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Occurrence, biological activity and synthesis of cheilanthane sesterterpenoids

Nicon Ungur *, Veaceslav Kulciţki

Institutul de Chimie al A.Ş.M., str. Academiei, 3, Chişinău, MD-2028, Republic of Moldova

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Dedicated to Professor P.F. Vlad, mentor and friend, on the occasion of the 50th anniversary of his prodigious scientific activity

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Contents

1. Introduction

Cheilanthanes represent a relatively new class of tricyclic sesterterpenoids with a carbon skeleton of the hypothetic cheilanthane **1**. The name 'cheilanthane' is derived from the name of the fern *Cheilanthes farinosa*—the source of the first representative of this class of compounds, namely cheilanthatriol **2**, isolated in 1971 by Indian researchers.[1] Numerous cheilanthanic sesterterpenoids have been isolated later on from other plant sources, marine organisms and fossil sediments. Today, there are more then 50 known cheilanthanes. The majority of these compounds have been isolated in the 1990s, mostly from marine sources. The interest in these compounds is first of all due to their strong biological activity. This aspect has also inspired synthetic chemists to develop several synthetic routes to cheilanthane sesterterpenoids.

In this review, data on the structure and occurrence, biological activity and synthesis of cheilanthanes are presented. Cheilanthanes have been known for 35 years, but no review article has yet been published, although information has been collected periodically in reviews in *Natural Product Reports*.[2–5]

Abbreviations: Ac, acetyl; *n*-Bu, *n*-butyl; CSA, camphorsulfonic acid; *m*-CPBA, *m*-chloroperbenzoic acid; DBU, 1,8-diazobicyclo[5.4.0]undec-7-ene; DCC, 1,3-dicyclohexylcarbodiimide; DHP, 3,4-dihydro-2*H*-pyran; DME, ethylene glycol dimethyl ether; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; Et, ethyl; HMPA, hexamethylphosphoramide; LDA, lithium diisopropylamide; Me, methyl; Ms, mesyl; NaHMDS, sodium hexamethyldisilazide; NMO, 4-methylmorpholine *N*-oxide; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; Ph, phenyl; PhMe, toluene; PPTS, pyridinium *p*-toluenesulfonate; *i*-Pr, *i*-propyl; Py, pyridine; TBDMSCl, *tert*-butyldimethylsilyl chloride; THF, tetrahydrofuran; TPAP, tetrapropylammonium perruthenate; TPP, 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine.

* Corresponding author. Tel.: +373 22 739769; fax: +373 22 739954.
E-mail address: nicon.ungur@gmail.com (N. Ungur).

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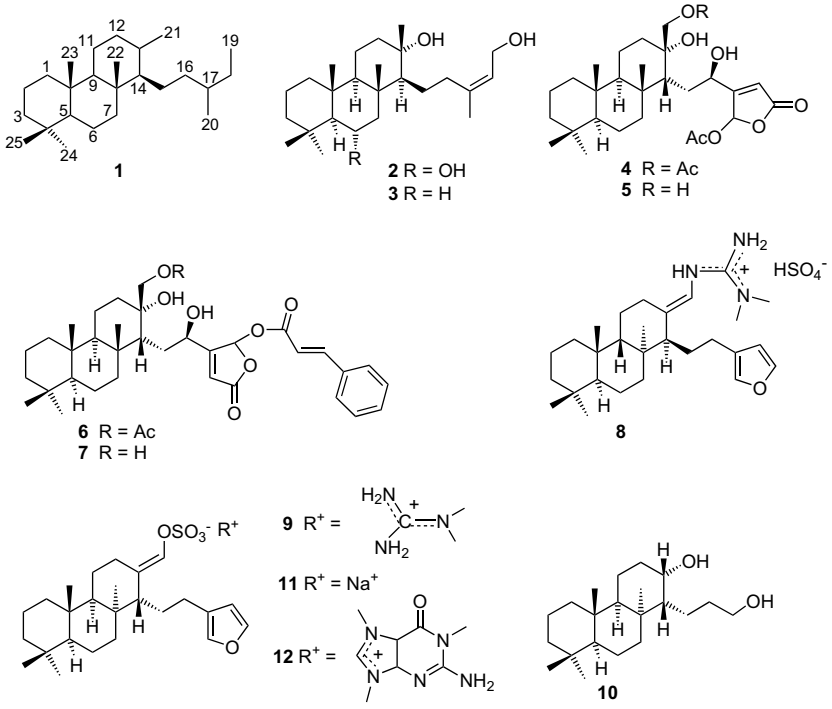
2. Structure and occurrence

The first representative of the cheilanthane sesterterpenoids is cheilanthatriol **2**, isolated from the fern *C. farinosa*.[1] Its structure was elucidated based on spectral data and chemical modifications. The stereochemistry at C6 and C13, as well as the configuration of the double bond in the side chain, were determined later,[6] using ^{1}H and ^{13}C NMR data. Cheilanthatriol **2** was also isolated by Japanese researchers from the ferns *Aleuritopteris khunii*[7] and *Aleuritopteris mexicana*,[8] along with cheilanthadiol **3**. It is noteworthy that **2** and **3** have the cis-configuration of the double bond in the side chain. The corresponding trans-isomers of cheilanthanes **2** and **3** have not yet been found in nature. The cheilanthanes **4**–**7**, with the general name vulgaroside, have been isolated from the aerial parts of *Cydonia vulgaris* Pers. (*Rosaceae*),[9] a small tree, widely cultivated in Italy and commonly known as 'melo cotogno', used in folk medicine for the treatment of various skin diseases. Their structure was elucidated based on spectral data. Unlike cheilanthatriol **2** and cheilanthadiol **3**, which have a β-orientation of the side chain, the vulgarosides **4**–**7** have an α-orientation of the side chain. The butenolide fragment in the side chain, which is a common structural fragment in cheilanthanes, is also present in the vulgarosides **4**–**7**.

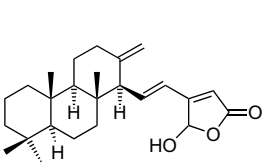
noteworthy that the suvanine salts **9**, **11** and **12** are epimeric at C9 and C14.

The same sponge *Ircinia*, collected in the Queensland area of Australia, provided the four cheilanthanes **13**–**16**.[14] Their structures were determined using NMR methods. All of the compounds contain a butenolide moiety. It is noteworthy that the cheilanthane **14** was reported earlier under the name lintenolide C,[15] isolated from the sponge *Cacospongia* cf. *linteiformis*, collected in the Caribbean Sea. The same sponge also provided the lintenolides A **17**, B **18**,[16] D **19**, E **20**,[15] F **21** and G **22**.[17] The cheilanthanes **17** and **18**, respectively, named as spongianolides C and D, have also been isolated from the marine sponge *Spongia* sp., collected in the channel between Ohio and Grassy Keys, Florida.[18] The spongianolides A **23**, B **24**, E **25** and F **26** have been isolated along with **17** and **18** from the same source. The structures of **17** and **18** and **23**–**26** were elucidated by spectral means. The cheilanthanes **17** and **18** and **23**–**26** contain extra functional groups at C13 and C21, and a butenolide group in the side chain.

The cheilanthanes **27** and **28** were isolated from the New Caledonian sponge species of the genus *Dactylospongia*.[19] Their structures were determined using 1D and 2D NMR spectroscopy. It was assumed that **27** and **28** result from intramolecular acetalisation of



The majority of the natural cheilanthanes have been extracted from marine organisms, especially from sponges, although they have also been found in nudibranch molluscs. The first cheilanthane isolated from the sponge of the genus *Ircinia* was suvanine.[10] The initial structure of suvanine, containing furan and guanidine sulfate groups, was assigned as **8**, based on spectral data.[10] Later, the structure of suvanine, isolated from the sponge *Coscinoderma matthewsi* from the Fiji islands, was revised to **9**, after re-examining the spectral data. The C9 stereochemistry was established by X-ray analysis of the diol **10**—a degradation product of suvanine **9**.[11] The suvanine sodium salt **11** was isolated from a sponge of the *Hippospongia* species[12] and the corresponding 1-methylherbipoline salt **12** was isolated later from the sponge *C. matthewsi*.[13] It is luffolide **29**, which was isolated from a sponge of the genus *Luffariella*.[20] The structure of **29** was established based on spectral data and confirmed by X-ray analysis. Later, the cheilanthanes **27** and **28** were also isolated from the sponge *Petrosaspongia nigra*, collected in New Caledonia, and named as petrosaspongiolides A and B.[21] Petrosaspongiolides C–J **30**–**37**,[21] M–N **38**–**39**[22] and P–R **40**–**42**[22] were isolated from the same source. The structures of compounds **26**–**38** were established based on spectral data. From the extract of the Vanuatuanian sponge of the genus *Spongia*, petrosaspongiolides D **31** and G **34** were isolated,[23] as well as cheilanthane **43**, which is a C25 hydroxylated petrosaspongiolide P. The hydroxylation of C25 is a characteristic feature also in the cheilanthanes **30**–**36** and **39**–**42**.



