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Chenopodolans E and F, two new furopyrans produced by *Phoma chenopodiicola* and absolute configuration determination of chenopodolan B

Marco Evidente [a], Alessio Cimmino [a], Maria Chiara Zonno [b], Marco Masi [a], Ernesto Santoro [c], Stefania Vergura [c], Alexander Berestetskiy [d], Stefano Superchi [c], Maurizio Vurro [b], Antonio Evidente [a, *]

[a] Department of Chemical Sciences, University of Naples "Federico II", Complesso Universitario Monte S. Angelo, Via Cintia 4, 80126 Napoli, Italy
[b] Institute of Sciences of Food Production, National Research Council, Via Amendola 122/O, 70125 Bari, Italy
[c] Department of Sciences, University of Basilicata, Via dell'Ateneo Lucano 10, 85100, Potenza, Italy
[d] All-Russian Institute of Plant Protection, Russian Academy of Agricultural Sciences, Pushkin, Saint-Petersburg, 196608, Russian Federation

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ABSTRACT

Two new furopyrans, named chenopodolans E and F (**1** and **2**), were isolated from the liquid culture of *Phoma chenopodiicola*, a fungal pathogen proposed for the biological control of *Chenopodium album*, a common worldwide weed of arable crops. They were characterized using spectroscopic methods as 3-(3-methoxy-2,6-dimethyl-7a*H*-furo[2,3*b*]pyran-4-yl)-but-2-enoic acid methyl ester and 1-(3-methoxy-2,6-dimethyl-7a*H*-furo[2,3*b*]pyran-4-yl)-ethanone, respectively. Furthermore, the absolute configuration of chenopodolan B (**3**) was established to be (7a*R*,9*S*) by a combined application of the advanced Mosher's method and of quantum mechanical calculations of chiroptical (ECD and ORD) properties. When **1** and **2** were assayed on punctured leaves at 2 μg/μL, only **2** was active on *Sonchus arvensis* while **1** caused around 75% larval mortality on *Artemia salina* larvae at 0.1 μg/μL.

1. Introduction

Phoma chenopodiicola Gruyter, Noordel. & Boerema is a fungal pathogen responsible for foliar and stem diseases of *Chenopodium album* L., commonly known as fat hen or common lambsquarter, a worldwide diffused weed of arable crops. Previous studies aimed at identifying phytotoxic metabolites produced by the fungus, possibly responsible of the appearance of symptoms and potentially suitable as natural herbicides, allowed us to purify and identify from its liquid culture filtrates a number of metabolites, i.e.: (i) chenopodolin and chenopodolin B, unrearranged *ent*-pimaradiene diterpenes[1,2]; (ii) chenopodolans A-D, tetrasubstituted furopyrans[2,3]; (iii) 6-hydroxymellein[3]; and (iv) chenoisocoumarine.[2]

A further analysis was carried out on a larger quantity of organic extract of the same fungus, to re-isolate chenopodolans A-C with the aim to assign their absolute configuration and to evaluate the possible presence of other interesting bioactive metabolites. This allowed us to isolate two new tetrasubstituted furopyrans, which were named chenopodolans E and F.

In particular this manuscript reports on: (a) the isolation and the chemical and biological characterization of the two new chenopodolans E and F (**1** and **2**, Fig. 1); (b) the assignment of the absolute configuration to chenopodolan B (**3**, Fig. 1) by quantum mechanical calculations of Optical Rotatory Dispersion (ORD) and Electronic Circular Dichroism (ECD) and to C-9 of **3** by the advanced Mosher's method.[4]

2. Results and discussion

Chenopodolans E and F (**1** and **2**, Fig. 1) were obtained from the purification of the organic extract of *P. chenopodiicola* as reported in

* Corresponding author.
E-mail address: evidente@unina.it (A. Evidente).

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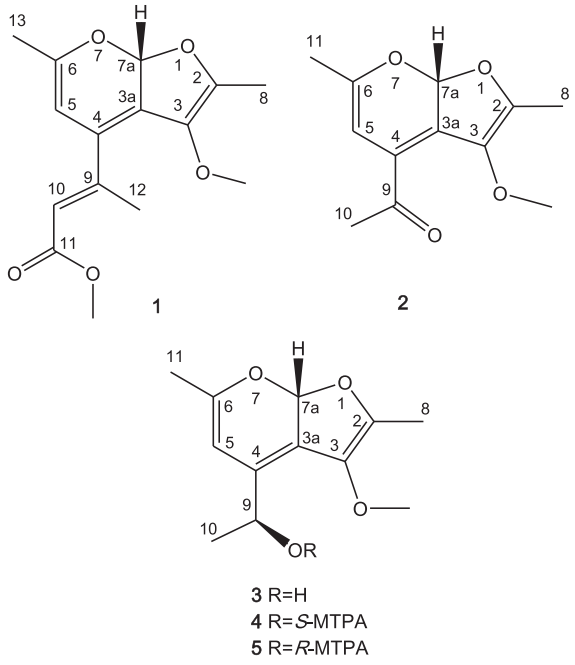

Fig. 1. Structures assigned to chenopodolans E (**1**), F (**2**) and B (**3**), and 9-*O*-*S*-MTPA- and 9-*O*-*R*-MTPA esters of chenopodolan B (**4** and **5**, respectively).

details in the Experimental. The preliminary investigation of their ^{1}H and ^{13}C NMR spectra (Table 1) allowed us to note that **1** and **2** were closely related to the chenopodolans already isolated presenting the same bicyclic furopyran ring and differing in the side chain at C-4.[2,3] Indeed, their UV spectra showed adsorption maxima typical for extended chromophores.[5]

