ChemPubSoc Europe

DOI: 10.1002/ejoc.201800047

EurJOC European Journal of Organic Chemistry

Full Paper

Marine Natural Products | *Very Important Paper* |

A Ring-Distortion Strategy from Marine Natural Product Ilimaquinone Leads to Quorum Sensing Modulators

Laurent Evanno,*[a] David Lachkar,[a] Assia Lamali,[a] Asmaa Boufridi,[a] Blandine Séon-Méniel,[a] Florent Tintillier,[b] Denis Saulnier,[c] Stéphanie Denis,[a] Grégory Genta-Jouve,[d] Jean-Christophe Jullian,[a] Karine Leblanc,[a] Mehdi A. Beniddir,[a] Sylvain Petek,[e] Cécile Debitus,[e] and Erwan Poupon*[a]

Abstract: We report herein a ring-distortion strategy applied to marine natural substances ilimaquinone and 5-*epi*-ilimaquinone. A chemically diverse library of molecules was synthesised that included rearrangements of the sesquiterpene moiety and original reorganisations of the quinone ring. Chemoinformatic analyses evaluated the rise of structural diversity and the exploration of chemical space. Some focussed biological activities of this library were also investigated; quorum sensing activity of *Vibrio harveyi* was envisaged and some of the new compounds were shown to be good quorum sensing inhibitor candidates, whereas others were activators. Toxicities were also evaluated and some products showed micromolar activities against human umbilical vein endothelium, human hepatocellular carcinoma and human lung carcinoma (A549) cells.

Introduction

The design of small-molecule libraries with structural diversity is a current challenge for drug discovery. Natural products are an impressive source of complex scaffolds and inspiration for the discovery of new lead structures for future small molecule based drugs.[1,2] Complementary to natural products isolation[3] and total synthesis,[4] synthetic methods have been developed, such as diversity-oriented synthesis (DOS),[5] biology-oriented synthesis,[6] skeletal diversifications or synthesis of natural product inspired scaffolds. Recently, Hergenrother and co-workers developed an elegant ring distortion strategy, called "complexity-to-diversity (CtD)", based on efficient and straightforward reaction sequences to alter molecular ring systems.[7] This strategy ideally generates libraries of complex molecules through ring contraction, ring aromatisation, ring fusion, ring expansion and ring cleavage reactions from readily available natural products. Gibberellic acid, adrenosterone, quinine, pleuromutilin, abietic acid,[8] sinomenine[9] and yohimbine[10] are some examples of compounds that went through the strategy to generate structural diversity. To date, no marine natural product has been investigated by this approach. As part of a program of valorisation of French Polynesia biodiversity, a DOS project from an abundant marine natural product was selected. Isolated in high yields from *Dactylospongia metachromia*, ilimaquinone (**1**)[11] and its isomer 5-*epi*-ilimaquinone (**2**)[12] were chosen as suitable starting materials because the sponge is common all over the French Polynesian atolls.[13,14] Notably, ilimaquinone (**1**) is a highly bioactive molecule that displays cytotoxic,[15] anti-HIV[16] and anti-inflammatory activities;[17] in addition it causes an impressive fragmentation of Golgi apparatus.[18]

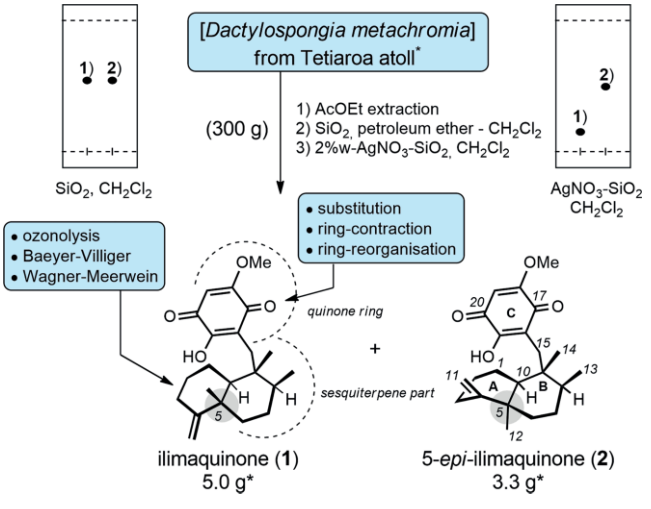


Figure 1. Isolation of ilimaquinone (**1**) and 5-*epi*-ilimaquinone (**2**) and diversification plans. * isolation ratio varies depending on the sample collection area (see ref.[13a]).

[a] *BioCIS, Université Paris-Sud, Université Paris-Saclay, CNRS, 92290 Châtenay-Malabry, France*
E-mail: laurent.evanno@u-psud.fr
erwan.poupon@u-psud.fr
http://www.biocis.u-psud.fr/
[b] *EIO, UPF-IRD-Ifremer, Institut Louis Malardé, IRD, BP529, 98713 Papeete, Tahiti, Polynésie française*
[c] *EIO, IRD-UPF-Ifremer, Institut Louis Malardé, Ifremer, BP 49, 98719 Taravao, Tahiti, Polynésie française*
[d] *Dr Grégory Genta-Jouve, Laboratoire de Chimie-Toxicologie Analytique et Cellulaire (C-TAC), Université Paris Descartes, UMR CNRS 8638 COMETE, 4 Avenue de l'observatoire 75006 Paris, France*
[e] *LEMAR, IRD-UBO-CNRS-IFREMER, IUEM, rue Dumont d'Urville, 29280 Plouzané, France*
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800047.

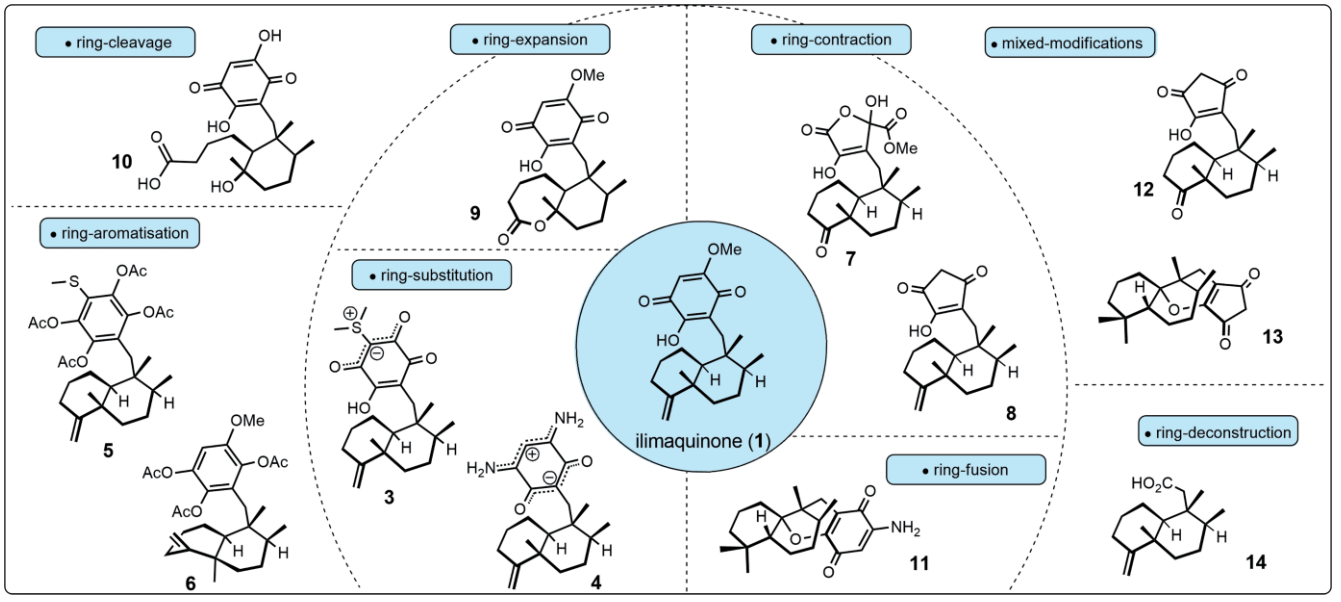


Figure 2. Overview of scaffolds generated from ilimaquinone (**1**) and 5-*epi*-ilimaquinone (**2**).

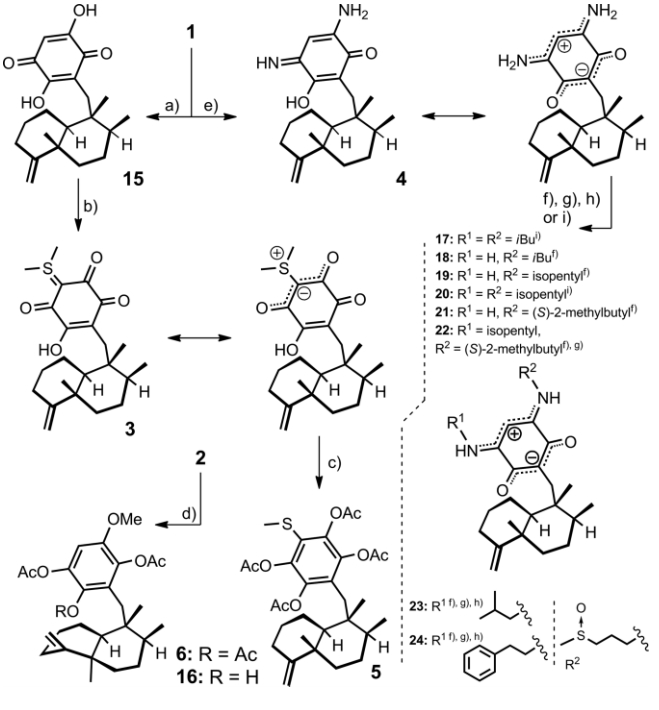
Compounds **1** and **2** were obtained on a gram scale from the freeze-dried sponge through a solid-liquid extraction with ethyl acetate, a single flash chromatography with silica gel and further resolution of the two diastereomers by using 2 %/w silver nitrate impregnated silica gel (Figure 1).[13a,19] Structurally, ilimaquinone (**1**) and 5-*epi*-ilimaquinone (**2**) are made up of a sesquiterpene domain connected to a penta-substituted quinone. The CtD strategy was applied to ilimaquinone (**1**)[20] and 5-*epi*-ilimaquinone (**2**) to generate a library of molecules with modified scaffolds in a limited number of steps (3 maximum).

The quinone moiety was modified furnishing π-delocalised sulfur ylide **3**, zwitterionic biscyanine **4** and aromatic rings **5** and **6** (Figure 2). Special attention was paid to the original reactivities that led to ring contractions of the quinone ring (compounds **7** and **8**). The sesquiterpene moiety was cleaved by using a one-pot ozonolysis/Baeyer–Villiger reaction followed by a saponification (compounds **9** and **10**). It was also possible to fuse the decalin and quinone rings by using Wagner–Meerwein shifts (compound **11**). Combined modifications of both the quinone and the decalin moieties were also performed (compounds **12** and **13**). More than thirty compounds were synthesised and evaluated for their biological properties against human umbilical vein endothelium (HUVEC), human hepatocellular carcinoma (Hep-G2) and human lung carcinoma (A549) cells. Importantly, some of these new compounds were good quorum sensing modulators in specific screening in connection with marine environment issues.

Results and Discussion

Quinone Substitutions

To start our investigations (Scheme 1), the quinone ring of **1** or **2** was reduced into an aromatic ring or converted into π-delocalised ring systems. The demethylation of **1** by sodium hydroxide in ethanol at reflux temperatures gave *O*-desmethylilimaquinone (**15**) in quantitative yield. As we will discuss below, this compound presents enhanced reactivity relative to **1**. Treatment of **15** with dimethyl sulfoxide (DMSO) and acetic anhydride produced stable π-delocalised sulfur-ylide **3** in 50 %



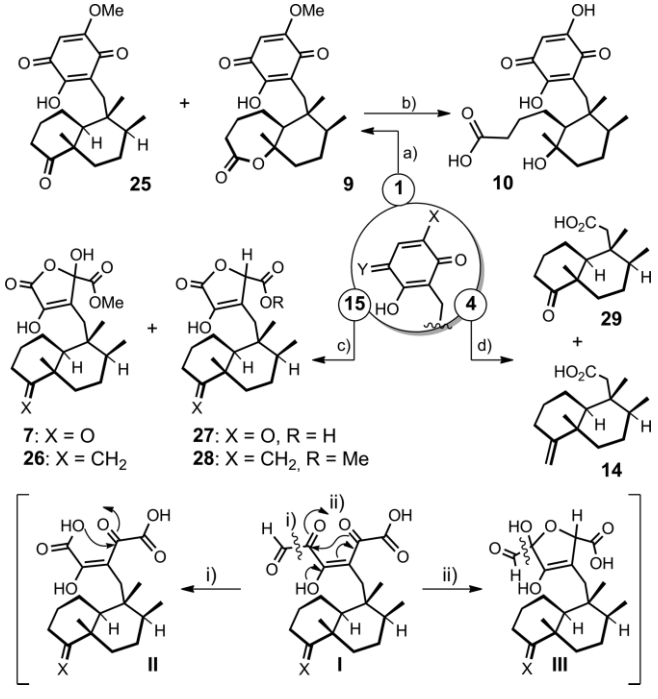
Scheme 1. Synthesis of aromatic and π-delocalised rings from **1** and **2**. Reaction conditions: a) aq. NaOH (2 M), EtOH, reflux, 97 %; b) Ac_2O, DMSO, 70 °C, 50 %; c) Ac_2O, Zn, NEt_3, 40 °C, 67 %; d) Ac_2O, Zn, NEt_3, 40 °C, (**6**: 80 %, **16**: 16 %); e) CH_3CN/NH_3(35 %) 1:1, 55 °C (smenospongine: 16 %, **4**: 65 %); f) R^1NH_2 (1 equiv.), CH_3CN, 35 °C (85–90 %); g) R^2NH_2 (1 equiv.), CH_3CN, 35 °C (**22**: 86 %); h) oxone®, CH_3CN, H_2O (80 %, 2 steps); i) RNH_2 (2 equiv.), CH_3CN, 35 °C (85–90 %).

yield.[21,22] Reduction of this ylide by zinc powder in acetic anhydride (catalytic amount of trimethylamine)[23] resulted in the formation of thio-substituted aromatic compound **5**. Similar reduction performed on **2**, furnished compounds **6** and **16** in 80 and 16 % yield, respectively. During the investigation of the quinone reactivity, it was discovered that treatment of **1** with aqueous ammonia in acetonitrile resulted in the isolation of an original π-delocalised blue dye **4** in 63 % yield.[24]

Recently, by using **4** as a "phishing probe", we reported the isolation of zwitterionic dactylocyanines A–H (**17**–**24**) from *D. metachromia* by using a "molecular networking" based dereplication approach.[25] Natural products **17**–**24** could be synthesised from **4** by sequential transamination followed by an oxone®-mediated oxidation of a thioether side chain for compounds **23** and **24**.

