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Chemo- and biocatalytic esterification of marchantin A and cytotoxic activity of ester derivatives

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ABSTRACT

Chemical and biocatalytic synthesis of seven previously undescribed marchantin A ester derivatives has been presented. Chemical synthesis afforded three peresterified bisbibenzyl products (**TE1-TE3**), while enzymatic method, using lipase, produced regioselective monoester derivatives (**ME1-ME4**). The antiproliferative activities of all prepared derivatives of marchantin A were tested on MRC-5 healthy human lung fibroblast, A549 human lung cancer, and MDA-MB-231 human breast cancer cell lines. All tested esters were less cytotoxic in comparison to marchantin A, but they also exhibited lower cytotoxicity against healthy cells. Monoesters displayed higher cytotoxic activities than the corresponding peresterified products, presumably due to the presence of free catechol group. Monohexanoyl ester **ME3** displayed the same IC_{50} like marchantin A against MDA-MB-231 cells, but the selectivity was higher. In this way, regioselective enzymatic monoesterification enhanced selectivity of marchantin A. **ME3** was also the most active among all derivatives against lung cancer cells A549 with the slightly lower activity and selectivity in comparison to marchantin A.

1. Introduction

Taxonomically positioned between algae and vascular plants, liverworts belong to an early-diverging lineage of land plants, and are considered the simplest of terrestrial plants [6,28,36,42]. Within oil bodies, intracellular membrane-bound organelles, liverworts contain numerous terpenes and lipophyllic aromatics [2,4,5,6,17,30]. Bisbibenenzyls are plant metabolites characteristically found in liverworts with a single exception represented by the isolation of Riccardin C from a different plant division, namely *Primula macrocalyx* Bge. (*Primulaceae*) [24]. Apart from their chemotaxonomic importance, bisbibenzyls display various biological activities. Among the known bisbibenzyls, Marchantin A is the most investigated, and has been reported to have cytotoxic ([14,18,20,21,32], antiprotozoal [21,33], vasorelaxant [31], antibacterial [3,23], anti-influenza activity [19], as well as lipopolysaccharide-induced NOS [16], and 5-lipoxygenase and cyclooxygenase inhibitory activity [3,39].

Lipophilicity is an important physicochemical property in drug discovery, affecting pharmaceutical, pharmacokinetic, and pharmacodynamic action of the active molecule. Namely, it influences several stages of drug action, including transport through cell membranes, binding to the target as well as ADMET (absorption, distribution, metabolism, excretion, toxicity) properties [37]. In accordance with this, it has been reported that increasing the lipophilicity of various target molecules (*e.g.* by acylation) results in an increase in hypo glycemic [27], antioxidant [9], and antitumor activities [12,29].

In this work, we report a chemical and biocatalytic synthesis of seven new marchantin A esters. Additionally, the anti-proliferative activities of all of the prepared derivatives of marchantin A were tested on MRC-5 healthy human fibroblast, A549 human lung cancer, and MDA-MB-231 breast cancer cell lines.

2. Results and discussion

2.1. Synthesis

The conversion of marchantin A into corresponding esters of several aliphatic carboxylic acids was envisaged in order to investigate the effect of increased lipophilicity on cytotoxic activity. Firstly, a base-promoted transesterification employing three vinyl esters (Table 1) was

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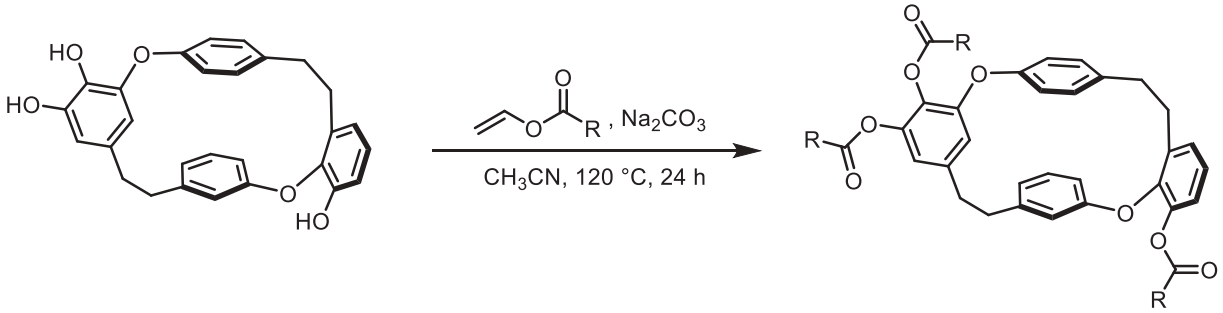
Table 1
The peracylation of marchantin A.