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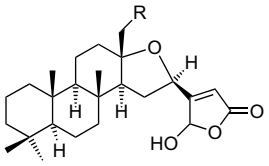
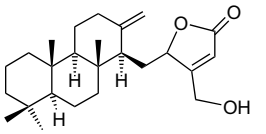


14 R = H
17 R = OC(O)Me
21 R = OH
25 R = OC(O)CH_2CH(OH)Me



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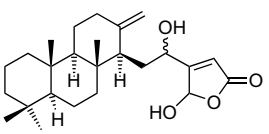

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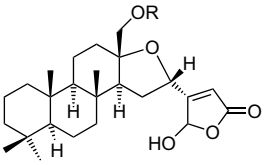
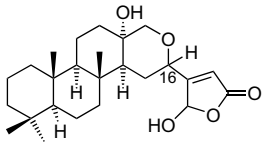
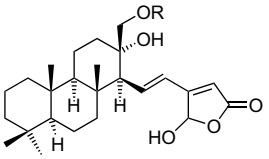


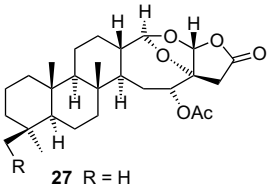
18 R = C(O)Me
22 R = H
26 R = C(O)CH_2CH(OH)Me



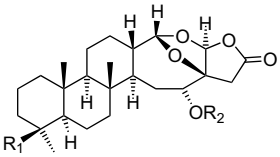
19 16αH
20 16βH



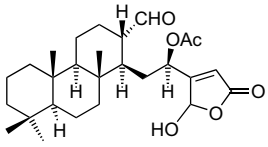
23 R = C(O)Me
24 R = C(O)CH_2CH(OH)Me



27 R = H
36 R = OAc



28 R_1 = Me; R_2 = Ac
34 R = CH_2OH; R_2 = H
35 R = CO_2H; R_2 = H



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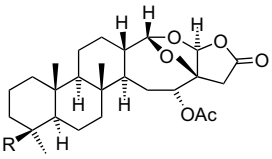
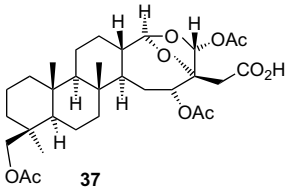


30 R = CH_2OAc
31 R = CH_2OH
32 R = CHO
33 R = CO_2H



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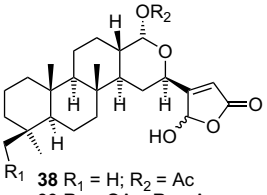
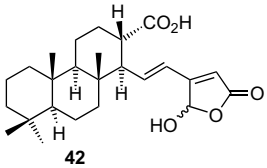


38 R_1 = H; R_2 = Ac
39 R_1 = OAc; R_2 = Ac
40 R_1 = R_2 = H
41 R_1 = OAc; R_2 = H
43 R_1 = OH; R_2 =H



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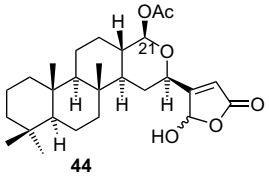


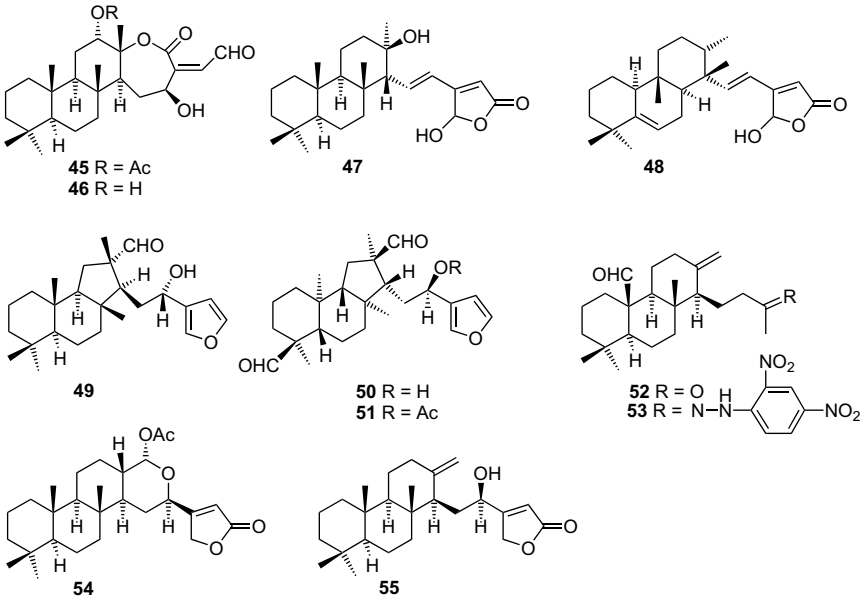
44

The Tyrrhenian sponge *Fasciospongia cavernosa* provided cavernosolide **44**.[24] Its structure has been suggested based on spectral analysis and the absolute stereochemistry was determined based on the CD curve comparison with those of known compounds.[25] The cheilanthane **44** represents the C21 epimer of the previously reported compound **38**.

Two new cheilanthanes, hyatolides A **45** and B **46**, were isolated recently[26] from the sponge *Hyatella intestinalis*, from the Gulf of California.

Investigation of the Indo-Pacific sponge *Aplysinopsis* led to the isolation of two cheilanthanes, aplyolide A **47** and aplysolide A **48**. Their structures were determined using 1D and 2D NMR spectroscopy.[27] Compound **48** has a rearranged cheilanthane skeleton.

Cheilanthanes are considered to be biosynthetic precursors of another kind of tricarbocyclic sesterterpenoid like hyrtiosal **49**, isolated from the Okinawan marine sponge *Hyrtios erecta* by Japanese researchers.[28] The structure of hyrtiosal **49** represents a cheilanthane skeleton with a contracted C-ring. Its structure was



established based on spectral data and chemical modifications,[28] and was recently[29] confirmed by X-ray analysis. The authors[28] have proposed a possible biosynthesis for the formation of hyrtiosal **49** from cheilanthane precursors. Compound **49** has, later, also been isolated from the same type of sponge, *H. erecta*, collected in the Red Sea.[30]

Chinese researchers[31] have recently isolated two new rearranged cheilanthanes from the sponge *H. erecta* collected from the South China Sea, namely 20-formyl-*ent*-hyrtiosal **50** and its acetate **51**. It is noteworthy that the structures of these compounds belong to the *ent*-series.

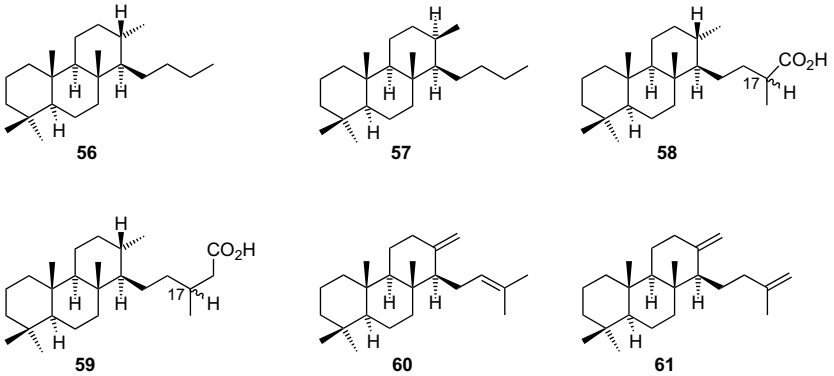
Investigation of molluscs has also led to the isolation of several cheilanthanes. Andersen and co-workers[32,33] reported the isolation of luteon **52** from the Dorid nudibranch *Cadlina luteomarginata*. The structure of luteon was suggested based on spectral data and confirmed by X-ray analysis of the crystalline derivative **53**. Luteon represents a bisnorcheilanthane, and lacks the carbon atoms C18 and C19. It is the only representative of this class of compounds, possessing an oxygenated functional group at C23.

The isolation of inorolide C **54** was reported from the Japanese nudibranch *Chromodoris inornata* (*Chromodorididae*),[34,35] and its structure was determined by X-ray analysis. This compound has a similar structure to that of petrosaspongiolide M **38**, except for the presence of a hydroxyl group at C20. The cheilanthane, hamiltonin C **55**, was isolated from the South African nudibranch *Chromodoris hamiltoni*,[36] and its structure was determined based on spectral data.

Other sources of cheilanthanes are petroleum fractions and sediments. The biosynthetic origin of these compounds is still not clear, and possible precursors are the di-*trans*-poly-*cis* polyprenols from plants.

Bisnorcheilanthane **56** and its isomer **57** were isolated from Athabasca oil sand bitumen. Their structures were based on mass spectra and on correlation of the ^{1}H NMR methyl shifts of **56** with those of cheilanthatriol **2**.[1,6] The hydrocarbon **56** is the most abundant member of the so-called terpane fraction (C_{20}–C_{45}), which constitutes an important class of biological markers for information about the processes affecting organic matter in geological environments.[37–39] It is noteworthy that these bisnorcheilanthane hydrocarbons **56** and **57** have also been found in other samples of oil sand.[40,41]

The two saturated tricyclic acids **58** and **59** were isolated from Alberta oil sands in Canada.[42]



The two novel C24 cheilanthane alkenes **60** and **61** have been isolated after solvent extraction of a sulfur-rich sediment from Lake Cadagno (near Andermatt, Switzerland) and their structures were determined by NMR studies.[43] They represent the first example of

Table 1
Cytotoxicity against NSLC-N6 tumour cells of petrosaspongiolides A–J[21]

Compound	IC_{50} (μg/ml)	Compound	IC_{50} (μg/ml)
Petrosaspongiolide A **27**	13.0	Petrosaspongiolide F **33**	8.7
Petrosaspongiolide B **28**	14.8	Petrosaspongiolide G **34**	Inactive
Petrosaspongiolide C **30**	0.5	Petrosaspongiolide H **35**	8.1
Petrosaspongiolide D **31**	5.2	Petrosaspongiolide I **36**	6.8
Petrosaspongiolide E **32**	4.5	Petrosaspongiolide J **37**	6.3

functionalised tricyclic hydrocarbons structurally related to the tricyclopolyprenanes, which are widespread in fossil sediments and petroleum samples.