Ozone-Mediated Transformations

Inspired by the structures of dactylolactones,[26] we sought to modify the quinone moiety by ozonolysis (Scheme 2). The reaction was investigated on compounds **1**, **4** and **15**. Performed on ilimaquinone (**1**), the reaction led to formation of ketone **25** and lactone **9** in 49 and 15 % yield, respectively. Formation of "abnormal" ozonolysis product **9** is rationalised by a Baeyer–Villiger oxidation of ketone **25**.[27] Then, saponification of lactone **9** with sodium hydroxide in ethanol furnished compound **10** to achieve the A ring opening. Simple demethylation of **1** completely modifies the reactivity of the quinone ring. Contrary to the results observed with **1**, ozone oxidises *O*-desmethyl-

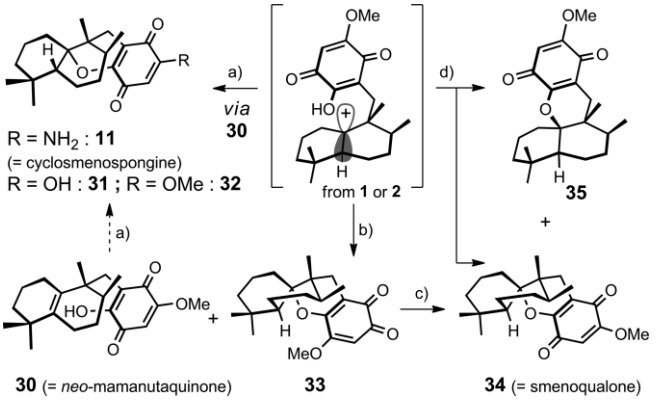


Scheme 2. Ozonolysis of **1**, **4** and **15**. Reaction conditions: a) ozone stream, CH_2Cl_2, –78 °C, then Me_2S, room temp. (**9**: 15 %, **25**: 49 %); b) aq. NaOH (2 M), EtOH, 65 %; c) ozone stream, CH_2Cl_2/MeOH, 1:1, –78 °C, then Me_2S, room temp. (**7**: 6 %, **26**: 2 %, **27**: 13 %, **28**: 4 %); d) ozone stream, MeOH, –78 °C, then Me_2S, room temp. (**29**: 38 %, **14**: 31 %).

ilimaquinone (**15**) into tetronic acids **7** and **26**–**28**. During the reaction, ozonolysis of **15** might produce keto-acid **I** that undergoes oxidative decarbonylation (pathway i, intermediate **II**).[28] Then, cyclisation of intermediate **II** might explain the formation of **7** and **26**. Formation of **27** and **28** is explained by a cyclisation that occurs before the decarbonylation process (pathway ii, intermediate **III**). To the best of our knowledge, this result is the first example of a ring contraction of a quinone with ozone.[29] Performed on blue dye **4** the quinone ring is completely truncated and furnishes **29** and smenospongic acid (**14**).[30] Acid **14** clearly opens prospects for the introduction of alternative aromatic rings through, for example, the Barton-Motherwell reaction.[31]

Ring Fusions

During attempts towards quinone reorganisation of **1** induced by sodium azide in sulfuric acid,[32] a ring-fusion phenomenon was observed (Scheme 3). Cyclosmenospongine (**11**),[33] **31** and **32** were formed stepwise by means of a Wagner–Meerwein shift[34]/olefin addition with a 30 % global yield. Notably, by using Faulkner's conditions, postulated intermediate **30** was isolated[13a,34] alongside *ortho*-quinone **33**.[35] Compound **33** was then converted into two steps into smenaqualone (**34**). Ring fusion performed on **2** in the presence of triflic acid at low temperatures (–50 °C) produced directly smenoqualone (**34**)[36] and isomer **35** through a Wagner–Meerwein shift followed by the direct trapping of the transient carbocation.

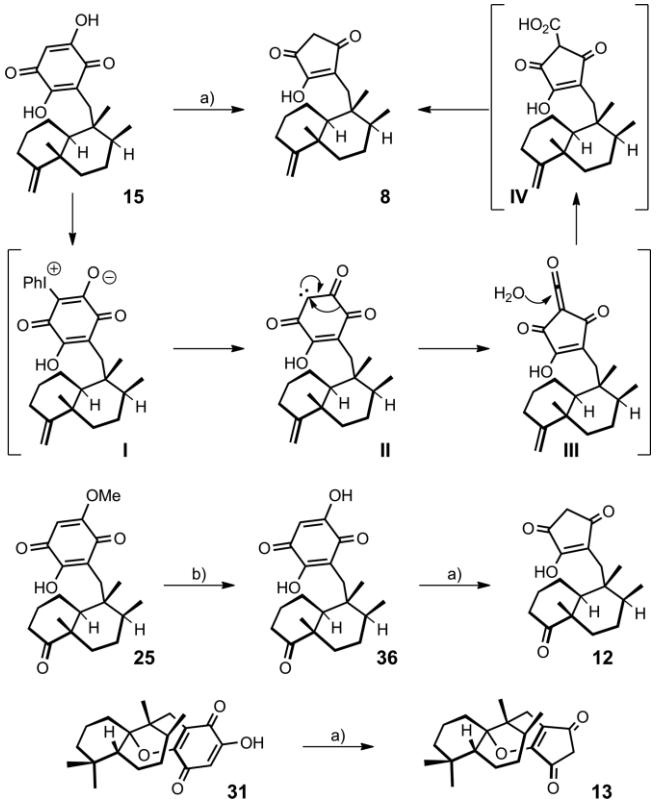


Scheme 3. Ring fusions from **1** and **2**. Reaction conditions: a) **1**, NaN_3, H_2SO_4 conc., (**11**: 13 %, **31**: 13 %, **32**: 4 %); b) **1**, $Et_2O{\cdot}BF_3$, benzene, (**30**: 58 %, **33**: 21 %); c) i) NaOH aq. (10 %), EtOH, reflux, ii) Me_2SO_4, acetone, 80 %; d) **2**, CF_3SO_3H, CH_2Cl_2, – 50 °C, (**34**: 30 %, **35**: 40 %).

Further Ring Contractions

Pursuing the modifications of the quinone ring (Scheme 4), ilimaquinone (**1**) was subjected to the action of phenyliodine(III) diacetate (PIDA) but no reaction was observed. Notably, key intermediate **15** that presents an enhanced reactivity reacts with PIDA in dichloromethane, followed by heating at reflux temperatures in acetonitrile to produce cyclopentenedione **8**[37] related to dactylospongenones[17] and smenohaimines.[38] The postulated mechanism suggests reaction between PIDA and **15**

in dichloromethane forms a phenyliodonium zwitterionic intermediate **I**. Then heating at reflux temperature in acetonitrile causes the elimination of iodobenzene, which leads to ketocarbene **II** that undergoes a ring contraction. Then, ketene **III** reacts with water (intermediate **IV**) and decarboxylates to afford contracted compound **8**.[37b,39] The method is also applicable to compounds **25** (after demethylation) and **31** as products **12** and **13** were obtained in 20 and 48 % yield, respectively, which achieves a noteworthy modification of both quinone and decalin rings.



Scheme 4. Ring contraction of **15**, **25** and **31**. Reaction conditions: a) PIDA, CH_2Cl_2,0 °C then CH_3CN, reflux, (**8**: 37 %, **12**: 20 %, **13**: 48 %); b) aq. NaOH (2 M), EtOH, reflux, 94 %.

Diversity Analysis

A molecular fingerprint of structural distances of the chemolibrary based on Tanimoto coefficient was calculated through chemoinformatic analyses (Figure 3).[40] The average distance for the entire library is 0.57 in a range from 0.14 to 0.85, which reflects a fair structural diversity. The distance matrix was also vectorised into a 3D map by an all-against-all analysis of compounds (Figure 4) that allows us to visualise both the chemical space explored and the clusters of structures. Prepared molecules only share the connectivities of the non-reactive hydrocarbon moiety present in starting material **1**. Aromatic compounds **5**, **6** and **25**, π-delocalised rings **3**, **4** and dactylocyanines A-H (**17**–**25**) constitute localised clusters of structures quite distant from parent molecule **1**. The chemoinformatic analysis identified tetronic acids **7**, **26**–**28** and cyclopentenediones **8**, **12** as two close clusters of structures. Calculations also revealed that isomerisation of the decalin produced a more important structure diversification than the quinone contraction induced by PIDA or ozone as reflected by the localisation of the clusters of structures and the distance index (d **1**–**34** = 0.45; d **1**–**8** = 0.33; d **1**–**26** = 0.36). The chemolibrary analysis is

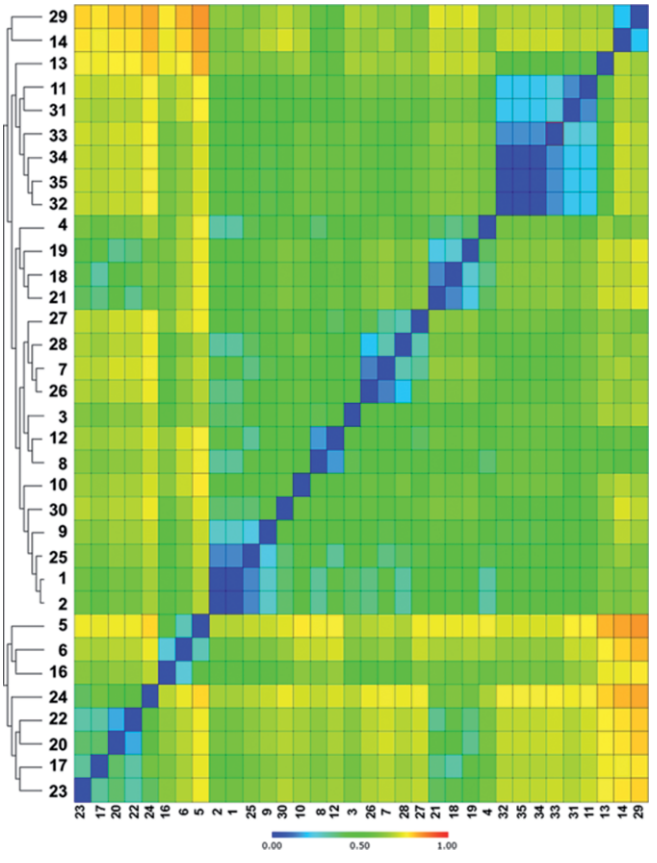


Figure 3. Molecular fingerprint similarity analysis, distance: (1.00 – tanimoto similarity coefficient). Generated with the ChemMine Tools.[40a]

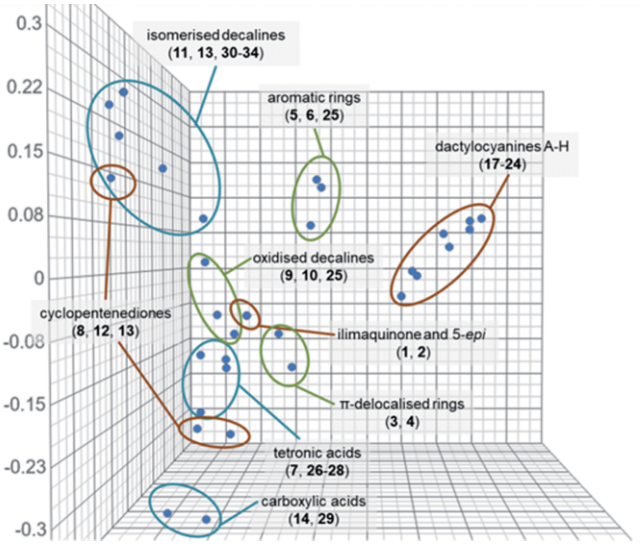


Figure 4. Chemical space of the chemolibrary based on structural distances. Generated with the ChemMine Tools.[40a]

based on the chemical connectivities without consideration of stereochemistry, which explains the failure to identify the 3D distance for structures **32**, **34** and **35** (distance index = 0).

Biological Evaluation: Toxicity

Compounds **1**–**19**, **21**, **23**–**29** and **31**–**32** were evaluated in vitro for their cytotoxic activities against three human cell lines (HUVEC, Hep-G2 and A549) by using doxorubicin as a positive control. Some products showed micromolar cytotoxicities and significant IC_{50} values (<50 μM) are reported in Table 1. Relative to ilimaquinone (**1**) and 5-*epi*-ilimaquinone (**2**), the modification of the quinone ring as π-delocalised ring systems (compound **3**, **4** and dactylocyanines B, C, E: **18**, **19** and **21**) moderately decreases cytotoxicities. Aromatisation of the quinone ring and demethylation (compounds **5**, **6**, **15** and **16**) does not affect significantly the cytotoxicity and IC_{50} are in the same range. When the decalin moiety is modified as found in lactone **9**, acid **10**, ketone **25** or rearranged compounds **11**, **31** and **32**, cytotoxicities significantly decrease and some of those products are considered barely cytotoxic. Truncated compounds **14** and **29**, tetronic acids **7** and **26**–**28** and contracted products **8**, **12** and **13**, are not active against the three cell lines (IC_{50} > 50 μM).

Table 1. Cytotoxicity evaluations, (IC_{50} in μM).