Compound **1** has the molecular formula $C_{15}H_{18}O_5$ as deduced from its HR ESI-MS spectrum, which is consistent with seven degrees of unsaturations. Compared to the above cited chenopodolans A-D, its ^{1}H and ^{13}C NMR spectra (Table 1) showed similar signals of the protonated olefinic carbon (HC-5), the bridgehead carbon (HC-7a), the methoxy, and the two methyl groups at C-3, C-2 and C-6 of the furopyran moiety, respectively. They appeared at δ 7.05 (br s)/134.8 (d), 6.28 (s)/94.3 (d), 3.93 (s)/56.1 (q), 1.98 (s)/8.8 (q) (Me-8) and 2.09 (d, J = 1.1 Hz)/14.4 (q) (Me-13),[5,6] respectively. Significantly, H-5 demonstrated allylic coupled (J = 1.1 Hz) with Me-13.

These assignments were confirmed by the coupling observed in the COSY and HSQC spectra (Table 1).[7] The couplings observed in the HMBC spectrum (Table 1)[7] between C-2 and H-7a and Me-8, C-3 and the geminal MeO group and Me-8, C-3a and H-7a and Me-8, C-4 and H-7a and Me-13, and C-6 and H-5, H-7a and Me-13 allowed us to assign the signals at δ 164.9, 166.5, 103.6, 128.3 and 158.4 to quaternary carbons C-2, C-3, C-3a, C-4 and C-6 of the same moiety.[6] The side chain of **1** differed from those of the above cited chenopodolans A-D. Indeed, beside the expected signal for the olefinic group, the IR spectrum showed a diagnostic band consistent with the presence of an ester carbonyl group.[8] The ^{1}H and ^{13}C NMR spectra of this moiety are consistent with the presence of a but-2-enoic acid methyl ester residue attached at C-4. In fact, the ^{1}H and ^{13}C NMR spectra (Table 1) also showed signals for a protonated olefinic carbon (HC-10), a methoxy and a vinylic methyl group at δ 5.81 (s)/119.9 (d) (HC-10), 3.76 (s)/51.1 (q) (COOMe) and 2.33 (br s)/19.3 (q) Me-12), respectively.

The ^{13}C NMR spectrum also showed δ 165.4 (C-11) the significant signal typical of an ester carbonyl group, which coupled with the corresponding MeO group in the HMBC spectrum.[5] The couplings observed in the HMBC spectrum between C-9 and Me-12 allowed us to assign this olefinic quaternary carbon at δ 152.4. The coupling between C-10 and H-5, and C-5 with H-10 and Me-12 confirmed the location of but-2-enoic acid methyl ester residue at C-4 of the furopyran ring. These results allowed us to assign the chemical shifts to all the protons and the corresponding carbons, as reported in Table 1, and to formulate **1** as 3-(3-methoxy-2,6-dimethyl-7a*H*-furo[2,3*b*]pyran-4-yl)-but-2-enoic acid methyl ester. The structure assigned to **1** was confirmed by all the other long range couplings observed in the HMBC spectrum (Table 1) and from the data obtained from its HR ESI-MS spectra. The HR ESI-MS spectrum showed: the sodiated $[2M + Na]^+$ and protonated $[2M + H]^+$ dimer forms at *m/z* 579 and 557, respectively, the sodiated cluster $[M + Na]^+$ and the pseudomolecular ion $[M + H]^+$ at *m/z* 301.1061 and 279.1217, respectively. The NOESY spectrum,[7] as expected, showed the correlation between H-5 and Me-13. The lack of correlation between H-10 and Me-12, allowed assignment of an *E* configuration to the double bond at the acrylic methyl ester

Table 1
^{1}H and ^{13}C NMR data of chenopodolan E and F (**1** and **2**)[a,b].

Position	**1**			**2**		
	δC[c]	δH (J in Hz)	HMBC	δC[c]	δH (J in Hz)	HMBC
2	164.9 C		H-7a, Me-8,	163.9 C		Me-8
3	166.5 C		C(3)-OMe, Me-8	164.8 C		H-7a, C(3)-OMe
3a	103.6 C		H-7a, Me-8	105.5 C		H-7a, Me-8
4	128.3 C		H-7a, Me-13	139.3 C		H-7a, Me-10
5	134.8 CH	7.05 br s[d]	H-9, H-10, Me-12, Me-13	126.1 CH	7.12 s	Me-9
6	158.4 C		H-5, H-7a, Me-13	157.7 C		H-5, H-7a, Me-11
7a	94.3 CH	6.28 s		96.9 CH	6.51 s	
8	8.8 CH_3	1.98 s		8.8 CH_3	2.01 s	
9	152.4 C		Me-12	199.1 C		H-5, Me-10
10	119.9 CH	5.81 s	H-5, Me-12	13.5 CH_3	2.35 s[e]	H-5
11	165.4 C		(CO)-OMe	32.7 CH_3	2.35 s[e]	
12	19.3 CH_3	2.33 br s				
13	14.4 CH_3	2.09 d (1.1)[d]				
CO-OMe	51.1 CH_3	3.76 s				
C(3)-OMe	56.1 CH_3	3.93 s		56.7 CH_3	3.94 s	

[a] The chemical shifts are in δ values (ppm), downfield from TMS.
[b] 2D ^{1}H, ^{1}H (COSY) ^{13}C, ^{1}H (HSQC) NMR experiments delineated the correlations of all the protons and the corresponding carbons.
[c] Multiplicities were assigned by DEPT spectrum.
[d] Allylic coupling was observed in the COSY spectrum.
[e] Overlapped signals.