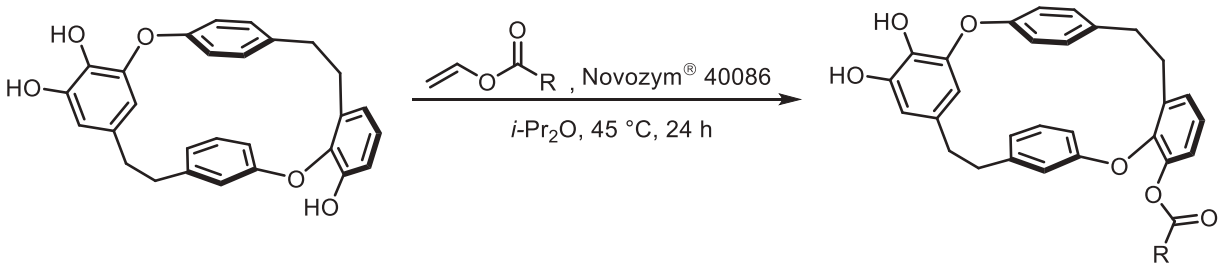


Entry	Compound	R	Isolated yield (%)
1	**TE1**	$-CH_2CH_3$	96
2	**TE2**	$-(CH_2)_2CH_3$	96
3	**TE3**	$-(CH_2)_4CH_3$	85

undertaken. An excess of vinyl esters was used, in the presence of sodium carbonate, in acetonitrile, at 120 °C. The applied reaction conditions afforded exclusively triacylated derivatives of marchantin A (**TE1-TE3**) in good to excellent yields, requiring no further purification. Additionally, in order to test the outcome of an acid-promoted transesterification Amberlyst 15 and vinyl propionate were used in acetonitrile, at 120 °C. A more complex reaction mixture was observed compared to the one performed in base-promoted conditions, and quantitative NMR analysis revealed that the corresponding triacylated product was obtained in 40% yield (using methyl benzoate as a standard).

Since no regioselectivity was observed in the previously described conditions, a method allowing partial esterification of marchantin A was sought thereafter. A literature search concerned with regioselective acylation revealed lipases as promising catalysts. Namely, lipases (EC 3.1.1.3) catalyze the hydrolysis of triglycerides, and are classified as hydrolase enzymes. They are produced ubiquitously by plants, animals, insects and microbes, the last of which represents the most common source of lipase due to ease of culture handling, availability and scale-up scope [38]. Their applications range from oleochemistry [1,15], detergent [22,41] and food industries [13], to the preparation of chiral intermediates [11,40]. Relevant to the scope of this work, lipases were also demonstrated to perform regioselective acylation [26,43,44] as well as hydrolysis [10]. As a catalyst of choice for the esterification of marchantin A, Novozym® 40,086 was selected. The reaction was initially tested with the excess of vinyl propionate, in *i*-Pr_2O at 45 °C (Table 2, entry 1). After 24 h, complete consumption of the starting material was observed by thin-layer chromatography, along with the formation of the complex reaction mixture. NMR analysis of the crude reaction mixture confirmed the complete consumption of the starting material and revealed three signals corresponding to the H-3′, suggesting that there may be three substituted marchantin A products (Fig. S2, Supporting Information). The dominant product was isolated and purified by preparative thin-layer chromatography, and structural analysis revealed that monosubstitution of marchantin A had occured, on the 13-OH. Comparison of the ^{1}H NMR spectra of the purified monoester and the crude reaction mixture confirmed that this product was indeed the dominant one. The separation of the other two products (probably different diesters) from the reaction mixture was not successful, and a mixture of inseparable products was obtained. The substrate scope of the described reaction was expanded with three more monoesters, all of them retaining the substitution in the C-13 position. Although low yields of corresponding marchantin A monoesters were obtained, compared to the base-promoted reaction, a notable selectivity was observed in the lipase-catalyzed reaction, in spite of the excess of vinyl esters employed in both conditions. The reason of regioselective enzymatic esterification of solely 13-OH could be due to an intramolecular H-bonding within the catechol moiety. Notably, the synthesis of corresponding marchantin A monoesters was accomplished by protecting-group-free strategy. Raising the temperature of the lipase-catalyzed reaction to 65 °C and analyzing the crude reaction mixture by NMR spectroscopy showed that the C-13 monoester remained the major

Table 2
The lipase-catalyzed monoacylation of marchantin A.