Compound	HUVEC[a]	Hep-G2[b]	A549[c]
1	3.9	6.0	3.3
2	4.7	7.1	4.5
3	27.8	42.3	30.0
4	28.3	33.6	24.6
5	3.6	4.9	4.3
6	0.9	1.9	1.2
9	18.0	43.3	>50
11	24.8	24.6	11.2
15	5.9	8.8	7.0
16	4.5	6.5	3.6
17	11.9	–	10.0
18	29.3	24.1	24.3
19	17.3	17.8	18.4
21	11.3	13.0	13.6
23	>50	>50	13.5
24	8.2	8.3	8.1
25	10.0	40.5	30.0
31	47.2	>50	>50
32	29.0	>50	>50

[a] HUVEC, doxorubicin (10 μM): 30 % cell survival. [b] Hep-G2, doxorubicin (10 μM): 30 % cell survival. [c] A549, doxorubicin (10 μM): 30 % cell survival.

Biological Evaluation: Activities Against *Vibrio harveyi* Quorum Sensing

Vibrio harveyi is an opportunistic pathogen bacterium of tropical marine organisms. This bacterium is known to induce severe economic losses in aquacultured species including farmed bat fish (*Platax orbicularis*) and pearl oysters (*Pinctada margaritifera*) in French Polynesia.[41] Quorum sensing is an intercellular communication[42] used by many bacteria that facilitates a collective organisation and a concerted production of e.g. virulence factors by the population of cells.[43] The establishment of a quorum sensing communication may be evidenced by a bioluminescence phenomenon of the *Vibrio harveyi* strain.[44] Molecules of the chemolibrary (50 μg mL^{-1}) were evaluated as quorum sensing inhibitors. Inhibition was determined by measuring the delay time for the onset of bioluminescence in *Vibrio harveyi* cultures by using a *Leucetta* chagosensis extract as a positive control (Table 2).[45] Ilimaquinone (**1**) and 5-*epi*-ilimaquinone (**2**) proved to be good quorum sensing inhibitors but are also cytotoxic (Table 1). The best delay value (150 min) is observed for molecule **15** that arises from its antibiotic activity.

Table 2. Quorum sensing inhibition evaluations (50 μg mL^{-1}).[a]

Compound	Bacterial growth inhibition	Bioluminescence lag time [min]	*Leucetta* sp. control [min]
1	–	40	70
2	–	30	70
5	–	–20	70
6	–	–10	40
7	–	–30	50
8	–	30	70
9	–	40	40
10	–	–10	70
11	–	20	70
12	–	40	70
13	–	20	70
15	inhibition	150	40
16	–	60	70
17	–	–20	40
18	–	10	70
19	–	10	70
21	–	10	40
23	–	–30	50
24	–	–20	50
25	–	10	40
27	–	–40	50
31	–	10	70
32	–	10	70

[a] *Vibrio haveyi* BB120 wild-type strain.

Compounds **9** and **16** are the best quorum sensing inhibitors of the chemolibrary (Table 2) associated with moderate toxicity for **9** (Table 1). The most promising quorum sensing inhibitor candidates are cyclopentenediones **8**, **12** and **13** because they are equally as good quorum sensing inhibitors as **1** (40 min for **12**), are not cytotoxic and do not display any antibiotic activity. Notably, mono-alkylated dactylocyanines **18**, **19** and **21** are barely inhibitors, whereas di-alkylated members **17**, **23**, and **24** stimulate the bioluminescence phenomenon. Tetronic acids **7** and **27** significantly stimulate quorum sensing by shortening the onset of bioluminescence with advance values of 30 and 40 minutes, respectively. The identification of quorum sensing activators is potentially valuable in strategies that aim to stimulate the host immune system when the pathogen bacterial population is low[46] or as "artificial autoinducers" to study extracellular communication in a chemical ecology context. Compounds **9**, **12** and **16** with the best inhibitions values were chosen and further investigated on three derived mutants kindly provided by Prof. Bassler,[45,47] each of them expresses one of three pathways that control luminescence activity. The selected compounds display better activity on *Vibrio* specific auto-inducers pathways (CAI-1 and HAI-1), especially compound **16**, which is more active than the reference extract, but all display

mild activity on the more general AI-2 pathway (see inhibitions values on *Vibrio harveyi* double mutants in the Supporting information).

Conclusions

In summary, a ring distortion strategy was applied to ilimaquinone (**1**) and 5-*epi*-ilimaquinone (**2**) isolated in high yields from the sponge *D. metachromia*. A chemically diversified chemolibrary was prepared that afforded already known natural products (**11**, **14**, **15**, **30** and **34**), recently described new natural products (**17–24**), known semisynthetic products (**29**, **31**–**33**) and, most importantly, original structures (**3–10**, **12**, **13**, **16**, **25**–**28** and **35**; see references in the Supporting information, Table 1). Products were synthesised in quantities that ranged from 10 mg to 1 gram; a prerequisite to carry out the multistep sequences and biological evaluations. Chemo-informatic calculations of the structure distances based on Tanimoto coefficient indicates a fair diversification with a 0.57 average distance for the entire library. The terpene moiety that contained an olefin as the sole reactive function was modified by a formal Baeyer–Villiger strategy or Wagner–Meerwein shifts to afford a set of diastereomeric fused decalins. The quinone moiety was modified to aromatic or π-delocalised ring systems. In addition, the action of PIDA and ozone shed light on original reactivities of the quinone ring and afforded contracted five-membered rings. Although some chemical transformations, such as Wagner–Meerwein shifts (e.g. **11**) or quinone reductions (e.g. **6**), seemed to reduce reactivity, the introduction of a ketone on the decalin (e.g. **25**) and contracted products (e.g. **7**, **8**) improves the molecular profiles by introducing new patterns of reactivity relative to sparsely functionalised ilimaquinone (**1**). Further prospects could start from these more reactive functionalities introduced on the ilimaquinone scaffold. Cytotoxicity evaluations indicated that compounds with quinone, aromatic or π-delocalised rings systems display IC_{50} values in the micromolar range. Without a quinone moiety compounds lose their cytotoxicity. Compounds of the chemolibrary were also evaluated as quorum sensing inhibitors of an economically important pathogen in French Polynesia. The cyclopentenedione series proved to be as good inhibitors as ilimaquinone (**1**), whereas tetronic acid derivatives significantly stimulated quorum sensing.

Experimental Section

All reactions were carried out under an argon atmosphere. Dichloromethane was distilled under argon over calcium hydride. Tetrahydrofuran was distilled under argon over sodium and benzophenone. Unless otherwise noted, all reagent-grade chemicals and other solvents were obtained from commercial suppliers and were used as received. IR spectra were recorded with a Vector 22 Bruker spectrometer. The NMR spectra were recorded with a Bruker Avance-300 (300 MHz) and Avance-400 (400 MHz) apparatus with [D]chloroform, [D_4]MeOH, [D_3]acetonitrile, and [D_6]DMSO as solvents. HRMS and LC/MS were obtained by using Electrospray Ionisation (ESI) on a Thermoquest TLM LCQ Deca ion-trap spectrometer with a Sunfire® analytical C_{18} column (150 × 2.1 mm; 3.5 μM, Waters) or with a XBridge® C18 column (150 × 2.1 mm; i.d. 3.5 μM). Sunfire® preparative C_{18} columns (150 × 30 mm; i.d. 5 μM, Waters) and XBridge® preparative C_{18} columns (150 × 46 mm; i.d. 5 μM, Waters) were used for preparative HPLC separations by using a Waters Delta Prep equipped with a binary pump (Waters 2525), a UV/Visible diode array detector (190–600 nm, Waters 2996). Medium pressure chromatography was run with an Armen-Spot-Prep® purification system with Grace® flash cartridges (330 g and 40 g; i.d. 40 μM). For silica-gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade. Analytical and preparative TLC were performed with Merck silica gel F254 (230–400 mesh) plates and analysed by direct observation or UV light or by staining upon heating with a vanillin solution (2 g of vanillin, 1 mL of conc. H_2SO_4, 100 mL of EtOH).

Isolation of Ilimaquinone (1) and 5-*epi*-Ilimaquinone (2) from *Dactylospongia metachromia*: Freeze-dried sponge collected from Tetiaroa atoll (300 g) is extracted by stirring in ethyl acetate (1.5 L) for 2 h. The operation is repeated twice on the grounds and combined extracts are concentrated to dryness. The crude extract (≈ 40 g) is fractionated by medium pressure chromatography [Grace® flash cartridges 330 g, eluent gradient: petroleum ether/dichloromethane/methanol, 20:80:0 → 0:1:0 → 0:99:1 (2.5 L, 62 min, 40 mL/min)]. Fraction (≈ 12 g) that contains ilimaquinone (**1**) and 5-*epi*-ilimaquinone (**2**) is purified by flash chromatography with 2 %w-silver nitrate impregnated silica gel (elution gradient: petroleum ether/dichloromethane/methanol, 20:80 → 0:1) to afford 5-*epi*-ilimaquione (**2**; 3.3 g, 1.1 %) and ilimaquinone (**1**; 5.0 g, 1.6 %).

Ilimaquinone (1): R_f: (SiO_2, CH_2Cl_2) = 0.45; ($AgNO_3$-SiO_2, CH_2Cl_2) = 0.12. IR (neat): $\tilde{\nu}_{max}$ = 3331, 2921, 1657, 1642, 1609, 1434 cm^{-1}. ^1H NMR (400 MHz, [D]chloroform): δ = 7.51 (s, OH), 5.83 (s, 1 H, 19-H), 4.42 (br. s, 1 H, 11-H), 4.40 (br. s, 1 H, 11-H), 3.84 (s, 3 H), 2.52 (d, *J* = 13.7 Hz, 1 H, 15-H), 2.45 (d, *J* = 13.7 Hz, 1 H, 15-H), 2.30 (m, 1 H), 2.02–2.09 (m, 2 H), 1.84 (m, 1 H), 1.31–1.51 (m, 5 H), 1.11–1.19 (m, 2 H), 1.02 (s, 3 H), 0.95 (d, *J* = 6.4 Hz, 3 H), 0.82 (s, 3 H), 0.75 (dd, *J* = 12; 1.8 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 182.3 (C-17), 182 (C-20), 161.6 (C-18), 160.4 (C-4), 153.3 (C-21), 117.3 (C-16), 102.4 (C-11), 101.9 (C-19), 56.8 (OCH_3), 50.0 (C-10), 43.2 (C-9), 40.4 (C-5), 38.0 (C-8), 36.6 (C-6), 32.9 (C-3), 32.3 (C-15), 28.6 (C-2), 27.9 (C-7), 23.1 (C-1), 20.5 (C-12), 17.8 (C-13), 17.3 (C-14) ppm. HRMS (ESI): *m/z* calcd. for $C_{22}H_{29}O_4^+$ $[M + H]^+$ 357.2071; found 357.2071.

5-*epi*-Ilimaquinone (2): R_f: (SiO_2, CH_2Cl_2) = 0.45; ($AgNO_3$-SiO_2, CH_2Cl_2) = 0.42. IR (neat): $\tilde{\nu}_{max}$ = 3330, 2929, 1662, 1642, 1601, 1458, 1433 cm^{-1}. ^1H NMR (400 MHz, [D]chloroform): δ = 7.45 (s, OH), 5.88 (s, 1 H, 19-H), 4.69 (br. s, 1 H, 11-H), 4.66 (br. s, 1 H, 11-H), 3.87 (s, 3 H), 2.59 (d, *J* = 13.7 Hz, 1 H, 15-H), 2.49 (d, *J* = 13.7 Hz, 1 H, 15-H), 2.43 (m, 1 H), 2.16–2.08 (m, 2 H), 2.0 (m, 1 H), 1.91–1.63 (m, 3 H), 1.48 (m, 1 H), 1.23–1.17 (m, 3 H), 1.1 (dd, *J* = 13.9, 3.2 Hz, 1 H), 1.05 (s, 3 H), 0.92 (d, *J* = 6.2 Hz, 3 H), 0.87 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 182.4 (C-17, C-20), 161.7 (C-18), [153.5, 153.3 (C-4, C-21)], 117.6 (C-16), 105.7 (C-11), 102.0 (C-19), 56.8 (C-22), 48.5 (C-10), 44.9 (C-9), 39.5 (C-5, C-8), 37.9 (C-6), 33.2 (C-12), 32.7 (C-15), 32.0 (C-3), 27.8 (C-7), 24.9 (C-2), 22.5 (C-1), 18.6 (C-14), 18.2 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{22}H_{29}O_4^+$ $[M + H]^+$ 357.2071; found 357.2071.

***O*-Desmethyl-ilimaquinone (15):** To a solution of ilimaquinone (**1**; 200 mg, 0.56 mmol) in ethanol (20 mL) is added NaOH (2 M, 12 mL). The reaction mixture is heated to reflux temperatures for 1 h. After cooling, the reaction mixture is quenched with HCl (1 M, 50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound as a red solid (186 mg, 97 %). IR (neat): $\tilde{\nu}_{max}$ = 3119, 3289, 2921, 2860, 2445, 1704, 1639, 1601,

1449 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 11.10, (br. s, 1 H, OH), 5.79 (s, 1 H, 19-H), 4.41 (s, 1 H, 11-H), 4.39 (s, 1 H, 11-H), 3.36 (br. s, 1 H, OH), 2.40 (d, *J* = 13.5 Hz, 1 H, 15-H), 2.32 (d, *J* = 13.6 Hz, 1 H, 15-H), 2.24 (dt, *J* = 17.0, 8.7 Hz, 1 H), 2.08–1.97 (m, 2 H), 1.76 (m, 1 H), 1.58–1.10 (m, 5 H), 0.99 (s, 3 H, 12-H), 0.92 (d, *J* = 6.3 Hz, 3 H, 12-H), 0.78 (s, 3 H, 14-H), 0.73 (m, 1 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 159.3 (C-4), 115.4 (C-16), 103.6 (C-19), 102.9 (C-11), 49.5 (C-10), 42.4 (C-9), 39.8 (C-2), 37.5, 36.3, 32.4, 27.9, 27.5, 22.7, 20.1 (C-12), 18.0 (C-13), 17.1 (C-14) ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{27}O_4^+$ [M + H]$^+$ 343.1915; found 343.1911. $[\alpha]_D^{20}$ = –184 (*c* = 0.038, $CHCl_3$).