3. Biological activity of cheilanthane sesterterpenoids

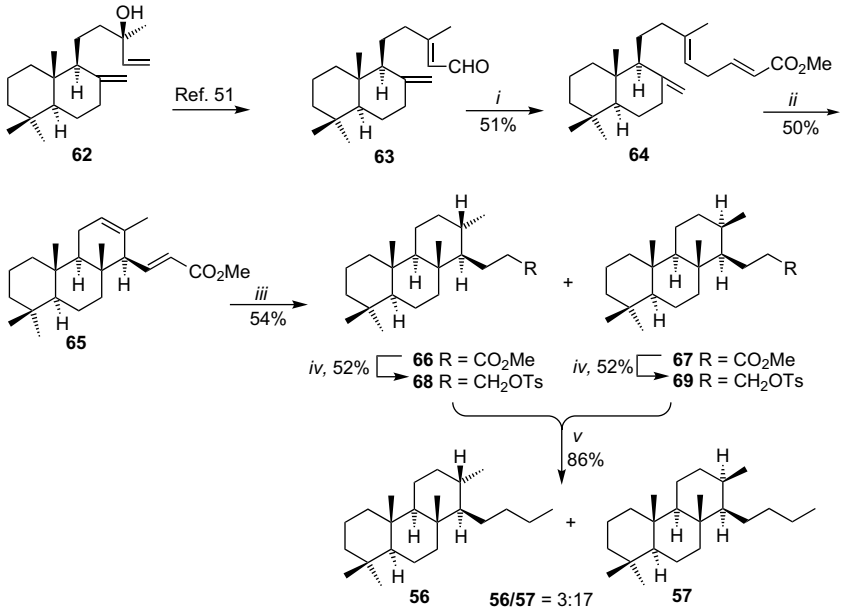
Suvanine **9** possesses a chemical defensive role, suggested by its ichthyotoxicity to goldfish at 10 μg/ml.[10] It exhibits >90% inhibition of sea egg cell division at 16 μg/ml.[44] Jacobs and co-workers[44] have found that suvanine facilitates neuromuscular transmission in indirectly stimulated rat hemidiaphragm preparations. Suvanine is also an acetylcholinesterase inhibitor, and similar properties are exhibited by the suvanine sodium salt **11** (Jacobs, unpublished data). It is also a reductase inhibitor, and a modest inhibitor of *Mycobacterium smegmatis* mycothiol-*S*-conjugate amidase with an IC_{50} value of 60 μM.[45]

Suvanine and its salts **11**, **12** and **9** possess serine protease-inhibiting activity against thrombin and trypsin.[13] For inhibition against thrombin, **11** shows moderate activity (IC_{50}=9 μg/ml), **12**: IC_{50}=27 μg/ml and **9**: IC_{50}=25 μg/ml. For inhibition against trypsin, suvanine and its salts show the following values **11**: IC_{50}=27 μg/ml, **12**: IC_{50}=12 μg/ml and **9**: IC_{50}=23 μg/ml.

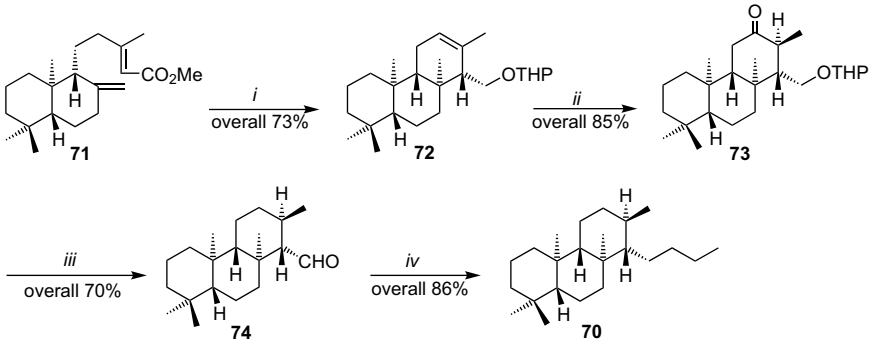
The anti-HIV activity of compounds **4**–**7** has been tested in vitro. They are inactive at the highest nontoxic concentration of 2.5 μg/ml.[9]

Lintenolides A **17** and B **18** show high ichthyotoxicity and antifeedant activity, which suggests their potential role as natural feeding deterrents. Ichthyotoxicity tests on the mosquito fish *Gambusia affinis* show that lintenolides A **17** and B **18** are toxic at a concentration of 10 ppm. Antifeedant assays conducted with the fish *Carassium auratus* show that both compounds **17** and **18** possess a high feeding deterrence at a concentration of 30 μg/cm^2 of food pellets.[16]

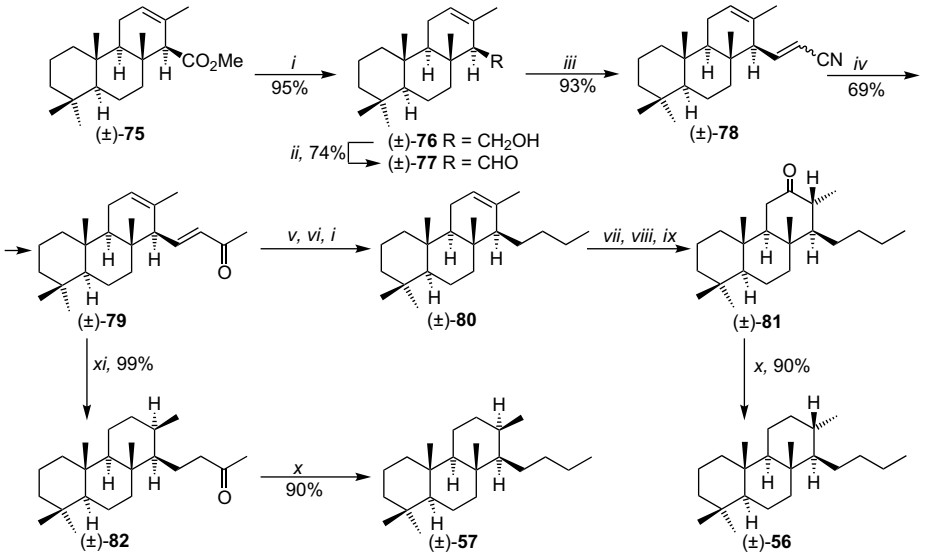
Lintenolides A **17** and B **18** also inhibit PKC at IC_{50}=20–30 μg/ml, and do not inhibit human 85-kD phospholipase A_2 (PLA_2). These compounds potently inhibit (IC_{50}=0.50–1.40 μg/ml) proliferation of the mammary tumour cell line MCF-7.[18]



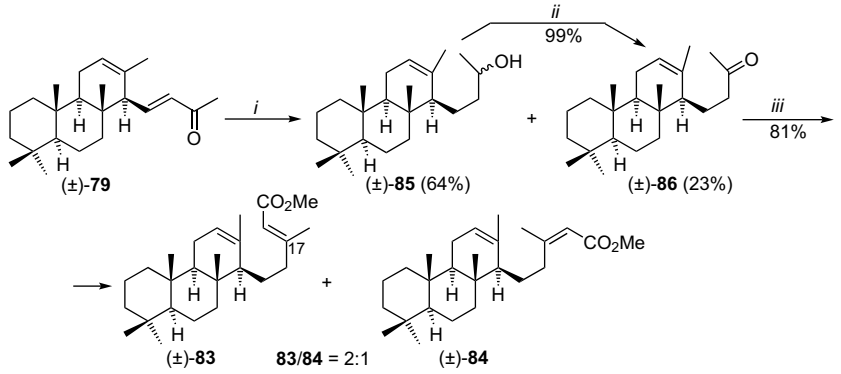
Scheme 1. Reagents and conditions: (i) $(MeO)_2P(O)CH_2CO_2Me$, NaH, DMSO, 60 °C, 30 min; (ii) $BF_3{\cdot}Et_2O$, C_6H_6, 10 °C to rt, 72 h; (iii) H_2, PtO_2, AcOH, rt, 6 h; (iv) (1) $LiAlH_4$, Et_2O, rt; (2) *p*-TsCl, Py, rt; (v) MeMgCl, Li_2CuCl_4, THF.