Entry	Compound	R	Isolated yield (%)
1	**ME1**	$-CH_2CH_3$	36
2	**ME2**	$-(CH_2)_2CH_3$	43
3	**ME3**	$-(CH_2)_4CH_3$	52
4	**ME4**	$-(CH_2)_6CH_3$	24

Table 3
Comparison of ^{1}H NMR data of marchantin A and its monoester derivatives ME1-ME4.

Position	MA δ_H	ME1 δ_H	ME2 δ_H	ME3 δ_H	ME4 δ_H
1	–	–	–	–	
2,6	6.58 d (8.5)	6.59 d (8.5)	6.59 d (8.5)	6.59 d (8.5)	6.59 d (8.0)
3,5	6.93 d (8.5)	6.98 d (8.5)[a]	6.97 d (8.5)[a]	6.97 d (8.5)[a]	6.97 d (8.0)[a]
4	–	–	–	–	
7,8	2.96–3.01 m	3.02–3.10 m	3.03–3.09 m	3.02–3.09 m	3.03–3.09 m
9	–	–	–	–	–
10	7.02 dd (8.0; 1.5)	7.33 dd (8.0; 1.5)	7.33 dd (8.0; 1.5)	7.32 brd (7.5)	7.33 dd (8.0; 1.5)
11	7.15 t (8.0)	7.20 t (8.0)	7.20 t (8.0)	7.20 t (8.0)	7.21 t (8.0)
12	6.87 dd (8.0; 1.5)	6.98 dd (8.0; 1.5)[a]	6.98 dd (8.0; 1.5)[a]	6.95–7.00 m[a]	6.99 m[a]
13	–	–	–	–	–
14	–	–	–	–	–
1′	–	–	–	–	–
2′	–	–	–	–	–
3′	5.13 d (2.0)	5.21 d (1.5)	5.21 d (1.5)	5.19 brs	5.18 d (1.5)
4′	–	–	–	–	–
5′	6.47 d (2.0)	6.46 d (1.5)[b]	6.46 brs[b]	6.45 brs[b]	6.46 brs[b]
6′	–	–	–	–	–
7′,8′	2.72–2.78 m	2.70–2.82 m	2.71–2.81 m	2.70–2.80 m	2.71–2.81 m
9′	–	–	–	–	–
10′	6.57 t (8.0)	6.44 m[b]	6.43 m[b]	6.43–6.48 m[b]	6.45–6.48 m[b]
11′	–	–	–	–	–
12′	6.55 dd (7.5; 1.5)	6.48 dd (8.0; 1.5)[b]	6.43 m[b]	6.43–6.48 m[b]	6.45–6.48 m[b]
13′	6.98 t (7.5)	6.92 t (7.5)	6.92 t (7.5)	6.91 t (7.5)	6.92 t (7.5)
14′	6.41 brd (7.5)	6.38 brd (7.5)	6.38 brd (7.5)	6.37 brd (7.5)	6.36 brd (7.5)
α-CH_2	–	1.90 q (7.5)	1.87 t (7.5)	1.89 t (7.5)	1.89 t (7.5)
$(CH_2)_n$	–	–	1.30–1.33 m	1.09–1.34 m	1.09–1.28 m
CH_3	–	0.82 t (7.5)	0.76 t (7.5)	0.81 t (7.5)	0.86 t (7.5)

a,b - signals overlapped; α-CH_2 - methylene group next to ester moiety; $(CH_2)_n$ - other methylene groups of ester.

product (37% yield), and a peak corresponding to the H-3′ of the starting compound was found as well, perhaps due to partial enzyme deactivation. Replicating the reaction conditions outlined in Table 2, in the absence of lipase, led to no product formation.