3-(Dimethyl-λ⁴-sulfanylidene)-5-hydroxy-6-[(5*S*,9*R*,10*R*)-14(4→5),15-(10→9)-bisabeodriman-4(13)en-11-yl]cyclohex-5-ene-1,2,4-trione (3): A solution of ilimaquinone (1, 20 mg, 0.058 mmol) in a mixture of DMSO and acetic anhydride (6:4 v/v, 1 mL) was heated to 70 °C for 1 h. After cooling, the reaction mixture is quenched with water (5 mL), pH is adjusted to 8 with Na_2CO_3, and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by preparative TLC with silica gel (eluent: dichloromethane/methanol, 95:5) afforded the title compound as a yellow oil (11.8 mg, 50 %). IR (neat): $\tilde{\nu}_{max}$ = 2921, 2852, 1668, 1634, 1620, 1575 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 8.32 (br. s, 1 H, OH), 4.43 (s, 1 H, 11-H), 4.42 (s, 1 H, 11-H), 3.10 (s, 3 H, SCH_3), 3.09 (s, 3 H, SCH_3), 2.54 (d, *J* = 13.5 Hz, 1 H, 15-H), 2.48 (d, *J* = 13.5 Hz, 1 H, 15-H), 2.38–2.27 (m, 2 H), 2.18–2.04 (m, 2 H), 1.86 (m, 1 H), 1.68–1.59 (m, 2 H), 1.49 (m, 1 H), 1.42–1.35 (m, 2 H), 1.04 (s, 3 H, CH_3), 0.99 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.84 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 175.1, 162.8, 162.5, 161.2 (Cq, C-4′), 157.3, 117.9 (C-18), 102.4 (C-11), 50.1 (C-8), 43.4 (C-5), 40.7 (C-9), 38.1 (C-10), 36.9 (CH_2), 33.2 (CH_2), 33.0 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 26.3 (2 SCH_3), 23.4 (CH_2), 20.9 (H-12), 18.1 (H-13), 17.7 (H-14) ppm. HRMS (ESI): *m/z* calcd. for $C_{23}H_{33}O_4S^+$ [MH]$^+$ 405.2104; found 405.2094. $[\alpha]_D^{20}$ = –366 (*c* = 0.030, $CHCl_3$).

1,2,4,5-Tetracetoxy-3-(methylthio)-5-hydroxy-6-[(5*S*,9*R*,10*R*)-14(4→5),15(10→9)bisabeo-driman-4(13)-en-11-yl]benzene (5): To a solution of **3** (12.5 mg, 0.046 mmol) in acetic anhydride (0.50 mL) are added zinc dust (36 mg, 0.55 mmol) and trimethylamine (20 µL). The reaction mixture is heated to 45 °C for 1 h. After cooling, the reaction mixture is filtered and concentrated to dryness. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol, 1:0 then 9:1) affords the title compound as a colourless oil (17.2 mg, 67 %). IR (neat): $\tilde{\nu}_{max}$ = 2926, 2859, 1785, 1769, 1634, 1426 cm^{-1}. ^1H NMR (300 MHz, [D]Chloroform): δ = 4.49 (s, 2 H, 11-H), 2.51–2.46 (m, 1 H), 2.33–2.23 (m, 15 H, 4 OAc, CH_3S), 2.14–2.07 (m, 2 H), 1.88–1.81 (m, 1 H), 1.50–1.42 (m, 5 H), 1.38–1.25 (m, 3 H), 1.04 (s, 3 H, CH_3), 0.85 (s, 3 H, CH_3), 0.70 (d, *J* = 6.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D]Chloroform): δ = 167.6 (2 × C=O), 167.5 (C=O), 167.4 (C=O), 160.2 (C-4), 143.2, 141.1 (2 C), 130.4, 124.1, 116.1 (C-16), 103.2 (C-11), 54.6 (C-8), 44.0 (C-5), 41.0 (C-9), 40.9 (C-10), 39.7 (CH_2), 37.0 (CH_2), 33.1 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 24.0 (CH_2), 20.9 (OAc), 20.8 (OAc), 20.7 (OAc), 20.5 (OAc), 18.7 (C-12), 18.5 (C-13), 18.3 (C-14), 15.8 (CH_3S) ppm. HRMS (ESI): *m/z* calcd. for $C_{30}H_{44}NO_8S^+$ [M + NH_4]$^+$ 578.2782; found 578.2798. $[\alpha]_D^{20}$ = –9 (*c* = 0.104, $CHCl_3$).

Reduction of 2 to Afford 6 and 16: To a solution of 5-*epi*-ilimaquinone (**2**; 20.0 mg, 0.057 mmol) in acetic anhydride (0.50 mL) are added zinc dust (21 mg, 0.32 mmol) and trimethylamine (20 µL). The reaction mixture was heated to 40 °C for 1 h. After cooling, the reaction mixture is filtered and concentrated to dryness. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol, 1:0) affords **16** as a white powder (4.0 mg, 16 %) and then **6** as a white power (21.8 mg, 80 %).

1,4,5-Triacetoxy-2-methoxy-6-[(5*R*,9*R*,10*R*)-14(4→5),15(10→9)-bisabeo-driman-4(13)-en-11-yl]benzene (6): IR (neat): $\tilde{\nu}_{max}$ = 2985, 2902, 2854, 1767, 1482, 1464, 1443, 1426 cm^{-1}. ^1H NMR (300 MHz, [D]Chloroform): δ = 6.73 (s, 1 H, 19-H), 4.70 (s, 1 H, 11-H), 4.66 (s, 1 H, 11-H), 3.79 (s, 3 H, OMe), 2.44 (d, *J* = 4.4 Hz, 2 H, 15-H), 2.31 (s, 3 H, OAc), 2.29 (s, 3 H, OAc), 2.26 (s, 3 H, OAc), 2.17–1.99 (m, 3 H), 1.93–1.84 (m, 1 H), 1.74–1.63 (m, 3 H), 1.49–1.45 (m, 3 H), 1.10 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 0.81 (d, *J* = 5.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D]Chloroform): δ = 168.2 (2 × C=O), 168.1 (C=O), 153.5 (C-4), 149.1,140.2,137.5,135.5,128.9,106.2 (C-11), 105.3 (C-19), 56.4 (OCH_3), 50.2 (C-10), 45.0 (C-9), 41.4 (C-8), 39.9 (C-5), 38.5 (CH_2), 37.9 (CH_2), 32.1 (C-12), 28.2 (CH_2), 25.1 (CH_2), 23.4 (CH_2), 21.0 (3CH_3 OAc), 20.9 (CH_2), 19.0 (C-14), 17.9 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{38}O_7Na^+$ [M + Na]$^+$ 509.2510; found 509.2523. $[\alpha]_D^{20}$ = –43 (*c* = 0.046, $CHCl_3$).

1,4-Diacetoxy-5-hydroxy-2-methoxy-6-[(5*R*,9*R*,10*R*)-14(4→5),15(10→9)-bis-abeodriman-4(13)-en-11-yl]benzene (16): IR (neat): $\tilde{\nu}_{max}$ = 2924, 2852, 1767, 1712, 1486, 1464, 1442 cm^{-1}. ^1H NMR (300 MHz, [D]Chloroform): δ = 6.63 (s, 1 H, 19-H), 5.73 (s, 1 H, OH), 4.70 (s, 1 H, 11-H), 4.66 (s, 1 H, h-11), 3.86 (s, 3 H, OMe), 2.57 (s, 2 H, 10-H), 2.29 (s, 3 H, OAc), 2.25 (s, 3 H, OAc), 2.12–1.87 (m, 4 H), 1.65–1.46 (m, 6 H), 1.09 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 0.85 (d, *J* = 5.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D]Chloroform): δ = 168.9 (C=O), 168.8 (C=O), 153.8 (C-4), 143.7,143.4,136.2,134.5,120.9,105.9 (C-11), 103.8 (C-19), 56.4 (CH_3 OMe), 49.5 (C-10), 44.9 (C-9), 40.4 (C-8), 39.9 (C-5), 37.8 (CH_2), 36.8 (CH_2), 32.2 (C-12), 28.3 (CH_2), 25.3 (CH_2), 23.4 (CH_2), 20.9 (2 × OAc), 20.8 (CH_2), 19.2 (C-14), 18.2 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{36}O_6Na^+$ [M + Na]$^+$ 467.2404; found 467.2410. $[\alpha]_D^{20}$ = +19 (*c* = 0.054, $CHCl_3$).

(5*S*,9*R*,10*R*)-(2-Hydroxy-5-amino-1-imino-quinon-3-yl)-14(4→5),15(10→9)-bisabeodriman-4(13)-ene (4): A solution of ilimaquinone (**1**; 600 mg, 1.75 mmol) in a 1:1 mixture of aqueous ammonia (35 %) and acetonitrile (5 mL) is heated to 35 °C for 16 h. The reaction mixture is diluted with ethyl acetate (50 mL) and washed with water (15 mL). The organic extract is dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol, 95:5 then 85:15) affords smenospongine (100 mg, 16 %) and then the title compound as a deep blue solid (390 mg, 65 %). IR (neat): $\tilde{\nu}_{max}$ = 3385, 2927, 1739, 1684, 1433, 1205 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 9.03 (s, 2 H, NH_a), 8.33 (s, 2 H, NH_b), 5.55 (s, 1 H, 19-H), 4.36 (s, 1 H, 11-Ha), 4.34 (s, 1 H, 11-Hb), 2.37 (d, *J* = 10.3 Hz, 1 H, 7-H), 2.29 (d, *J* = 13.5 Hz, 1 H, 15-H), 2.25 (m, 1 H, 3-H), 2.20 (d, *J* = 13.5 Hz, 1 H, 2–15), 1.96 (d, *J* = 13.9 Hz, 1 H, 3-H), 1.68 (m, 1 H, 1-H), 1.39 (d, *J* = 10.9 Hz, 1 H, 6-H), 1.32–1.15 (m, 5 H), 0.98–0.95 (m, 7 H, 10-H 12-H 13-H), 0.83 (d, *J* = 10.2 Hz, 1 H, 8-H), 0.71 (s, 3 H, 14-H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 171.8 (C-17, C21), 160.1 (C-4), 159.9 (C-18, C-20), 107.7 (C-16), 102.4 (C-11), 85.4 (C-19), 48.7 (C-8), 41.9 (C-9), 39.8 (C-5), 37.0 (C-10), 36.7 (C-6), 32.7 (C-3 C-15), 28.5 (C-1), 27.8 (C-2), 22.7 (C-7), 20.2 (C-12), 18.4 (C-13), 17.6 (C-14) ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{31}N_2O_2^+$ [M + H]$^+$ 343.2380; found 343.2382. $[\alpha]_D^{20}$ = –51 (*c* = 0.04, MeOH).

Transaminations of 4 to Afford Dactylocyanines A-H (17–24): To a solution of **4** (50 mg, 0.15 mmol) in acetonitrile (2 mL) is added the corresponding amine R^1-NH_2 (for **17** and **20**: 0.30 mmol, 2 equiv.; for **18**, **19**, **21** and **S-i**: 0.15 mmol, 1 equiv.). The reaction mixture is heated to 35 °C (20–24 h) and concentrated to dryness. Purification by flash chromatography with silica gel (eluent: CH_2Cl_2/MeOH, 98:2 then 95:5) affords the title compounds as deep blue solids (85–90 %). To a solution of **18** (20 mg), or **19** (40 mg) or **S-i**

(20 mg; 1 equiv.) in acetonitrile (2 mL) is added the corresponding amine R^2-NH_2 [(*S*)-2-methylbututylamine or 3-(methylthio)propylamine] [1 equiv. (100 µL of a solution of 10 equiv. of amine in 1.00 mL of acetonitrile)]. For compound **22**: The reaction mixture is heated to 35 °C (24 h) and concentrated to dryness. Purification by flash chromatography with silica gel (eluent: CH_2Cl_2/MeOH, 98:2) affords **22** as a deep blue solid (40 mg, 86 %). For compound **23** and **24**: the reaction mixture is heated to 35 °C (24 h) and then water (0.5 mL) and oxone® (50 mg, 0.162 mmol) are added. After 35 min of stirring, the reaction mixture is diluted with water (5 mL) and extracted with ethyl acetate (2 × 15 mL). The combined extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by preparative TLC with silica gel (eluent: dichloromethane/methanol, 95:5) affords title compounds as deep blue solids (**23**/**24**, both 80 %).[25]

(5*S*,9*R*,10*R*)-[2-Hydroxy-5-(2-phenylethylamino)-1-iminoquinon-3-yl]-14(4→5),15(10→9)-bisabeodriman-4(13)-ene (*S*-i): IR (neat): $\tilde{\nu}_{max}$ = 3300, 2977, 2921, 2856, 1655, 1554, 1535, 1527 cm^{-1}. ^1H NMR (400 MHz, [D]chloroform): δ = 7.31 (dd, *J* = 8.0, 6.3 Hz, 2 H, H-*o*), 7.24 (m, 1 H, H-*p*), 7.19–7.14 (m, 2 H, H-*m*), 5.32 (s, 1 H, 19-H), 4.42 (s, *J* = 1.7 Hz, 2 H, 11-H), 3.53 (t, *J* = 7.1 Hz, 2 H, H-β), 2.95 (t, *J* = 7.2 Hz, 2 H, H-α), 2.45 (d, *J* = 13.7 Hz, 1 H, H-15), 2.39 (d, *J* = 14.2 Hz, 1 H, H-15), 2.37–2.23 (m, 2 H), 2.05 (dt, *J* = 12.9, 2.9 Hz, 1 H), 1.81 (dd, *J* = 12.1, 4.9 Hz, 1 H), 1.51 (tt, *J* = 11.4, 5.4 Hz, 1 H), 1.43–1.22 (m, 3 H), 1.36 (s, 3 H), 1.17 (qd, *J* = 12.6, 10.6, 6.4 Hz, 1 H), 1.02 (s, 3 H), 1.01 (d, *J* = 4.5 Hz, 3 H), 0.88 (dd, *J* = 11.5, 2.0 Hz, 1 H), 0.79 (s, 3 H). ^{13}C NMR (101 MHz, [D]chloroform): δ = [171.7, 171.0 (C-17, C-21)], 161.5 (C-4), 159.6 (C-20), 156.9 (C-18), 136.9 (C-*ipso*), 129.0, 128.6, 127.2, 110.7 (C-16), 101.9 (C-11), 83.6 (C-19), 49.9 (C-8), 44.6 (C-β), 42.7 (C-5), 40.5 (C-9), 38.0 (C-10), 36.9, 34.7 (C-α), 33.3, 33.2, 29.0, 28.1, 23.4, 20.6 (C-12), 18.2 (C-13), 17.4 (C-14) ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{39}N_2O_2^+$ $[M + H]^+$ 447.3011; found 447.3011. $[\alpha]_D^{20}$ = –129 (*c* = 0.007, $CHCl_3$).

