40.1, 39.0, 34.2, 33.7, 28.4, 25.5, 21.8, 19.8, 19.5, 17.8, 16.8; HRMS (ESI): calcd for $C_{23}H_{36}NO_3NaS$ $(M+Na)^+$: 429.2230, found 429.2249.

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