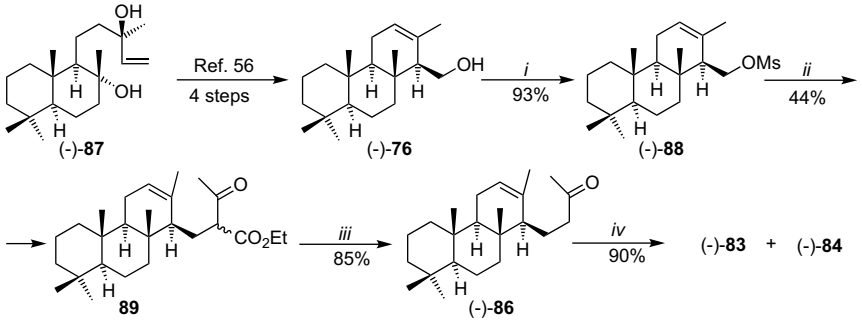
Scheme 2. Reagents and conditions: (i) (1) HCO_2H (98%), rt, 12 h; (2) $LiAlH_4$, Et_2O, reflux, 4 h; (3) DHP, CH_2Cl_2, CSA, rt; (ii) (1) $BH_3{\cdot}SMe_2$, THF, 20 h; (2) H_2O_2, 3 M NaOH aq, EtOH, reflux, 1 h; (3) $CrO_3{\cdot}2Py$, CH_2Cl_2, rt; (iii) (1) $N_2H_2{\cdot}H_2O$, *p*-TsOH, $(HOCH_2)_2$, 130 °C, 4 h, then KOH, 210 °C, 3 h; (2) 10% HCl aq, MeOH, hexane, (3) $CrO_3{\cdot}2Py$, CH_2Cl_2, rt; (iv) (1) $Ph_3P{=}CHEt$, DMSO; (2) H_2, 10%Pd/C, MeOH/EtOAc.



Scheme 3. Reagents and conditions: (i) $LiAlH_4$, Et_2O, reflux, 2 h; (ii) PCC–Al_2O_3, C_6H_6, rt, 3 h; (iii) NaH, $(MeO)_2P(O)CH_2CN$, THF; (iv) (1) MeLi, Et_2O, 0 °C; (2) 1 N H_2SO_4/Me_2CO (1:9), 1 h; (v) Na/NH_3 (liq.), −69 °C, 1 h; (vi) *p*-TsCl, Py, CH_2Cl_2, rt, 15 h; (vii) (1) $BH_3{\cdot}SMe_2$, rt, 20 h; (2) H_2O_2, 3 M NaOH, 40 °C, 1.5 h; (viii) Jones reagent, Me_2CO, 0 °C, 30 min; (ix) MeONa, MeOH, rt, 30 min, overall yield after 6 steps (v, vi, i, vii–ix) ~40%; (x) (1) $(HSCH_2)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 14 h; (2) Ni-Raney, EtOH, reflux, 4 h; (xi) PtO_2, H_2 (3 atm), EtOAc, rt, 4 h.



Scheme 4. Reagents and conditions: (i) Na/NH_3 (liq.), −69 °C, 1 h; (ii) Jones reagent, Me_2CO, 0 °C, 30 min; (iii) $(MeO)_2P(O)CH_2CO_2Me$, C_6H_6, NaOMe, 70 °C, 1 h.



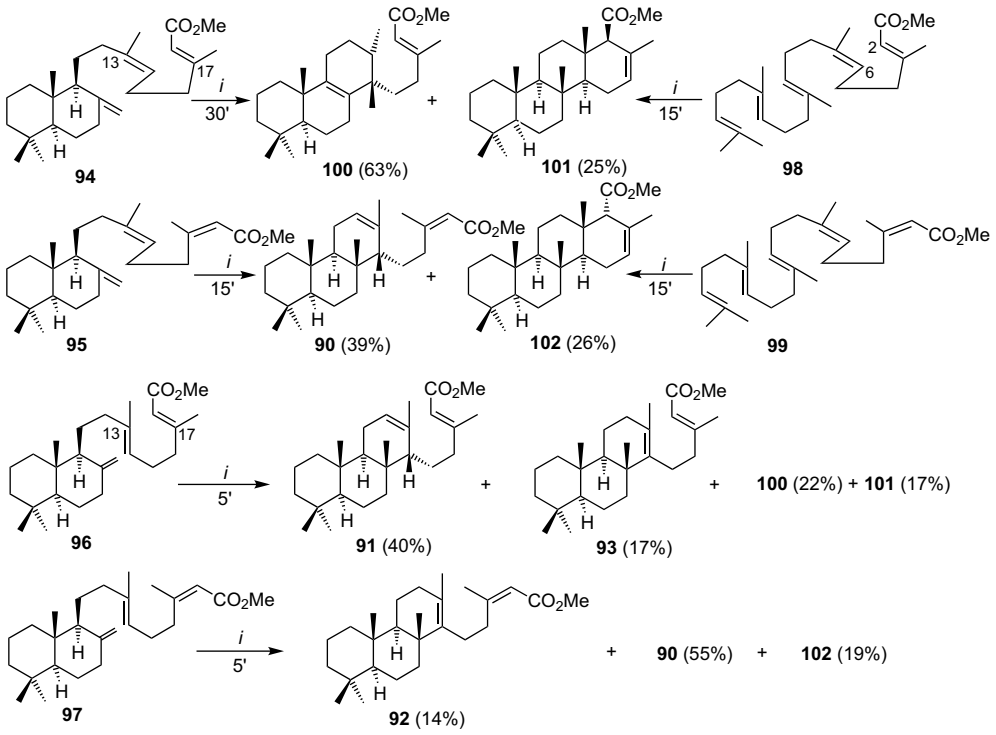
Scheme 5. Reagents and conditions: (i) MsCl/Py, DMAP, 0 °C, 6 h and rt, 12 h; (ii) MeC(O)CH(Na)CO_2Et, PhMe, reflux, 4 h; (iii) 10% NaOH/EtOH, reflux, 3 h; (iv) $(MeO)_2$-$P(O)CH_2CO_2Me$, C_6H_6, NaOMe, 70 °C, 2 h.

Spongianolides A, B, E and F **23**–**26** inhibit PKC at IC_{50}= 20–30 μg/ml, but show no activity towards human 85-kD phospholipase A_2. Compounds **23** and **24** potently inhibit (IC_{50}=0.50–1.40 μg/ml) proliferation of the mammary tumour cell line MCF-7.[18]

Cheilanthane sesterterpenes **13**–**16** inhibit MSK1 (mitogen and stress activated kinase) and MAPKAPK-2 (mitogen activated protein kinase/activated protein kinase), two protein kinases involved in mitogen and stress signal transduction. Both enzymes are located in the nucleus and are thus late in the signal transduction pathway. Selective inhibitors of these enzymes will be most likely to exhibit highly specific cellular effects.[14]

Luffolide **29** possesses anti-inflammatory activity and inhibits the hydrolysis of phosphatidylcholine by bee venom PLA_2.[20]

Carvernosolide **44** shows potent activity (IC_{50}=0.37 μg/ml) in an *Artemia salina* bioassay and moderate toxicity (IC_{50}=0.75 μg/ml) in a fish (*Gambusia affinis*) lethality assay.[24]



Scheme 6. Reagents and conditions: (i) FSO_3H (5 equiv), *i*-$PrNO_2$, −78 °C, then Et_3N.

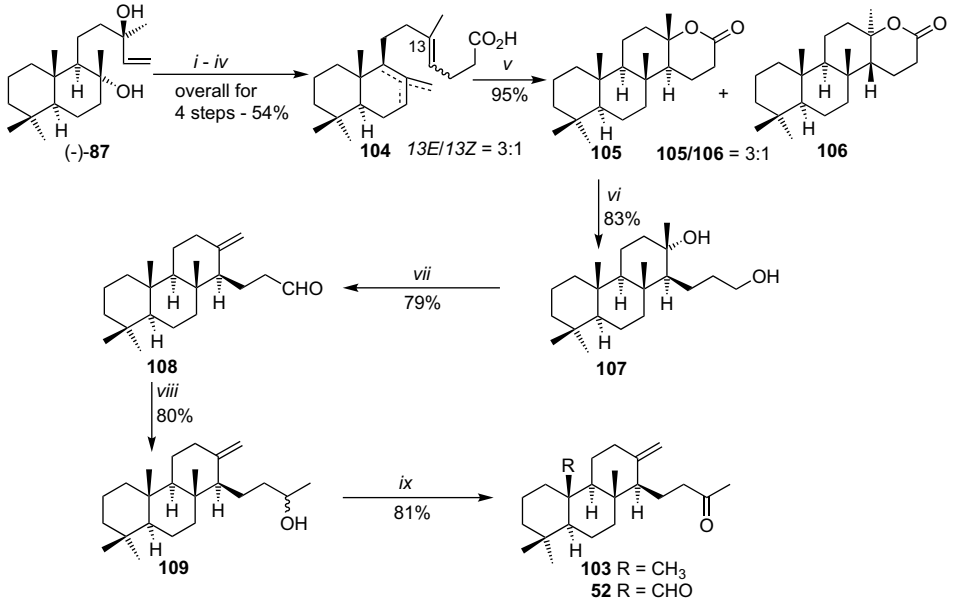
Hyatolide A **45** shows activity as a growth inhibitor of several tumour cell lines.[26]

Inorolide C **54** possesses cytotoxic and neurotogenic activity (IC_{50}=0.20 μg/ml) for murine lymphoma L1210 and for human epidermoid carcinoma KB cell lines (IC_{50}=2.80 μg/ml).[34,35]