Ozonolysis of 1 Affording 9 and 25: A solution of ilimaquinone (126 mg, 0.35 mmol) in dichloromethane (25 mL) cooled to –78 °C is subjected to an ozone stream (0.3 NL/min, 5 × 15 s, TLC monitoring) and then Me_2S (0.20 mL) is added. After 16 h of stirring, the reaction mixture is concentrated under reduced pressure. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol, 199:1 → 99:1 → 98:2) affords recycled ilimaquinone (**1**; 8 mg, 6 %), then ketone **25** as yellow solid (62 mg, 49 %) and lactone **9** as a yellow solid (20 mg, 15 %).

2-Hydroxy-5-methoxy-3-[(5*S*,9*R*,10*R*)-4-oxo-13-nor-14(4→5),15-(10→9)-bisabeodriman-11-yl]quinone (25): IR (neat): $\tilde{\nu}_{max}$ = 3343, 2975, 2930, 1721, 1701, 1665, 1642, 1609 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 7.65 (s, 1 H, OH), 5.84 (s, 1 H, 19-H), 3.84 (s, 3 H, OMe), 2.60–2.43 (m, 3 H, 15-H), 2.20 (m, 1 H), 2.08 (dt, *J* = 14.3, 3.5 Hz, 1 H), 1.97 (m, 1 H), 1.63–1.55 (m, 2 H), 1.49–1.15 (m, 5 H), 1.11 (s, 3 H, CH_3), 1.10 (m, 1 H), 0.94 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.88 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 216.7 (C-4), 182.2 (C-17, C-21), 161.8 (C-18), 153.8 (C-21), 116.7 (C-16), 102.3 (C-19), 57.0 (OMe), 49.5 (C-8), 49.4 (C-10), 43.6 (C-5), 37.6 (CH_2), 37.4 (C-9), 32.5 (CH_2), 32.3 (CH_2), 27.1 (CH_2), 26.1 (CH_2), 22.2 (CH_2), 19.0 (CH_3), 17.9 (2 × CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{28}O_5Na^+$ $[M + Na]^+$ 383.1829; found 383.1842. $[\alpha]_D^{20}$ = –125 (*c* = 0.024, $CHCl_3$).

2-Hydroxy-5-methoxy-4,5-epoxy-3-[(5*S*,9*R*,10*R*)-4-oxo-13-nor-14(4→5),15(10→9)-bisabeodriman-11-yl]quinone (9): IR (neat): $\tilde{\nu}_{max}$ = 2934, 2886, 1778, 1712, 1661, 1643, 1609 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 7.68 (s, 1 H, OH), 5.90 (s, 1 H, 19-H), 3.87 (s, 3 H, OMe), 2.74–2.43 (m, 5 H), 1.98–1.80 (m, 2 H), 1.62–1.58 (m, 2 H), 1.48 (s, 3 H, CH_3), 1.34–1.13 (m, 3 H), 0.99 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.77 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 182.4, 182.2 (C-17, C-21), 175.9 (C-4), 161.9 (C-18), 154.1 (C-21), 116.3 (C-16), 102.3 (C-19), 86.5 (C-5), 57.1 (OMe), 50.2 (C-10), 44.7 (C-9), 41.7 (CH_2), 37.5 (C-8), 37.2 (CH_2), 31.6 (CH_2), 28.3 (CH_2), 27.0 (CH_2), 24.2 (CH_2), 22.0 (CH_3), 17.8 (CH_3), 16.4 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{28}O_6Na^+$ $[M + H]^+$ 399.1778; found 399.1771. $[\alpha]_D^{20}$ = –64 (*c* = 0.110, $CHCl_3$).

4-{(1*S*,3*S*,6*S*)-2-[(3,6-Dihydroxy-quinon-2-yl)methyl]-6-hydroxy-2,3,6-trimethylcyclohexyl}butanoic Acid (10): To a solution of lactone **9** (44 mg, 0.012 mmol) in ethanol (4.5 mL) is added a solution of NaOH (2 M, 2.5 mL). The reaction mixture is heated to reflux for 1 h. After cooling, the reaction mixture is quenched with HCl solution (1 M, 50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure. Solubilisation in chloroform and precipitation by the addition of petroleum ether afford the title compound as a brown solid (29 mg, 65 %). IR (neat): $\tilde{\nu}_{max}$ = 3310, 2923, 2853, 2360, 2340, 1703, 1647, 1625 cm^{-1}. ^1H NMR (300 MHz, [D_3]-acetonitrile): δ = 8.52–8.39 (br. s, 2 H, 2OH), 5.94 (s, 1 H, 19-H), 2.51 (d, *J* = 2.5 Hz, 2 H, 15-H), 1.62–1.53 (m, 3 H), 1.44–1.34 (m, 4 H), 1.32–1.27 (m, 3 H), 1.10 (s, 3 H, CH_3), 0.87 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.74 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D_4]MeOH): δ = 179.1 (C-4), 178.7 (C-17, C-20), 134.9 (C-18, C-21), 117.4 (C-16), 104.5 (C-19), 75.4 (C-5), 55.0 (C-10), 45.7 (C-9), 44.3 (CH_2), 40.5 (C-8), 36.7 (CH_2), 34.2 (CH_2), 30.9 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 23.5 (C-12), 18.6 (C-13), 16.4 (C-14) ppm. HRMS (ESI): *m/z* calcd. for $C_{20}H_{28}O_7Na^+$ $[M + Na]^+$ 379.1762; found 379.1761. $[\alpha]_D^{20}$ = –125 (*c* = 0.048, $CHCl_3$).

Ozonolysis of 15 Affording 7, 26–28: A solution of **15** (265 mg, 0.77 mmol) in a 3:1 mixture of dichloromethane and methanol (30 mL) cooled to –78 °C is subjected to an ozone stream (0.3 NL/min) for 2 min. The reaction mixture is quenched by the addition of dimethyl sulfide (1.0 mL, 13.5 mmol). After 16 h stirring at room temp. the reaction mixture is concentrated under reduced pressure. Purification by preparative HPLC (Sunfire® preparative C_{18} columns 150 × 30 mm; i.d. 5 µm, Waters) 20 % to 100 % MeCN in H_2O (0.2 % HCOOH) over 20 min at 42 mL/min affords **27** (R_T = 8.40 min, 35 mg, 13 %), **7** (R_T = 10.25 min, 16 mg, 6 %), **28** (R_T = 13.10 min, 13.0 mg, 4 %), and **26** (R_T = 15.30 min, 3 mg, 2 %). See NMR spectroscopy data charts in the Supporting information.

2-Hydroxy-3-[(5*S*,9*R*,10*R*)-4-oxo-13-nor-14(4→5),15(10→9)-bisabeo-driman-11-yl]-2-butenolide-4-carboxylic Acid (27): IR (neat): $\tilde{\nu}_{max}$ = 2935, 1774, 1744, 1668 cm^{-1}; 3:2 diastereomeric mixture: ^1H NMR (400 MHz, [D]chloroform, diastereomer A): δ = 6.71 (br. m, 2 H), 5.10 (s, 1 H), 2.65 (d, *J* = 13.5 Hz, 1 H), 2.57 (m, 1 H), 2.22 (d, *J* = 13.5 Hz, 1 H), 2.19 (m, 1 H), 2.19–2.00 (m, 3 H), 1.69 (m, 1 H), 1.63–1.44 (m, 3 H), 1.44–1.30 (m, 2 H), 1.24 (m, 1 H), 1.15 (s, 3 H), 0.97 (d, *J* = 5.0 Hz, 3 H), 0.90 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 217.3, 169.80, 169.4, 141.0, 127.3, 78.8, 49.4, 49.2, 44.1, 37.6, 37.3, 33.0, 32.31, 26.6, 25.6, 20.9, 18.8, 17.7, 16.8 ppm. ^1H NMR (400 MHz, [D]chloroform), δ (ppm; diastereomer B): 6.71 (br. m, 2 H), 5.28 (s, 1 H), 2.76 (d, *J* = 13.5 Hz, 1 H), 2.62 (m, 1 H), 2.13 (d, *J* = 13.5 Hz, 1 H), 2.26 (m, 1 H), 2.19–2.00 (m, 3 H), 1.78 (m, 1 H), 1.63–1.44 (m, 3 H), 1.44–1.30 (m, 2 H), 1.19 (m, 1 H), 1.15 (s, 3 H), 0.97 (d, *J* = 5.0 Hz, 3 H), 0.90 (s, 3 H). ^{13}C NMR (101 MHz, [D]chloroform): δ = 218.0, 169.84, 169.80, 140.4, 127.6 78.9, 49.8, 49.2, 44.1, 38.2, 37.3, 32.8, 32.35, 26.6, 25.5, 21.3, 18.9, 17.7, 16.3. HRMS (ESI): *m/z* calcd. for $C_{19}H_{26}O_6Na^+$ $[M + Na]^+$ 373.1627; found 373.1616. $[\alpha]_D^{20}$ = +10 (*c* = 0.100, $CHCl_3$).

2-Hydroxy-3-[(5*S*,9*R*,10*R*)-4-oxo-13-nor-14(4→5),15(10→9)-bisabeo-driman-11-yl]-2-butenolide-4-carboxylic Acid (7): IR (neat): $\tilde{\nu}_{max}$ = 3300, 2931, 1782, 168 cm^{-1}. ^1H NMR (400 MHz, [D]chloroform, diastereomer A): δ = 3.83 (s, 3 H), 2.57 (td, *J* = 14.0, 7.3 Hz, 1 H), 2.37 (d, *J* = 16.0 Hz, 1 H), 2.34 (d, *J* = 16.0 Hz, 1 H), 2.18 (dd, *J* =

14.0, 4.7 Hz, 1 H), 2.03–1.90 (m, 2 H), 1.70–1.42 (m, 3 H), 1.40–1.22 (m, 4 H), 1.13 (s, 3 H), 0.86 (s, 3 H), 0.85 (m, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 216.8, 168.8, 167.4, 143.0, 125.8, 100.9, 54.5, 49.0, 49.0, 42.7, 37.9, 37.4, 34.3, 32.4, 26.7, 25.5, 21.3, 18.7, 17.6, 16.6 ppm. ^{1}H NMR (400 MHz, [D]chloroform, diastereomer B): 3.83 (s, 3 H), 2.57 (td, *J* = 14.0, 7.3 Hz, 1 H), 2.37 (d, *J* = 16.0 Hz, 1 H), 2.34 (d, *J* = 16.0 Hz, 1 H), 2.18 (dd, *J* = 14.0, 4.7 Hz, 1 H), 2.03–1.90 (m, 2 H),1.70–1.38 (m, 5 H), 1.38–1.27 (m, 2 H), 1.13 (s, 3 H), 0.86 (s, 3 H), 0.85 (m, 3 H). ^{13}C NMR (101 MHz, [D]chloroform): δ = 216.9, 168.8, 167.4, 143.3, 125.7, 100.9, 54.5, 49.2, 49.0, 42.7, 37.3, 37.1, 34.5, 32.2, 26.7, 25.3, 21.3, 18.7, 17.7, 16.9. HRMS (ESI): *m/z* calcd. for $C_{20}H_{28}O_7Na^+$ [M + Na]$^+$ 403.1733; found 403.1735. $[\alpha]_D^{20}$ = –29 (*c* = 0.070, $CHCl_3$).

2-Hydroxy-3-[(5*S*,9*R*,10*R*)-14(4→5),15(10→9)-bisabeodrim-4(13)-en-11-yl]-2-butenolide-4-carboxylic Acid (26): IR (neat): $\tilde{\nu}_{max}$ = 3390, 2924, 2860, 1781, 1739, 1663 cm^{-1}. ^{1}H NMR (400 MHz, [D]chloroform, diastereomer A): δ = 5.89 (s br., H), 5.14 (s br., 1 H), 4.49 (s, 1 H), 4.47 (s, 1 H), 3.85 (s, 3 H), 2.47 (d, *J* = 15.3 Hz, 1 H), 2.34 (d, *J* = 15.3 Hz, 1 H), 2.34–2.25 (m, 1 H), 2.14–2.05 (m, 1 H), 1.85–1.75 (m, 3 H), 1.60–1.30 (m, 5 H), 1.19 (m, 1 H), 1.03 (s, 3 H), 1.02 (m, 1 H), 0.87 (s, 3 H), 0.80 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 169.0, 167.3, 160.2, 142.5, 126.2, 102.6, 100.9, 54.5, 49.6, 42.5, 40.3, 38.6, 36.7, 34.6, 32.9, 28.2, 27.6, 22.5, 20.4, 17.3, 16.7 ppm. ^{1}H NMR (400 MHz, [D]chloroform, diastereomer B): δ = 5.89 (s br., H), 5.14 (s br., 1 H), 4.49 (s, 1 H), 4.47 (s, 1 H), 3.85 (s, 3 H), 2.47 (d, *J* = 15.3 Hz, 1 H), 2.34 (d, *J* = 15.3 Hz, 1 H), 2.34–2.25 (m, 1 H), 2.14–2.05 (m, 1 H), 1.85–1.75 (m, 3 H), 1.60–1.30 (m, 5 H),1.19 (m, 1 H),1.19 (m, 1 H), 1.03 (s, 3 H), 1.02 (m, 1 H), 0.87 (s, 3 H), 0.80 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 169.0, 167.3, 160.1, 142.4, 125.8, 102.7, 100.9, 54.6, 49.5, 42.5, 40.3, 37.7, 36.4, 34.3, 32.7, 28.2, 27.7, 22.4, 20.4, 17.4, 17.0 ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{30}O_6Na^+$ [M + H]$^+$ 401.1940; found 401.1918. $[\alpha]_D^{20}$ = –36 (*c* = 0.055, $CHCl_3$).

