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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

A R T I C L E I N F O

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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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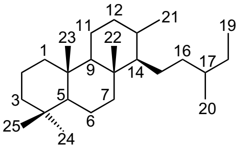
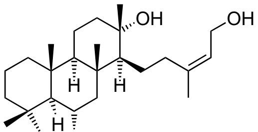
2. Structure and occurrence

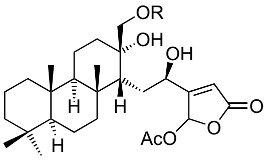
The first representative of the cheilanthane sesterterpenoids is cheilanthatriol **2**, isolated from the fern *C. farinosa*.[1] Its structure was elucidated based on spectral data and chemical modifications. The stereochemistry at C6 and C13, as well as the configuration of the double bond in the side 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**.



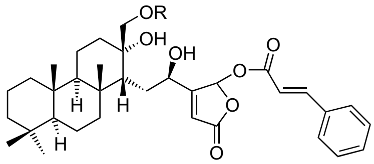
1



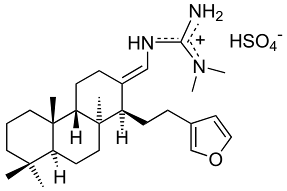
2 R = OH
3 R = H



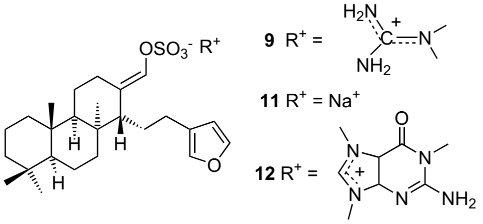
4 R = Ac
5 R = H



6 R = Ac
7 R = H



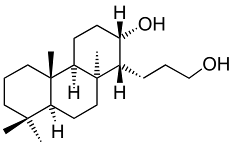
8



9 R^{+} =

11 R^{+} = Na^{+}

12 R^{+} =



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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 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 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**.