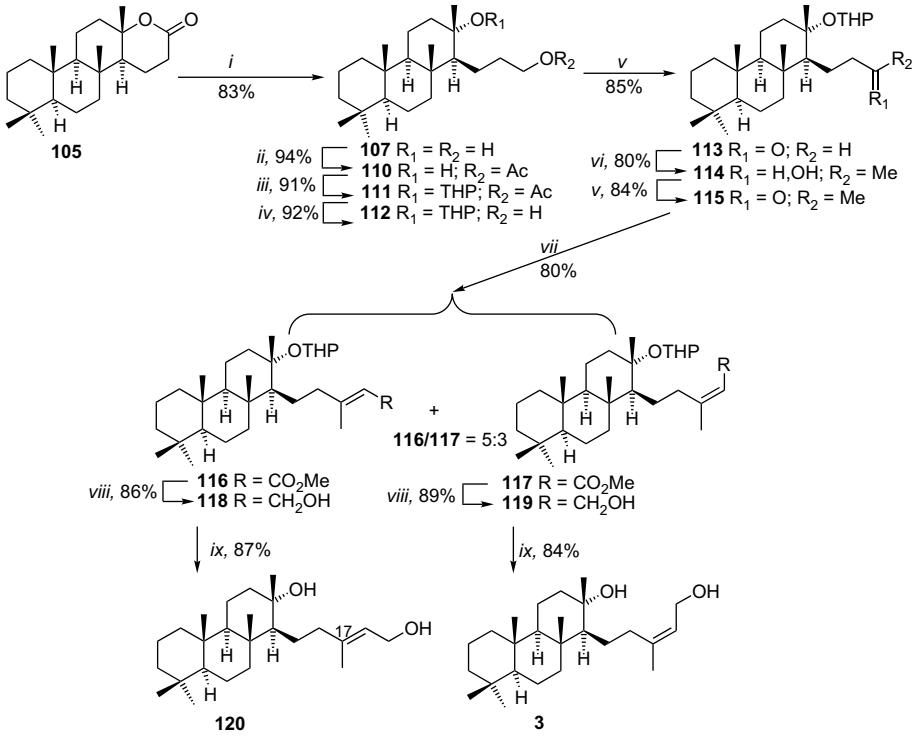
Aplyolide A **47** has been evaluated at Syntex Research in an anti-inflammatory assay for inhibition of human PMN PLA_2 enzyme. Aplyolide A shows 100% inhibition at 30 μM and IC_{50}=10.50 μM. This represents a mild positive activity result.[27]

Petrosaspongiolides A–J **27** and **28** and **30**–**37** have been submitted to in vivo tests on immunodepressed rats carrying a bronchopulmonary tumour (NSCLC-N6). An inhibition of tumour proliferation is observed (Table 1), without significant toxicity.[21]

Petrosaspongiolides M–N **38**–**39** and P–R **40**–**42** inhibit different preparations of PLA_2 by irreversibly blocking these enzymes (particularly human synovial and bee venom). These compounds display a much lower activity (or no activity at all) towards porcine pancreas and *Naja naja* venom PLA_2 enzymes. The most potent is



Scheme 7. Reagents and conditions: (i) PBr_3/Et_2O, Py, 0 °C, 12 h; (ii) K_2CO_3, $CH_2(CO_2Et)_2$, DMF, Me_2CO, $Et_3BnN^+Cl^-$, 75 °C, 20 h, 77%; (iii) NaCl/DMSO–H_2O, 155 °C, 26 h, 83%; (iv) 10% KOH/EtOH, reflux, 5 h, 90%; (v) FSO_3H (11 equiv), *i*-$PrNO_2$, −80 °C, 20 min, 95%; (vi) $LiAlH_4$, THF, rt, 3.5 h, 83%; (vii) $(COCl)_2$/DMSO, CH_2Cl_2, −60 °C, 45 min, then Et_3N, 79%; (viii) MeMgI (2.5 equiv), Et_2O, rt, 30 min, 80%; (ix) PDC/CH_2Cl_2, rt, 4 h, 81%.



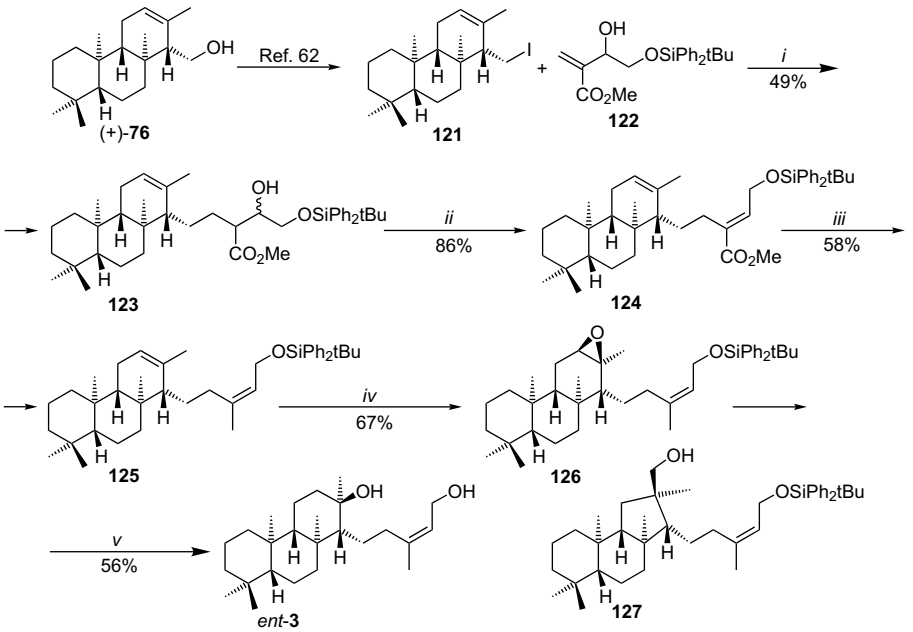
Scheme 8. Reagents and conditions: (i) $LiAlH_4$, THF, rt, 3.5 h; (ii) Ac_2O/Py, rt, 10 h; (iii) DHP, C_6H_6, *p*-TsOH (cat), rt, 2 h; (iv) 10% KOH/EtOH, rt, 3 h; (v) PDC/CH_2Cl_2, rt; (vi) MeMgI (3 equiv), Et_2O, rt, 45 min; (vii) LDA, THF, −78 °C, $Me_3SiCH_2CO_2Me$, 40 min; (viii) $LiAlH_4$–$CeCl_3$/THF, rt, 20 min; (ix) 0.02 N H_2SO_4/MeOH, rt, 40 min.

petrosaspongiolide M **38** (IC_{50} 1.6 and 0.6 μM for human synovial and bee venom PLA_2 enzymes, respectively).[22,46–49]

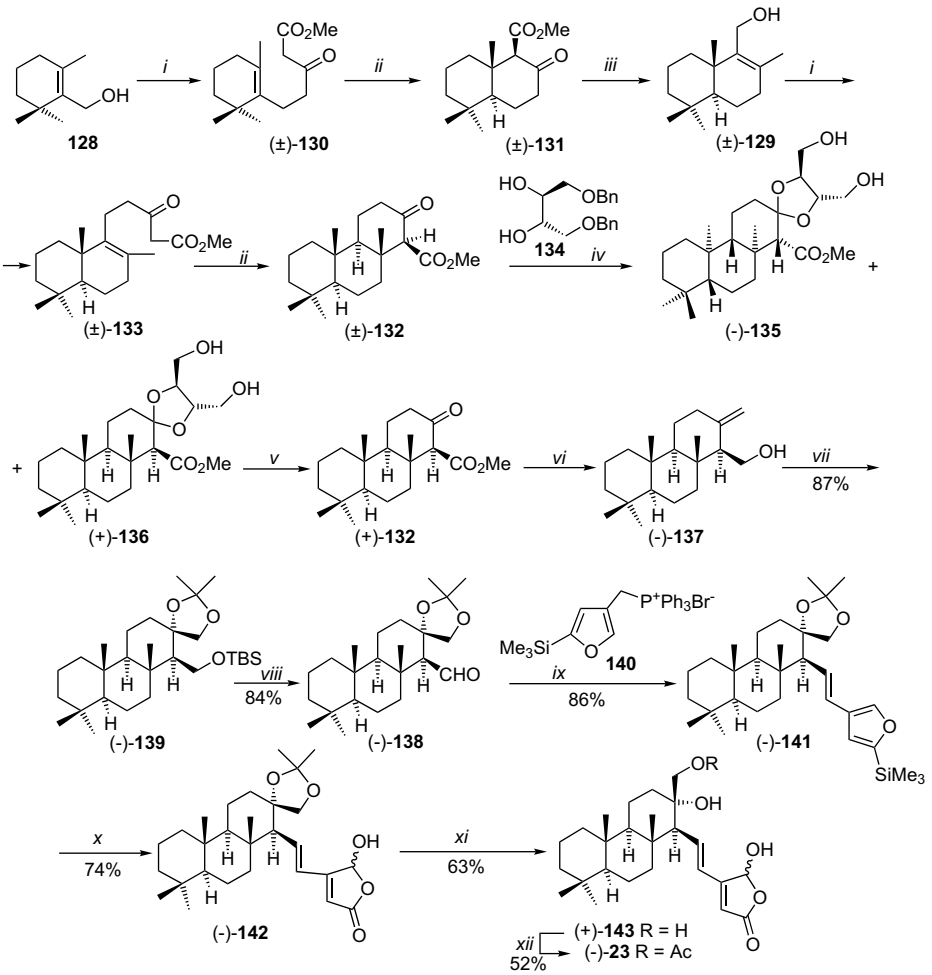
Hyrtiosal **49** inhibits the proliferation of KB cells in vitro.[28]

4. Synthesis of cheilanthane sesterterpenoids

The first reports on the synthesis of cheilanthanes go back 20 years and concern the bisnorcheilanthane hydrocarbons **56** and **57**, isolated from petroleum sediments.[37–39] These syntheses were targeted to molecular markers in petroleum sediments. Herz and co-worker were the first to prepare the hydrocarbons **56** and **57**, starting from manool **62** (Scheme 1).[50] Manool was oxidised to aldehyde **63** according to a reported procedure,[51] followed by chain elongation by a Wittig–Horner reaction to provide the triene **64**. This triene was cyclised to the trisnorcheilanthanic ester **65**, followed by hydrogenation over PtO_2 to a mixture of esters **66** and **67** (~1:10), which was converted in two steps via tosylates **68** and **69** into a mixture of the hydrocarbons **56** and **57** (~3:17).