Ozonolysis of 4 Affording 14 and 29: A solution of **4** (35 mg, 0.10 mmol) in a 1:1 mixture of dichloromethane and methanol (20 mL) cooled to –78 °C is subjected to an ozone stream (0.3 mL/min) for 20 seconds. The reaction mixture is quenched by the addition dimethyl sulfate (1.0 mL, 13.5 mmol). After 16 h of stirring at room temp. the reaction mixture is concentrated under reduced pressure. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol: 98:2) affords **14** as an off white solid (8 mg; 31 %) and then **29** as an off white solid (10 mg; 38 %).

Smenospongic Acid (14): IR (neat): $\tilde{\nu}_{max}$ = 2921, 2859, 1730, 1448 cm^{-1}. ^{1}H NMR (400 MHz, [D]chloroform): δ = 4.50 (s, 2 H), 2.40 (d, *J* = 13.5 Hz, 1 H, 15-H), 2.29 (m, 1 H, 3-H), 2.28 (d, *J* = 13.5 Hz, 1 H, 15-H), 2.10 (m, 1 H, 3-H), 1.92–1.70 (m, 3 H), 1.61–1.53 (m, 2 H, 6-H), 1.52–1.40 (m, 3 H), 1.31 (m, 2 H, 1-H), 1.04 (s, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.80 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 176.5 (C=O), 156.0 (C-11), 102.8 (C-4), 49.9 (C-10), 42.7 (C-15), 41.4 (C-9), 40.2 (C-5), 37.8 (C-8), 36.9 (C-6), 33.0 (C-3), 28.2 (C-2), 27.4 (C-7), 22.5 (C-1), 20.7 (C-12), 17.2 (C-14), 16.4 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{16}H_{26}O_2Na^+$ [M + H]$^+$ 272.1830; found 272.1989. $[\alpha]_D^{20}$ = –36 (*c* = 0.028, MeOH).

(5*S*,9*R*,10*R*)-4-Oxo-13-nor-14(4→5),15(10→9)-bisabeodriman-11-carboxylic Acid (29): IR (neat): $\tilde{\nu}_{max}$ = 3338, 2927, 2863, 1702 cm^{-1}. ^{1}H NMR (400 MHz, [D]chloroform): δ = 2.55 (td, *J* = 14.0, 6.9 Hz, 1 H, 3-H), 2.43 (d, *J* = 13.7 Hz, 1 H, 15-H), 2.35 (d, *J* = 13.7 Hz, 1 H, 15-H), 2.21 (ddt, *J* = 14.0, 4.3, 1.7 Hz, 1 H, 3-H), 2.05 (m, 1 H, 2-H), 1.92 (dd, *J* = 13.0, 3.2 Hz, 1 H, 1-H), 1.74–1.64 (m, 2 H), 1.63–1.54 (m, 4 H), 1.50 (m, 1 H, 7-H), 1.37 (m, 1 H, 7-H), 1.13 (s, 3 H, H12), 0.91 (d, *J* = 6.7 Hz, 3 H, 13-H), 0.87 (s, 3 H, 14-H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 215.7 (C-4), 176.0 (C=O), 49.08 (C-10), 49.02 (C-5), 42.6 (C-15), 41.4 (C-9), 37.45 (C-3), 37.43 (C-8), 32.7 (C-6), 26.5 (C-7), 25.6 (C-2), 21.3 (C-1), 19.0 (C-12), 17.5 (C-14), 16.2 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{24}O_3Na^+$ [M + Na]$^+$ 275.1623; found 275.1628. $[\alpha]_D^{20}$ = –125 (*c* = 0.024, MeOH).

Rearrangement of 1 to Afford 11 and 31–32: To a solution of ilimaquinone (**1**; 515 mg, 1.44 mmol) in concentrated sulfuric acid (13.0 mL) cooled to –10 °C is added sodium azide (105.5 mg, 1.62 mmol). After 2 h of stirring at 10 °C, the reaction mixture is quenched with ice and extracted with dichloromethane (2 × 10 mL). The combined organic extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by preparative HPLC (Xbridge® preparative C_{18} columns 150 × 46 mm; i.d. 5 µm, Waters) 65 % to 100 % MeCN in H_2O (0.1 % HCOOH) over 20 min at 42 mL/min affords **11** as a red oil (R_T = 7.70 min, 62 mg, 13 %), **31** as a green oil (R_T = 9.90 min, 65 mg, 13 %) and **32** as a brown oil (R_T = 11.50 min, 10 mg, 2 %).

Smenospongamine (11): IR (neat): $\tilde{\nu}_{max}$ = 3471, 2958, 2250, 1666, 1596, 1555 cm^{-1}. ^{1}H NMR (300 MHz, [D]chloroform): δ = 6.16–5.77 (br. s, 2 H, NH_2), 5.60 (s, 1 H, 19-H), 2.56 (d, *J* = 18.6 Hz, 1 H, 15-H), 1.99 (d, *J* = 18.7 Hz, 1 H, 15-H), 1.84–1.79 (m, 2 H), 1.68–1.45 (m, 5 H), 1.40–1.24 (m, 3 H), 1.02 (s, 3 H, 11-H), 0.97 (2s, 6 H, 14-H 12-H), 0.78 (d, *J* = 6.3 Hz, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 181.5 (C-20), 177.0 (C-17), 154.3 (C-21), 153.9 (C-18), 113.3 (C-16), 97.5 (C-19), 88.6 (C-10), 45.8 (C-5), 41.0 (C-3), 37.6 (C-9), 33.3 (C-4), 32.4 (C-12), 32.3 (C-8), 30.2 (C-7), 29.1 (C-1), 26.8 (C-15), 22.6 (C-11), 22.1 (C-6), 17.8 (C-2), 17.2 (C-14), 16.4 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{29}O_3NNa^+$ [M + Na]$^+$ 366.2040; found 366.2039. $[\alpha]_D^{20}$ = –312 (*c* = 0.032, $CHCl_3$).

2,10′-Epoxy-5-hydroxy-3-[(5*R*,9*R*,10*S*)-15(10→9)-abeodriman-11-yl]quinone (31): IR (neat): $\tilde{\nu}_{max}$ = 2960, 2360, 2255, 1665, 1640 cm^{-1}. ^{1}H NMR (300 MHz, [D]chloroform): δ = 7.41–7.35 (br. s, 1 H, OH), 5.89 (s, 1 H, 19-H), 2.55 (d, *J* = 18.6 Hz, 1 H, 15-H), 2.02 (d, *J* = 18.6 Hz, 1 H, 15-H), 1.72–1.53 (m, 5 H), 1.50–1.27 (m, 5 H), 1.16 (s, 3 H, 11-H), 0.97 (s, 3 H, 14-H), 0.93 (s, 3 H, 12-H), 0.78 (d, *J* = 6.2 Hz, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 182.4 (C-20), 181.7 (C-17), 155.4 (C-21), 154.9 (C-18), 113.0 (C-16), 105.0 (C-19), 87.6 (C-10), 45.9 (C-5), 41.8 (C-3), 37.4 (C-9), 33.7 (C-4), 32.7 (C-12), 32.6 (C-8), 30.4 (C-7), 29.9 (C-1), 26.5 (C-15), 22.3 (C-11), 22.1 (C-6), 18.0 (C-2), 17.1 (C-14), 16.6 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{28}O_4Na^+$ [M + Na]$^+$ 367.1880; found 367.1901. $[\alpha]_D^{20}$ = –220 (*c* = 0.050, $CHCl_3$).

2,10′-Epoxy-5-methoxy-3-[(5*R*,9*R*,10*S*)-15(10→9)-abeodriman-11-yl]quinone (32): IR (neat): $\tilde{\nu}_{max}$ = 2959, 2939, 2362, 2251, 1659, 1639, 1599, 1458 cm^{-1}. ^{1}H NMR (300 MHz, [D]chloroform): δ = 5.74 (s, 1 H, 19-H), 3.81 (s, 3 H, OMe), 2.57 (d, *J* = 18.6 Hz, 1 H, 15-H), 2.00 (d, *J* = 18.7 Hz, 1 H, 15-H), 1.72–1.68 (m, 1 H), 1.49–1.31 (m, 9 H), 1.17 (s, 3 H, 11-H), 0.96 (s, 3 H, 14-H), 0.93 (s, 3 H, 12-H), 0.77 (d, *J* = 6.4 Hz, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 181.7 (C-20), 181.5 (C-17), 159.7 (C-21), 152.9 (C-18), 115.3 (C-16), 105.1 (C-19), 86.6 (C-10), 56.6 (OMe), 45.9 (C-5), 41.9 (C-3), 37.4 (C-9), 33.7 (C-4), 32.6 (C-12 C-8), 30.5 (C-7), 29.6 (C-1), 26.9 (C-15), 22.4 (C-11), 22.1 (C-6), 18.0 (C-2), 17.1 (C-14), 16.5 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{22}H_{30}O_4Na^+$ [M + Na]$^+$ 381.2036; found 381.2048;. $[\alpha]_D^{20}$ = –42 (*c* = 0.048, $CHCl_3$).

Rearrangements of 1 Affording 30 and 33: To a solution of ilimaquinone (**1**; 1.90 g, 5.30 mmol) in benzene (200 mL) cooled to 0 °C is added $Et_2O{\cdot}BF_3$ (3.20 mL, 25.94 mmol). After 10 min of stirring at 0 °C, the reaction mixture is quenched with water (150 mL) and extracted with dichloromethane (2 × 150 mL). The combined organic extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography with

silica gel (eluent: dichloromethane/methanol: 1:0 → 98:2) affords *neo*-mamanutaquinone (**30**) as a yellow-brown solid (1.10 g; 58 %) and then **33** as orange crystals after further crystallisation from hexane (400 mg; 21 %).

***Neo*-Mamanuthaquinone (30):** IR (neat): $\tilde{\nu}_{max}$ = 2925, 1632 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 7.36 (s, 1 H, OH), 5.84 (s, 1 H, 19-H), 3.85 (s, 3 H, OCH_3), 2.70 (d, *J* = 13.2 Hz, 1 H, 15-H), 2.56 (d, *J* = 13.2 Hz, 1 H, 15-H), 2.20–2.03 (m, 2 H), 2.03–1.79 (m, 3 H), 1.63–1.53 (m, 3 H), 1.45–1.27 (m, 3 H), 0.99 (s, 3 H, 11-H), 0.95 (s, 3 H, 12-H), 0.83 (s, 3 H, 14-H), 0.77 (d, *J* = 6.8 Hz, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 182.6 (C-20), 182.2 (C-17), 161.4 (C-18), 152.9 (C-21), 135.0 (C-5), 131.4 (C-10), 118.0 (C-16), 102.1 (C-19), 56.8 (OMe), 42.8 (C-9), 39.9 (C-3), 34.6 (C-8), 34.3 (C-4), 32.2 (C-15), 28.9 (C-12), 28.0 (C-11), 26.5 (C-7), 25.9 (C-1), 22.0 (C-14), 20.8 (C-6), 20.0 (C-2), 15.4 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{22}H_{31}O_4Na^+$ $[M + Na]^+$ 381.2036; found 381.2039. $[\alpha]_D^{20}$ = +22 (*c* = 0.047, $CHCl_3$).

4,10′-Epoxy-5-methoxy-3-[(5*S*,9*R*,10*S*)-15(10→9)-abeodriman-11-yl]-*ortho*-quinone (33): IR (neat): $\tilde{\nu}_{max}$ = 2984, 2935, 2871, 16666, 1652, 1625, 1599, 1400, 1376 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 5.63 (s, 1 H, 19-H), 3.85 (s, 3 H, OMe), 2.83 (d, *J* = 18.2 Hz, 1 H, 15-H), 2.08–1.90 (m, 3 H), 1.84 (m, 2 H), 1.79–1.82 (m, 2 H), 1.62–1.31 (m, 5 H), 1.18 (m, 1 H), 1.08 (d, *J* = 7.5 Hz, 3 H, 13-H), 1.03 (s, 3 H), 0.87 (s, 3 H, 14-H), 0.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 180.1 (C-21), 178.4 (C-20), 164.4 (C-18), 155.2 (C-17), 112.6 (C-16), 101.6 (C-19), 89.4 (C-10), 56.8 (OMe), 45.4 (C-5), 39.1 (C-8), 37.9 (C-9), 33.8 (C-4), 33.5 (C-3), 32.0 (C-14), 30.7 (C-15), 29.1, 29.1, 27.7 (C-7), 22.6, 20.1 (C-13), 18.3, 17.2 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{22}H_{31}O_4H^+$ $[M + H]^+$ 359.2217; found 359.2214. $[\alpha]_D^{20}$ = +132 (*c* = 0.062, $CHCl_3$).