Scheme 9. Reagents and conditions: (i) **122** (6 equiv), Bu_3SnH (1.8 equiv), Et_2O, hν (200 W tungsten lamp), 5 h; (ii) (1) MsCl, NEt_3, CH_2Cl_2, 0 °C; (2) DBU, PhMe, reflux, 4 h; (iii) (1) *i*-Bu_2AlH, PhMe, −78 °C; (2) CCl_4, PPh_3, reflux, 3 d; (3) $LiBHEt_3$, THF, 30 min; (iv) *m*-CPBA, CH_2Cl_2, −10 °C, 1.25 h; (v) (1) $LiAlH$*i*-Bu_2*n*-Bu, DME, reflux, 3.5 h; (2) *n*-Bu_4NF, THF, rt, 7.5 h.



Scheme 10. Reagents and conditions: (i) (1) PBr_3, Py, Et_2O; (2) NaH, THF, $MeC(O)CH_2CO_2Me$, 0 °C, *n*-BuLi; (ii) $SnCl_4$, CH_2Cl_2, −10 °C (0.5 h), rt (20 h); (iii) (1) NaH, THF, 0 °C, $ClP(O)(OEt)_2$, 0 °C to rt, 10 min; (2) MeLi, CuI, Et_2O, −10 to 0 °C, 30 min; (3) $LiAlH_4$, Et_2O, rt, overnight; (iv) (1) **134**, *p*-TsOH, C_6H_6, 90 °C, 2 h; (2) Pd/C, H_2, 68 atm, EtOAc, 23 °C, overnight; (3) SiO_2 separation; (v) 2 N H_2SO_4/aq MeOH, THF, 90 °C, 2 d; (vi) (1) $Ph_3P^+MeBr^+$, $NaNH_2$, THF, rt, 10 min; (2) $LiAlH_4$, THF, rt, 12 h; (vii) (1) Et_3N, DMAP, TBDMSCl, DMF, 0 °C, quant.; (2) OsO_4, Py, 4 h, then 2 M $NaHSO_3$ aq, 18 h, rt; (3) PPTS, $Me_2C(OMe)_2$, Me_2CO, rt; (viii) (1) *n*-Bu_4NF, THF, 60 °C, 3 h, quant.; (2) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 40 min, then Et_3N; (ix) *n*-BuLi, **140**, THF, then (−)-**138**, 0 °C, 1 h; (x) O_2, TPP, hν, CH_2Cl_2, −78 °C, 30 min; (xi) 2 N HCl aq, THF, 60 °C, 2 d; (xii) (1) Ac_2O, Py, 50 °C, 3 h; (2) $NaHCO_3$ aq, MeOH, rt, 30 min.

The synthesis of bisnorcheilanthane **70**, the enantiomer of **56**, was reported starting from the methyl ester of copalic acid **71** (Scheme 2),[52] which was transformed in three steps into the isocopalic THP-ether **72** in good yield. The later was converted in three steps into the ketoether **73**, and another three standard reactions provided the tricyclic saturated aldehyde **74**. Wittig olefination of **74** and hydrogenation then led to the hydrocarbon **70**.

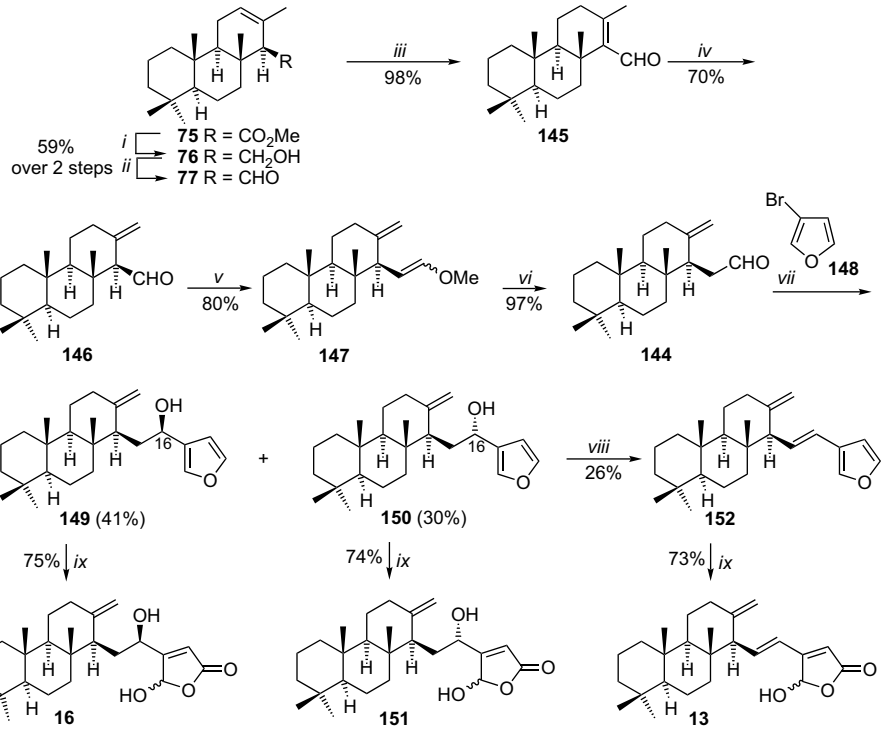
Racemic methyl isocopalate **75** was used as starting material by Ruveda and co-workers[53] in the synthesis of the bisnorcheilanthanic hydrocarbons **56** and **57** (Scheme 3). The side chain of the ester **75** was elongated in five steps. Initial reduction of the ester **75** to the corresponding alcohol **76** was followed by oxidation to the aldehyde **77**, olefinated with the corresponding phosphonate to the diene **78**. The latter was transformed to the α,β-unsaturated ketone **79**, which was converted into the individual bisnorcheilanthane hydrocarbons **56** and **57** by two different pathways. A three-step saturation-deoxygenation of the lateral chain in **79** provided the hydrocarbon **80**, which was transformed over other three steps to the tricyclic ketone **81**. Deoxigenation of **81** led to the hydrocarbon **56**. The hydrocarbon **57** was obtained in two steps from **79** via the tricyclic ketone **82**.

Ketodiene **79** was used in the synthesis of the racemic cheilanthane methyl esters **83** and **84** (Scheme 4).[54] Reduction of the double bond led also to reduction of the carbonyl group and a mixture of alcohol **85** and ketone **86** was obtained. Re-oxidation of the alcohol **85** with Jones reagent gave a quantitative yield of ketone **86**. A Wittig–Horner olefination led to the formation of a mixture of the cheilanthane esters **83** and **84**. Separation of this mixture was not reported, and the esters have been characterised as a mixture.

Recently, the synthesis of the individual optically active esters **83** and **84** has been reported, starting from (−)-sclareol **87** (Scheme 5).[55]

(−)-Sclareol **87** was transformed in four steps into the *ent*-isocopalic alcohol **76** according to a known procedure.[56] The *ent*-isocopalenol **76**, was converted to the corresponding mesylate **88**, that was coupled with sodium-ethyl acetoacetate, to give with a moderate yield (44%) the ethylcarboxy-*ent*-isocopalylacetone **89**. Compound **89** was decarboxylated with refluxing ethanolic NaOH to give *ent*-isocopalylacetone **86**. This compound was then submitted to Wittig–Horner reaction to afford a mixture of the two isomeric 17*E*- and 17*Z*-cheilanthanic esters (−)-**83** and (−)-**84**, which was separated chromatographically into the individual compounds.

A different synthetic strategy was used for the synthesis of C14 *epi*-cheilanthanic esters **90** and **91**, as well as the 17*Z*- and 17*E*-cheilanthane esters **92** and **93**, having a tetrasubstituted double bond in ring C of the tricyclic skeleton. The starting

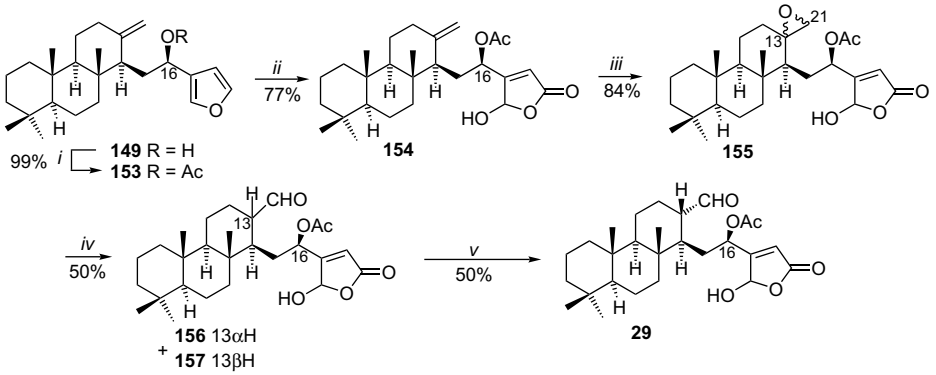


Scheme 11. Reagents and conditions: (i) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 2 h; (ii) TPAP, NMO, CH_2Cl_2, sieves 4 Å, rt, 1 h; (iii) *p*-TsOH, C_6H_6, 80 °C, 2 h; (iv) (1) LDA, HMPA, THF, −78 °C, 20 min; (2) H_2O/THF 1:3; (v) $(MeOCH_2Ph_3)^+Cl^-$, NaHMDS, THF, −78 °C, 1 h; (vi) *p*-TsOH, acetone/H_2O 45:1, rt, 12 h; (vii) 3-bromofuran **148**, *n*-BuLi, −78 °C, 1 h; (viii) $POCl_3$, Py, 0 °C to rt, 4 h; (ix) $^1O_2$ hν, Rose Bengal, CH_2Cl_2, −78 °C, 3 h.

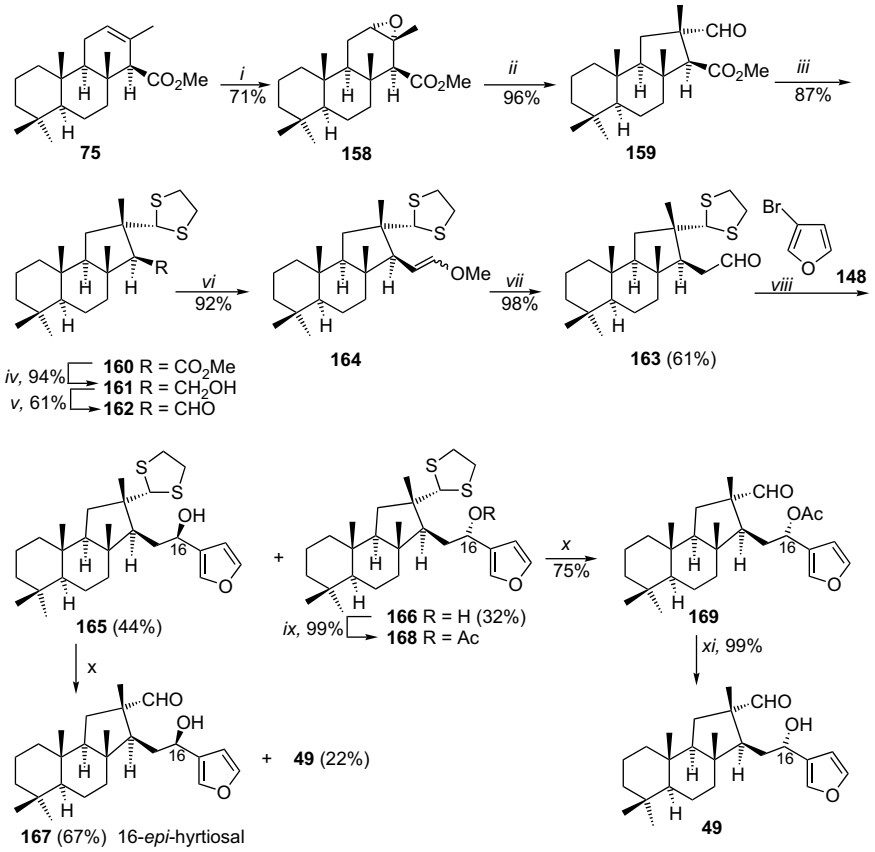
bicyclogeranylfarnesic methyl esters **94**–**97** and methyl (6*Z*)-geranylfarnesoates **98** and **99** were submitted to a biomimetic superacidic cyclisation (Scheme 6).[55,57,58] The reaction conditions were chosen to provide a moderate selectivity for the cyclisation of just one extra ring, but along with the tricyclic cheilanthanes **90**–**93** and rearranged cheilanthane **100**, some tetracyclic scalaranes **101** and **102** were also obtained. The cheilanthane esters **83** and **84**, as well as their C14 epimers **90** and **91**, can be used for the synthesis of natural cheilanthanes with the indicated configuration of the side chain.

The synthesis of 23-deoxoluteone **103**, an analogue of the natural compound, luteon **52**, has been performed starting from (−)-sclareol **87**, which was converted in four steps into a mixture of the bishomolabdanic acids **104**.[59] This mixture was submitted to a low-temperature superacidic cyclisation to provide a mixture of the lactones **105** and **106** in excellent yield (95%). The prevailing lactone **105** was transformed into the corresponding diol **107**, which was oxidised with Swern reagent to the aldehyde **108**. It is noteworthy that the oxidation is accompanied by a selective dehydration process to the exocyclic isomer, matching exactly the structure of the natural compound. Subsequent transformation of compound **108** via alcohol **109** led to the bisnorcheilanthane ketone **103** in good yields (Scheme 7).

Lactone **105** has served as starting material for the synthesis of the natural cheilanthadiol **3** and its 17*E*-isomer. All subsequent transformations of lactone **105** are represented in Scheme 8. Although the synthetic sequence in this approach is quite long, it is attractive, due to the high yields of all transformations.[60] Reduction of lactone **105** to the diol **107**, followed by the selective acetylation, led to the monoacetate **110**. Protection of the free hydroxyl group as a THP-derivative **111** and the following removal of acetyl protection produced the primary alcohol **112**. This was oxidised to the aldehyde **113**, which was methylated with methylmagnesium iodide. Further oxidation of the resulting secondary alcohol **114** provided the ketoether **115**.



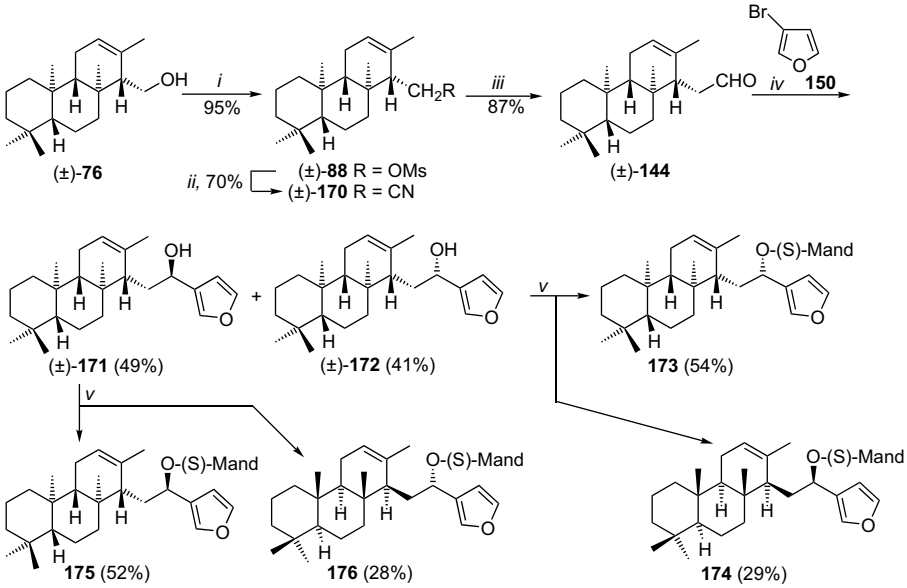
Scheme 12. Reagents and conditions: (i) Ac_2O, Py, rt, 12 h; (ii) $^1O_2$ hν, Rose Bengal, CH_2Cl_2, −78 °C, 3 h; (iii) *m*-CPBA, CH_2Cl_2, rt, 1 h; (iv) $BF_3{\cdot}Et_2O$, C_6H_6, 10 °C, 5 min; (v) *p*-TsOH, C_6H_6, rt, 12 h.



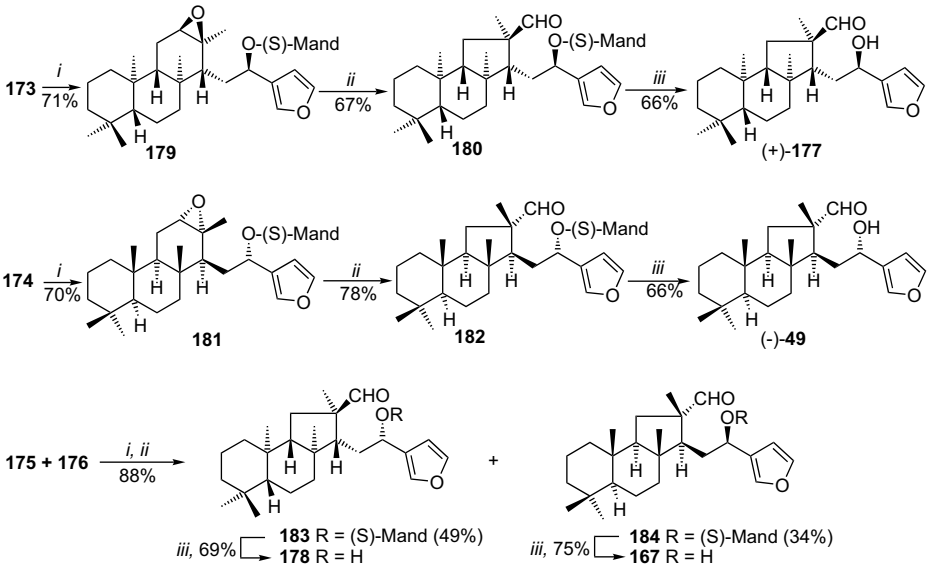
Scheme 13. Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, 10 °C, 12 h; (ii) $BF_3{\cdot}Et_2O$, C_6H_6, 60 °C, 1 h; (iii) ethanedithiol, CH_2Cl_2, rt, 12 h; (iv) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 1 h; (v) CrO_3, Py, rt, 0.25 h; (vi) $Ph_3P{=}CHOMe$, NaHMDS, THF, −78 °C, 1 h; (vii) Me_2CO, *p*-TsOH, rt, 8 h; (viii) *n*-BuLi, 3-bromofuran **148**, THF, −78 °C, 1 h; (ix) Ac_2O, Py, rt, overnight; (x) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, rt, 10 min; (xi) 2% K_2CO_3/MeOH, rt, 2 h.