Smenoqualone (34): To a solution of **33** (50 mg, 0.14 mmol) in ethanol (5 mL) is added a solution of NaOH (2 M, 3 mL). The reaction mixture is heated to reflux for 1 h. After cooling the reaction mixture is quenched with a HCl solution (1 M, 12 mL) and extracted with ethyl acetate (2 × 15 mL). The combined extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure. Crude product is dissolved in acetone (5.0 mL) and potassium carbonate (200 mg, 1.45 mmol) and dimethylsulfate (100 µL, 1.06 mmol) are added. After 16 h of stirring reaction mixture is concentrated to dryness and then partitioned between dichloromethane (2 × 15 mL) and water (10 mL). The combined extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol, 99:1) affords **34** as a yellow oil (40 mg, 80 %). IR (neat): $\tilde{\nu}_{max}$ = 2962, 2935, 2872, 1665, 1644, 1601, 1219 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 5.71 (s, 1 H, 19-H), 3.81 (s, 3 H, OMe), 2.85 (d, *J* = 18.7 Hz, 1 H, 15-H), 2.16 (m, 1 H), 1.94 (d, *J* = 18.7 Hz, 1 H, 15-H), 1.85 (d, *J* = 3.8 Hz, 1 H), 1.82–1.68 (m, 3 H), 1.60–1.43 (m, 2 H), 1.43–1.31 (m, 2 H), 1.30–1.18 (m, 2 H), 1.09 (d, *J* = 7.5 Hz, 3 H, 14-H), 1.00 (s, 3 H, 12-H), 0.85 (s, 3 H, 13-H), 0.83 (s, 3 H, 12-H) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 181.6 (C-17, C-20), 159.6 (C-18), 151.2 (C-21), 115.4 (C-16), 104.8 (C-19), 87.9 (C-10), 56.5 (OMe), 45.2 (C-5), 39.2 (C-8), 38.1 (C-9), 33.9 (C-4), 33.6 (C-3), 32.1 (C-12), 30.8 (C-15), 29.9 (C-11), 29.1 (C-1), 27.9 (C-7), 22.6 (C-6), 20.2 (C-14), 18.4 (C-2), 17.3 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{22}H_{31}O_4H^+$ $[M + H]^+$ 359.2217; found 359.2201. $[\alpha]_D^{20}$ = +144 (*c* = 0.083, $CHCl_3$).

Rearrangements of 2 Affording 34 and 35: To a solution of 5-*epi*-ilimaquinone (**2**; 50 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL) cooled to –78 °C is added triflic acid (62 µL, 0.71 mmol). After 4 h of stirring at –50 °C, the reaction mixture is quenched with water (100 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography with silica gel (eluent: dichloromethane) affords smenoqualone **34** as a yellow oil (15 mg; 30 %) and then **35** a yellow oil (20 mg; 40 %).

2,10′-epoxy-5-methoxy-3-[(5*S*,9*R*,10*R*)-15(10→9)-abeodriman-11-yl]quinone (35): IR (neat): $\tilde{\nu}_{max}$ = 3050–2850, 1653, 1621, 1592, 1384, 1353 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 5.63 (s, 1 H, 19-H), 3.83 (s, 3 H, OMe), 2.55 (d, *J* = 18.5 Hz, 1 H, 15-H), 1.97 (d, *J* = 18.5 Hz, 1 H, 15-H), 1.82–1.67 (m, 2 H), 1.64–1.33 (m, 8 H), 1.33–1.15 (m, 2 H), 1.04 (s, 3 H, 11-H), 0.94 (s, 3 H, 13-H), 0.93 (s, 3 H, 12-H), 0.76 (d, *J* = 6.3 Hz, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 179.9 (C-20), 178.3 (C-17), 164.6 (C-18), 156.3 (C-21), 112.6 (C-16), 101.5 (C-19), 87.8 (C-10), 56.8 (OMe), 45.7 (C-5), 41.6 (C-3), 37.2 (C-9), 33.4 (C-4), 32.5 (C-8, C-12), 30.3 (C-7), 29.7 (C-1), 26.7 (C-15), 22.1 (C-6), 21.8 (C-11), 18.0 (C-3), 17.0 (C-14), 16.4 (C-13) ppm. HRMS (ESI): *m/z* calcd. for $C_{22}H_{31}O_4H^+$ $[M + H]^+$ 359.2217; found 359.2214. $[\alpha]_D^{20}$ = –39 (*c* = 0.051, $CHCl_3$).

4-Hydroxy-5-[(5*S*,9*R*,10*R*)-14(4→5),15(10→9)-bisabeodrim-4(13)-en-11-yl]cyclopent-4-en-1,3-dione (8): To a solution of **15** (20 mg, 0.058 mol) in dichloromethane (1.0 mL) cooled to 0 °C is added PIDA (18.7 mg, 0.058). After 30 min of stirring the reaction mixture is concentrated under reduced pressure. Acetonitrile (1.0 mL) is added and mixture is heated to reflux for 3 h. After cooling, the reaction mixture is concentrated to dryness. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol, 95:5 then 9:1) affords **8** as a red oil (6.7 mg, 37 %). IR (neat): $\tilde{\nu}_{max}$ = 2923, 2855, 1745, 1685, 1635, 1448 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 4.46 (s, 1 H, 11′-H), 4.43 (s, 1 H, 11′-H), 2.93 (s, 2 H, 2-H), 2.53 (d, *J* = 13.2 Hz, 1 H, 15′-H), 2.41 (d, *J* = 13.2 Hz, 1 H, 15′-H), 2.30 (m, 1 H), 2.12–2.04 (m, 2 H), 1.90–1.86 (m, 2 H), 1.55–1.51 (m, 2 H), 1.48–1.46 (m, 1 H), 1,43–1.39 (m, 2 H), 1.04 (s, 3 H, CH_3), 1.01 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.88 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 196.6 (C=O), 196.5 (C=O), 166.0 (C-4), 160.5 (C-4′), 134.6 (C-5), 102.9 (C-11′), 50.6 (C-10′), 44.1 (C-9′), 40.6 (C-5′), 40.3 (C-2), 38.9 (C-8), 37.0 (C-6′), 33.1 (C-3′), 31.7 (C-15′), 28.7 (C-7′), 27.9 (C-1′), 23.0 (C-12′), 20.8 (C-12′), 17.7 (C-13′), 17.5 (C-14′) ppm. HRMS (ESI): *m/z* calcd. for $C_{20}H_{29}O_3^+$ $[M + H]^+$ 317.2111; found 317.2113. $[\alpha]_D^{20}$ = –15 (*c* = 0.068, $CHCl_3$).

2,5-Hydroxy-3-[(5*S*,9*R*,10*R*)-4-oxo-13-nor-14(4→5),15(10→9)-bis-abeodriman-11-yl]quinone (36): To a solution of **25** (52 mg, 0.144 mmol) in ethanol (5.1 mL) is added a solution of NaOH (2 M, 3.1 mL). The reaction mixture is heated to reflux for 1 h. After cooling, the reaction mixture is quenched with a HCl solution (1 M, 10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined extracts are dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound as a red solid (47 mg, 94 %). IR (neat): $\tilde{\nu}_{max}$ = 2996, 2926, 2861, 1702, 1689, 1649, 1625 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 6.03 (s, 1 H, 19-H), 2.61–2.45 (m, 3 H), 2.25–2.13 (m, 2 H), 2.09–2.00 (m, 1 H), 1.77–1.64 (m, 2 H), 1.52–1.32 (m, 4 H), 1.14 (s, 3 H, CH_3), 0.97 (d, *J* = 5.9 Hz, 3 H, CH_3), 0.91 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 216.8 (C-4), 114.3 (C-16), 102.5 (C-19), 49.6 (C-10), 49.4 (C-8), 43.6 (C-5), 37.6 (CH_2), 37.5 (C-9), 32.6 (CH_2), 32.5 (CH_2), 27.2 (CH_2), 26.2 (CH_2), 22.3 (CH_2), 19.1 (CH_3), 17.9 (2 × CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{20}H_{25}O_5^+$ $[M + H]^+$ 345.1707; found 345.1706. $[\alpha]_D^{20}$ = –63 (*c* = 0.032, $CHCl_3$).

4-Hydroxy-5-[(5*S*,9*R*,10*R*)-4-oxo-13-nor-14(4→5),15(10→9)-bis-abeo-drim-11-yl]cyclopent-4-en-1,3-dione (12): To a solution of **36** (20.0 mg, 0.058 mmol) in dichloromethane (1.3 mL) cooled to 0 °C is added PIDA (25.5 mg, 0.058 mmol). After 30 min of stirring the reaction mixture is concentrated under reduced pressure. Acetonitrile (1.3 mL) is added and mixture is heated to reflux for

3 h. After cooling, the reaction mixture is concentrated to dryness. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol, 0:1 → 95:5 → 9:1) to afford **12** as a yellow oil (3.7 mg, 20 %). IR (neat): $\tilde{\nu}_{max}$ = 2960, 2918, 2854, 1746, 1690, 1649, 1451 cm^{-1}. ^1H NMR (300 MHz, [D]chloroform): δ = 2.93 (s, 2 H, 2-H), 2.64–2.43 (m, 3 H), 2.28–2.03 (m, 3 H), 1.79–1.66 (m, 2 H), 1.57–1.50 (m, 1 H), 1.46–1.33 (m, 3 H), 1.14 (s, 3 H), 1.01 (d, *J* = 6.0 Hz, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D]chloroform): δ = 216.5 (C-4′), [196.7, 196.1 (C-1/C-3)], 160.1 (C-4), 133.7 (C-5′), 49.9 (C-10′), 49.5 (C-9′), 44.1 (C-5′), 40.3 (C-2), 38.2 (C-8′), 37.6 (CH_2), 32.7 (CH_2), 31.6 (CH_2), 27.0 (CH_2), 26.1 (CH_2), 21.9 (CH_2), 19.1 (CH_3), 18.0 (CH_3), 17.3 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{19}H_{26}O_4Na^+$ $[M + Na]^+$ 341.1723; found 341.1736. $[\alpha]_D^{20}$ = –29 (*c* = 0.034, $CHCl_3$).

4,10′-Epoxy-5-[(5*S*,9*R*,10*S*)-15(10→9)-abeodriman-11-yl]cyclopent-4-en-1,3-dione (13): To a solution of **31** (32.5 mg, 0.094 mmol) in dichloromethane (1.6 mL) cooled to 0 °C is added PIDA (30.4 mg, 0.094 mmol). After 30 min of stirring the reaction mixture is concentrated under reduced pressure. Acetonitrile (1.6 mL) is added and mixture is heated to reflux for 3 h. After cooling, the reaction mixture is concentrated to dryness. Purification by flash chromatography with silica gel (eluent: dichloromethane/methanol, 95:5 then 9:1) affords **13** as a yellow oil (14.2 mg, 48 %). IR (neat): $\tilde{\nu}_{max}$ = 2958, 2941, 2905, 2870, 1746, 1695, 1633, 1460 cm^{-1}. ^1H NMR (400 MHz, [D]chloroform): δ = 2.81 (s, 2 H, 2-H), 2.47 (d, *J* = 18.8 Hz, 1 H, 15′-H), 1.97 (d, *J* = 18.8 Hz, 1 H, 15′-H), 1.60–1.50 (m, 3 H), 1.47–1.38 (m, 3 H), 1.36–1.10 (m, 4 H), 1.01 (s, 3 H, 11′-H), 0.93 (s, 3 H, 14-H), 0.86 (s, 3 H, 12′-H), 0.71 (d, *J* = 6.2 Hz, 3 H, 13′-H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 195.7 (C=O), 193.7 (C=O), 166.3 (C-4), 132.8 (C-5), 89.9 (C-10′), 45.8 (C-5′), 42.3 (C-2), 41.6 (C-3′), 37.9 (C-9′), 33.7 (C-4′), 32.6 (C-8′/C-12′), 30.4 (C-7′), 29.5 (C-1′), 26.2 (C-15′), 22.4 (C-11′), 21.9 (C-6′), 17.8 (C-2′), 17.5 (C-14′), 16.5 (C-3′) ppm. HRMS (ESI): *m/z* calcd. for $C_{20}H_{29}O_3^+$ $[M + H]^+$ 317.2111; found 317.2121. $[\alpha]_D^{20}$ = –31 (*c* = 0.064, $CHCl_3$).

Cell Proliferation Assay: The in vitro cytotoxic activity of compounds **1**–**19**, **21**, **23**–**29**, **31**–**32** was evaluated by using the 3-[4,5-dimethylthiazol-2-yl]-3,5-diphenyltetrazolium bromide (MTT) test. Cells were seeded in growth medium (100 µL; HUVEC: 5×10^3 cells mL^{-1}; Hep-G2: 5×10^3 cells mL^{-1}; A549: 5×10^3 cells mL^{-1}), in 96-well plates (TPP), and incubated for 24 h. Cells were then treated with test compounds (DMSO 100 µL) at a series of concentrations and incubated at 37 °C for 48 h. The initial cell densities and incubation times were determined to allow the cells to remain in exponential growth. At the end of the incubation period, MTT (Sigma–Aldrich; 5 mg mL^{-1} solution in phosphate buffered saline; 20 µL) was added to each well. After 1 to 4 h of incubation at 37 °C, the culture medium was removed and replaced by DMSO (200 µL) to dissolve the formazan crystals. After 5 min of stirring, the absorbance of the solubilized dye was measured spectrophotometrically with a microplate reader (LAB System Original Multiscan MS) at 570 nm. The percentage of viable cells for each treatment was calculated from the ratio of the absorbance of the well containing the treated cells versus the average absorbance of the control wells (i.e., untreated cells). All experiments were set up in triplicate to determine means and standard deviations. To circumscribe the IC_{50} values cells were treated with test compounds at a series of concentrations: 0.5, 1.0, 5.0, 10.0, 20.0, 30.0 and 50.0 µM and if necessary at 2.5, 7.5 and 12.5 µM.