Olefination of the ketogroup in **115** with methyl trimethylsilylacetate led to a mixture of esters **116** and **117**, which were separated chromatographically. Cerium-assisted reduction of the individual isomers provided the alcohols **118** and **119**, respectively. A final deprotection step gave the individual cheilanthadiols (17*E*)-**120** and (17*Z*)-**3**. The overall synthetic sequence counted ten steps and provided the target cheilanthanes in 26% overall yield, starting from the readily available lactone **105**.

The synthesis of *ent*-cheilanthadiol **3** was realised by Heisler and co-worker.[61] The starting compound was isocopalic iodide **121**, obtained from isocopalic alcohol (+)-**76** by the same group (Scheme 9).[62] The key step in this synthesis was the radical-induced coupling



Scheme 14. Reagents and conditions: (i) MsCl/Py, rt, 15 h; (ii) NaCN, Adogen 464®, PhMe/H_2O (10:1), 60 °C, 36 h; (iii) *i*-Bu_2AlH, PhMe, 0 °C, 1.5 h; (iv) *n*-BuLi, 3-bromofuran **148**, THF, −78 °C, 1.5 h; (v) (*S*)-(+)-methyl mandelic acid, DCC, DMAP, CH_2Cl_2, rt, 2 h.



Scheme 15. Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, −40 °C, 1.5 h; (ii) $BF_3{\cdot}Et_2O$, $MeNO_2$, −23 °C, 40 min; (iii) K_2CO_3–MeOH/THF/H_2O (1:1:0.5), rt, 16 h.

of iodide **121** with compound **122**. This provided the cheilanthane skeleton **123**, which was transformed in two steps into compound **124** and another three steps provided the *ent*-cheilanthane derivative **125**. This was selectively epoxidised to **126** and reduction of this epoxide with a complex hydride in DME followed by removal of the protective group led to *ent*-cheilanthadiol **3**. It is noteworthy that this final reduction step, performed with the same reagent in toluene, led selectively to the rearranged product **127**.

A cascade method of (−)-spongianolide A **23** synthesis was developed starting from β-cyclogeraniol **128** (Scheme 10).[63,64] The later was transformed into the racemic isodrimenol **129** via compounds **130** and **131**. After a similar reaction sequence, isodrimenol **129** was transformed via the ester **133** to the tricyclic ketoester **132**. It was coupled with the optically active 1,4-*O*-benzyl-L-threitol **134**, and the resulting mixture of diastereomers **135** and **136** was separated chromatographically. After the hydrolysis of the ester **136** to the optically active ketoester **132**, the tricyclic alcohol **137** was obtained over two additional steps. Transformation to the aldehyde **138** was achieved via compound **139**. Following coupling with the phosphorane **140** led to the sesterterpenic derivative **141**, which was photolytically oxidised into the butenolide **142**. The last two steps included removal of acetonide protection to give the diol **143**, followed by acetylation to complete the synthesis of (−)-spongianolide A **23**.

Recently the synthesis of three biologically active cheilanthanes has been accomplished.[65] Aldehyde **144** was obtained in six steps from the optically active methyl *ent*-isocopalate **75** as a key synthon in the synthesis of natural cheilanthanes **13** and **16** (Scheme 11). Accordingly, the aldehyde **77** was isomerised to the tetrasubstituted isomer **145**, which was transformed over two steps into the aldehyde **146** containing the exocyclic double bond. Additional two steps provided the aldehyde **144**, via the ether **147**.

Aldehyde **144** was coupled with 3-bromofurane **148** to give the 16*R* **149** and 16*S* **150** epimeric alcohols, which were separated chromatographically. Photo-oxidation in the presence of Rose Bengal then led to the natural cheilanthane **16**[14] and its epimer **151**. Dehydration of the mixture of alcohols **149** and **150** with phosphorus oxychloride provided the diene **152** in a modest 26% yield. The later was converted into the natural cheilanthane **13** by photo-oxidation.[14]

Luffolide **29** was obtained in a five-step sequence from the cheilanthanic furo-alcohol **149** (Scheme 12).[20] Initial protection of the secondary hydroxyl provided acetate **153**, transformed over three steps via compound **154** into a mixture of α- and β-epoxides **155**, which upon isomerisation with boron trifluoride-etherate led to a mixture of C13-epimeric aldehydes **156** and **157**. An additional isomerisation with *p*-toluenesulfonic acid gave the natural compound **29** in 50% yield.

The synthesis of hyrtiosal **49** was realised independently via two different pathways. The first approach was developed by Urones and co-workers,[66,67] starting from the optically active methyl isocopalate **75** (Scheme 13). Their synthetic strategy included a ring-contraction reaction of ring C, followed by side-chain elongation to hyrtiosal **49**.

The starting methyl isocopalate **75** was epoxidised, followed by treatment of the epoxide **158** with boron trifluoride-etherate to provide the aldehyde **159**. The latter was transformed into thioketal **160**, sequentially reduced and oxidised into the alcohol **161** and aldehyde **162**. Homologation to the aldehyde **163** was performed via the ether **164**. Aldehyde **163** was coupled with 3-bromofuran **148** to give the C16 epimeric mixture of alcohols **165** and **166**. Removal of the thioketal protecting group in the prevailing epimer **165**, led to the formation of 16-*epi*-hyrtiosal **167**, accompanied by a small amount (22%) of hyrtiosal **49**. Alcohol **166** with the desired configuration of the secondary hydroxyl group was protected by acetylation, and removal of the thioketal then gave the 16-acetoxyhyrtiosal **169**. Hydrolysis of the acetate group led to natural hyrtiosal **49**.

An alternative synthetic solution for the synthesis of natural hyrtiosal **49** was published by Imamura and co-workers[68] starting from racemic isocopalic alcohol **76**, which was obtained by a known method.[69] The transformation of **76** into racemic homoaldehyde **144** via nitrile **170** is shown in Scheme 14. The aldehyde **144** was transformed into furyl alcohols **171** and **172**. Separation of these compounds and coupling with (*S*)-(+)-methyl mandelic acid provided two pairs of diastereomers **173**, **174** and **175**, **176**, respectively, which were separated by chromatography.

The transformation of the obtained diastereomers **173**–**176** into hyrtiosal **49** and its diastereomers **167**, **177** and **178** is shown in Scheme 15. Accordingly, **173** and **174** provided after epoxidation the corresponding epoxides **179** and **181**, which were isomerised with boron trifluoride-etherate into aldehydes **180** and **182**. The latter provided on basic hydrolysis the *ent*-hyrtiosal **177** and natural hyrtiosal **49**. The diastereomeric mixture of **175** and **176** was epoxidized, followed by isomerisation under acidic conditions to form the mixture of compounds **183** and **184**.

The rearrangement of cheilanthanes **173**–**176** into compounds with hyrtiosal skeleton is in accordance with the biogenetic scheme

proposed previously by Iguchi and co-workers,[28] and represents a biomimetic solution for the synthesis of cheilanthanes with a contracted C-ring.

5. Conclusions

The scientific investigation of the cheilanthane family of sesterterpenoids has been an active field during the last three decades. Nearly 40 papers on the isolation and structural characterisation of its members including several preliminary biological studies have been published. Despite their important biological properties, however, only a limited number of synthetic studies have been produced. The complexity of this group of sesterterpenes hampers their total syntheses, as well as studies on their structure–activity relationships, although it is clear that novel pharmaceutical agents and biological probes may be found in this class of compounds.

Acknowledgements

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Biographical sketch

Dr. Sci. Nicon Ungur was born in 1954. He graduated from Moldova State University in 1976 and obtained his Ph.D. degree in 1985 from the A. V. Bogatsky Physico-Chemical Institute of the Ukrainian Academy of Sciences, Odessa under the supervision of Professor P. F. Vlad. In 1994, he finished his Habilitation and obtained a Dr. Sci. degree. He was a postdoctoral fellow with Professor G. Cimino (ICB, Naples, Italy), where he got his training in the synthesis of natural terpenoids. He is the author of more than 80 scientific papers including reviews and ten patent applications. He is currently principal scientific researcher at the Institute of Chemistry, Moldova Academy of Sciences. His research interests include the synthesis of mono-, sesqui-, di- and sesterterpenoids; the electrophilic, superacidic cyclisation and molecular rearrangements of terpenoids; and the synthesis of natural terpenoids, including the biologically active compounds.

Dr. Veaceslav Kulciţki was born in 1969. He graduated from Moldova State University in 1992 and obtained his Ph.D. degree in 1998 from the Institute of Chemistry, Moldova Academy of Sciences, under the supervision of Professor P. F. Vlad and Dr. Sci. N. Ungur. He was a postdoctoral fellow with Professor G. Cimino (ICB, Naples, Italy), being involved in different projects connected to marine natural product chemistry. He is the author of more than 50 publications, including review articles and two patents. Dr. Kulciţki has been appointed Associate Professor in 2006 and holds currently the position of a senior scientific researcher at the Institute of Chemistry, Moldova Academy of Sciences. His research interests include synthesis of natural terpenoids by biomimetic approaches, including electrophilic cyclisations and molecular rearrangements.