***Quorum sensing* Inhibition Screenings:** Artificial sea water was purchased by SIGMA, S9883 (St. Quentin Fallavier, France); Lennox broth (Invitrogen™, 12780–052) by Life technologies (Saint Aubin, France); Bacto™ Peptone and yeast extract for Zobell liquid media bioassays by Becton Dickinson Co. (Le Pont de Claix, France). The strains used for this bioassay are *V. harveyi* BB120 wild type (ATCC BAA-1116) and its derived double mutants (JAF 375, JMH 597 and JMH 612) obtained from Bassler's laboratory.[47] BB120 strain was shown to exhibit strong virulence in brine shrimp *Artemia franciscana* whereas the use of HAI-1, AI-2 and CAI-1-deficient mutants abolished virulence of *V. harveyi* to brine shrimp.[48] Twenty four hour old bacteria colonies were suspended in Lennox broth (5 mL, Invitrogen™ 12780–052) prepared in artificial sea water 3.5 % w/v and incubated for 16 h whilst stirring at 27 °C. The optical absorbance (OD) of each bacterial culture at wavelength λ = 600 nm was adjusted at 0.012 (approx. 10^7 bacteria mL^{-1} after numeration on a Malassez cell) by dilution in Zobell media (0.5 % w/v Bacto™ peptone, 0.1 % w/v yeast extract in artificial sea water). The compounds were dissolved in ethanol and deposited in the 96 wells plates and dried. Bacterial suspension (200 µL, final concentration of compounds: 50 µg mL^{-1}) was added in the wells and incubated at 27 °C in a BMG FLUOstarOPTIMA microplate reader (Labtech), in which luminescence and absorbance at 600 nm wavelength were measured every 10 min after 5 min of double orbital stirring during 11 h 50 min (71 cycles). At the end of the incubation time, the absence of bacterial growth inhibition due to the tested compounds was verified by OD_{600} measurements and comparison with the control experiment performed without tested compound. A Spearman's rank correlation test was used to determine the correlation between OD_{600} measurements. Every compound was tested in quadruplicate, for both luminescence production (relative luminescence units) and antibiotic or bacteriostatic activity (OD_{600}). An extract (CH_2Cl_2/CH_3OH, 1:1) of free dried *Leucetta Chagosensis* (50 µg mL^{-1}) was used as positive control. For each strain, luminescence and absorbance values were obtained after subtracting the background signal obtained with media and compounds sterility tests to the raw data.

Contributions: L. E., E. P. and C. D. conceived the project. D. L., L. E. and A. L. performed the synthetic experimental work. A. B. performed prospective experiments. D. L., A. B., B. S. M, L. E., M. A. B. and A. L. extracted ilimaquinone and 5-*epi*-ilimaquinone. S. P. and C. D. collected sponges. K. L. developed conditions for analytical and preparative HPLC. M. A. B. and L. E. reported the discovery of dactylocyanines series. G. G.-J. advised on chemoinformatic aspects. L. E. performed chemoinformatic analysis. J.-C. J. recorded 400 MHz NMR spectra. S. D. performed cytotoxicity evaluations. F. T., D. S. and C. D. performed quorum sensing inhibition evaluations. L. E. and E. P. wrote the manuscript with the help of D. L.

Acknowledgments

Camille Dejean (Université Paris-Sud) is gratefully acknowledged for assistance with NMR spectroscopy. This project was supported by the ANR (11-EBIM-006-01 Netbiome project POMARE). We gratefully acknowledge the French Polynesian authorities and Délégation à la Recherche-France in Tahiti for their help and support in the sponge survey in French Polynesia and collection of samples. We thank IRD and GOPS for funding the sampling trip aboard R/V ALIS, her crew, and IRD's diving team for their on-field help. Prof. Bonnie L. Bassler is gratefully acknowledged for *Vibrio harveyi* mutant strains she provided.

Keywords: Synthetic methods · Ilimaquinone · Ring-distortion · Quinones · Molecular diversity · Quorum sensing

[1] a) G. M. Cragg, D. J. Newman, *Biochim. Biophys. Acta BBA - Gen. Subj.* **2013**, *1830*, 3670–3695; b) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2016**, *79*, 629–661; c) K. Hübel, T. Leßmann, H. Waldmann, *Chem. Soc. Rev.* **2008**, *37*, 1361–1374; d) A. Reayi, P. Arya, *Curr. Opin. Chem. Biol.* **2005**, *9*, 240–247.

[2] a) A. A. Shelat, R. K. Guy, *Nat. Chem. Biol.* **2007**, *3*, 442–446; b) M. Garcia-Castro, S. Zimmermann, M. G. Sankar, K. Kumar, *Angew. Chem. Int. Ed.* **2016**, *55*, 7586–7605; *Angew. Chem.* **2016**, *128*, 7712.

[3] S. Sasidharan, Y. Chen, D. Saravanan, K. M. Sundram, L. Y. Latha, *Afr. J. Tradit. Complement. Altern. Med.* **2011**, *8*, 1–10.

[4] a) K. C. Nicolaou, S. A. Snyder, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11929–11936; b) E. A. Crane, K. Gademann, *Angew. Chem. Int. Ed.* **2016**, *55*, 3882–3902; *Angew. Chem.* **2016**, *128*, 3948.

[5] D. R. Spring, *Org. Biomol. Chem.* **2003**, *1*, 3867–3870.

[6] H. van Hattum, H. Waldmann, *J. Am. Chem. Soc.* **2014**, *136*, 11853–11859.

[7] R. W. Huigens III, K. C. Morrison, R. W. Hicklin, T. A. Flood Jr., M. F. Richter, P. J. Hergenrother, *Nat. Chem.* **2013**, *5*, 195–202.

[8] R. J. Rafferty, R. W. Hicklin, K. A. Maloof, P. J. Hergenrother, *Angew. Chem. Int. Ed.* **2014**, *53*, 220–224; *Angew. Chem.* **2014**, *126*, 224.

[9] A. Garcia, B. S. Drown, P. J. Hergenrother, *Org. Lett.* **2016**, *18*, 4852–4855.

[10] N. G. Paciaroni, R. Ratnayake, J. H. Matthews, V. M. Norwood, A. C. Arnold, L. H. Dang, H. Luesch, R. W. Huigens, *Chem. Eur. J.* **2017**, *23*, 4327–4335.

[11] R. T. Luibrand, T. R. Erdman, J. J. Vollmer, P. J. Scheuer, J. Finer, J. Clardy, *Tetrahedron* **1979**, *35*, 609–612.

[12] B. Carte, C. B. Rose, D. J. Faulkner, *J. Org. Chem.* **1985**, *50*, 2785–2787.

[13] For the **1**/**2** ratio distribution, see: a) A. Boufridi, D. Lachkar, D. Erpenbeck, M. A. Beniddir, L. Evanno, S. Petek, C. Debitus, E. Poupon, *Aust. J. Chem.* **2017**, *70*, 743–750; For further reading about similar anomalies, see: b) J. M. Finefield, D. H. Sherman, M. Kreitman, R. M. Williams, *Angew. Chem. Int. Ed.* **2012**, *51*, 4802–4836; *Angew. Chem.* **2012**, *124*, 4886.

[14] C. Debitus, *TUAM'2011 cruise, RV Alis*, **2011**, https://doi.org/10.17600/11100010.

[15] M.-L. Kondracki, M. Guyot, *Tetrahedron* **1989**, *45*, 1995–2004.

[16] S. Loya, R. Tal, Y. Kashman, A. Hizi, *Antimicrob. Agents Chemother.* **1990**, *34*, 2009–2012.

[17] D. M. Kushlan, D. J. Faulkner, L. Parkanyi, J. Clardy, *Tetrahedron* **1989**, *45*, 3307–3312.

[18] F. A. Barr, G. Warren, *Semin. Cell Dev. Biol.* **1996**, *7*, 505–510.

[19] K. W. L. Yong, A. Jankam, J. N. A. Hooper, A. Suksamrarn, M. J. Garson, *Tetrahedron* **2008**, *64*, 6341–6348.

[20] A. Boufridi, S. Petek, L. Evanno, M. A. Beniddir, C. Debitus, D. Buisson, E. Poupon, *Tetrahedron Lett.* **2016**, *57*, 4922–4925.

[21] T. Rosenau, K. Mereiter, C. Jäger, P. Schmid, P. Kosma, *Tetrahedron* **2004**, *60*, 5719–5723.

[22] H. W. Moore, R. J. Wikholm, *Tetrahedron Lett.* **1968**, *9*, 5049–5052.

[23] R. H. Thomson, *J. Chem. Soc. Resumed* **1951**, 1237–1239.

[24] F. B. Tamboura, C. S. J. Cazin, R. Pattacini, P. Braunstein, *Eur. J. Org. Chem.* **2009**, 3340–3350.

[25] N. Bonneau, G. Chen, D. Lachkar, A. Boufridi, J.-F. Gallard, P. Retailleau, S. Petek, C. Debitus, L. Evanno, M. A. Beniddir, E. Poupon, *Chem. Eur. J.* **2017**, *23*, 14454–14461.

[26] H. Mitome, T. Nagasawa, H. Miyaoka, Y. Yamada, R. W. M. van Soest, *J. Nat. Prod.* **2003**, *66*, 46–50.

[27] P. R. Story, J. R. Burgess, *Tetrahedron Lett.* **1968**, *9*, 1287–1292.

[28] E. Mvula, S. Naumov, C. von Sonntag, *Environ. Sci. Technol.* **2009**, *43*, 6275–6282.

[29] a) E. Bernatek, *Acta Chem. Scand.* **1954**, *8*, 1943–1943; b) E. Bernatek, K. N. Straumsgård, *Acta Chem. Scand.* **1959**, *13*, 178–185; c) E. Bernatek, K. Valen, *Acta Chem. Scand.* **1960**, *14*, 224–226.

[30] M. D. López, E. Quiñoá, R. Riguera, S. Omar, *J. Nat. Prod.* **1994**, *57*, 992–996.

[31] T. Ling, E. Poupon, E. J. Rueden, E. A. Theodorakis, *Org. Lett.* **2002**, *4*, 819–822; T. Ling, E. Poupon, E. J. Rueden, S. H. Kim, E. A. Theodorakis, *J. Am. Chem. Soc.* **2002**, *124*, 12261–12267.

[32] H. W. Moore, H. R. Shelden, D. W. Deters, R. J. Wikholm, *J. Am. Chem. Soc.* **1970**, *92*, 1675–1681.

[33] N. K. Utkina, V. A. Denisenko, O. V. Scholokova, A. E. Makarchenko, *J. Nat. Prod.* **2003**, *66*, 1263–1265.

[34] S. Urban, R. J. Capon, *Aust. J. Chem.* **1994**, *47*, 1023–1029.

[35] T. Katoh, S. Atsumi, R. Saito, K. Narita, T. Katoh, *Eur. J. Org. Chem.* **2017**, 3837–3849.

[36] M.-L. Bourguet-Kondracki, M.-T. Martin, M. Guyot, *Tetrahedron Lett.* **1992**, *33*, 8079–8080.

[37] a) E. Malamidou-Xenikaki, S. Spyroudis, M. Tsanakopoulou, *J. Org. Chem.* **2003**, *68*, 5627–5631; b) N. A. Calandra, S. M. King, S. B. Herzon, *J. Org. Chem.* **2013**, *78*, 10031–10057.

[38] P. V. Kiem, L. T. Huyen, D. T. Hang, N. X. Nhiem, B. H. Tai, H. L. T. Anh, P. V. Cuong, T. H. Quang, C. V. Minh, N. V. Dau, Y.-A. Kim, L. Subedi, S. Y. Kim, S. H. Kim, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1525–1529.

[39] E. G. Bakalbassis, S. Spyroudis, C. A. Tsipis, *Eur. J. Org. Chem.* **2008**, 1783–1788.

[40] a) T. W. H. Backman, Y. Cao, T. Girke, *Nucleic Acids Res.* **2011**, *39*, W486–W491; b) D. Bajusz, A. Rácz, K. Héberger, *J. Cheminf.* **2015**, *7*, 20.

[41] L. Owens, N. Busico-Salcedo in *Biol. Vibrios* (Eds.: F. L. Thompson, B. Austin, J. Swings), American Society of Microbiology, **2006**, pp. 266–280.

[42] J. A. Shapiro, *Annu. Rev. Microbiol.* **1998**, *52*, 81–104.

[43] H. L. Swaminath Srinivas, X. H. Guoli Gong, *J. Bacteriol. Parasitol.* **2013**, *04*, https://doi.org/10.4172/2155–9597.1000172.

[44] K. H. Nealson, T. Platt, J. W. Hastings, *J. Bacteriol.* **1970**, *104*, 313–322.

[45] T. Mai, F. Tintillier, A. Lucasson, C. Moriou, E. Bonno, S. Petek, K. Magré, A. Al Mourabit, D. Saulnier, C. Debitus, *Lett. Appl. Microbiol.* **2015**, *61*, 311–317.

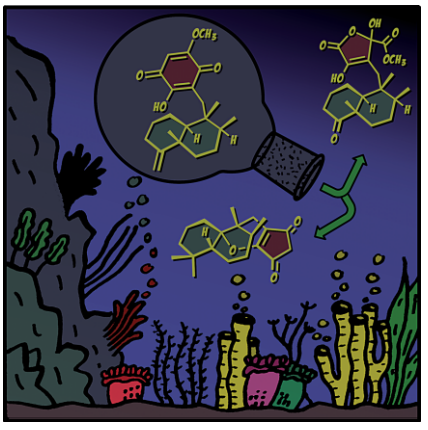
[46] a) G. D. Geske, J. C. O'Neill, H. E. Blackwell, *ACS Chem. Biol.* **2007**, *2*, 315–320; b) W. R. J. D. Galloway, J. T. Hodgkinson, S. Bowden, M. Welch, D. R. Spring, *Curr. Trends Microbiol.* **2012**, *20*, 949–958; c) W. R. J. D. Galloway, J. T. Hodgkinson, S. D. Bowden, M. Welch, D. R. Spring, *Chem. Rev.* **2011**, *111*, 28–67.

[47] J. M. Henke, B. L. Bassler, *J. Bacteriol.* **2004**, *186*, 6902–6914.

[48] T. Defoirdt, P. Sorgeloos, *ISME J.* **2012**, *6*, 2314–2319.

Received: January 11, 2018

Marine Natural Products



A ring-distortion strategy is applied to ilimaquinone and 5-*epi*-ilimaquinone. A diverse compound library was synthesised that included rearrangements of the sesquiterpene moiety and the quinone ring. Quorum sensing activity of *Vibrio harveyi* was evaluated and some of the new compounds were shown to be good quorum sensing inhibitor candidates.

DOI: 10.1002/ejoc.201800047