2.2. Structural analysis

Obtained esters were characterized using NMR data. In comparison to marchantin A the main differences in the ^{1}H NMR spectra of monoester derivatives (**ME1-ME4**) were new signals of protons of ester aliphatic chains at δ_H 0.8 and 1.09–1.35, as well as protons of α-methylene group (to carbonyl) at δ_H 1.9 (Table 3, Figs. S8, S12, S16, and S20, Supporting Information). The positions of ester groups (13-OH) in all monoester derivatives were determined according to the shifted signals of H-10 (δ_H 7.3) and H-12 (δ_H 7.0) towards lower fields in comparison to marchantin A for 0.30–0.31 and 0.12 ppm (Tables 3 and S1, Figs. S9, S13, S17, and S21, Supporting Information), respectively, as it was expected according to the theoretical calculations after substitution of a hydroxyl group with an ester group [35]. Additionally, in all monoester derivatives signals of unesterified 3′-OH and 5′-OH groups were noticed (for **ME1** at δ_H 5.30, for **ME2** at δ_H 2.89 and 2.95, for **ME3** at δ_H 5.29, and for **ME4** at δ_H 5.30) contrary to marchantin A which possess three OH groups (δ_H 4.86 (13-OH) and 5.32 (3′-OH and 5′-OH, Figs. S2, S8, S12, and S16, Supporting Information). In the ^{13}C NMR spectra of all monoester derivatives novel signals in comparison to marchantin A appeared at δ_C 171 ppm (ester carbonyl C) as well as below 30 ppm (aliphatic ester carbons) (Figs. S10, S11, S14, S15, S18, S19, S22, and S23, Supporting Information). The signals of C-10 and C-12 were shifted towards lower fields for ~ 6–7 ppm, while the signals of C-13 and C-14 were shifted to the higher fields for ~ 6 and 4 ppm, respectively (Table S2, Supporting Information).

In comparison to marchantin A the main differences in the ^{1}H NMR spectra of triesters (**TE1-TE3**) were new signals of protons of ester aliphatic chains at δ_H 0.8 and 1.07–1.79, as well as protons of α-methylene group (to carbonyl) at δ_H 1.9, similarly to monoesters (Table 4, Figs. S24, S28, and S32, Supporting Information). The positions of esterified hydroxyl groups (1′-, 6′-, and 13-OH) in all derivatives were

Table 4
Comparison of ^{1}H NMR data of marchantin A and its triester derivatives TE1-TE3.

Position	MA δ_H	TE1 δ_H	TE2 δ_H	TE3 δ_H
1	–	–	–	–
2,6	6.58 d (8.5)	6.59 d (8.5)	6.59 d (8.5)	6.59 d (8.5)
3,5	6.93 d (8.5)	6.95 d (8.5)[a]	6.94 d (8.5)[a]	6.95 d (8.5)[a]
4	–	–	–	–
7,8	2.96–3.01 m	3.00–3.10 m	3.01–3.10 m	3.02–3.09 m
9	–	–	–	–
10	7.02 dd (8.0; 1.5)	7.34 dd (8.0; 1.5)	7.33 dd (8.0; 1.5)	7.33 dd (8.0; 1.5)
11	7.15 t (8.0)	7.21 t (8.0)	7.20 t (8.0)	7.21 t (8.0)
12	6.87 dd (8.0; 1.5)	6.99 dd (8.0; 1.5)	6.99 dd (8.0; 1.5)	6.99 dd (8.0; 1.5)
13	–	–	–	–
14	–	–	–	–
1′	–	–	–	–
2′	–	–	–	–
3′	5.13 d (2.0)	5.58 d (1.5)	5.58 d (1.5)	5.56 d (1.5)
4′	–	–	–	–
5′	6.47 d (2.0)	6.65 d (1.5)	6.64 d (1.5)	6.64 d (1.5)
6′	–	–	–	–
7′,8′	2.72–2.78 m	2.70–2.90 m	2.73–2.91 m	2.73–2.89 m
9′	–	–	–	–
10′	6.57 t (8.0)	6.43 brs	6.43 brs	6.44 brs
11′	–	–	–	–
12′	6.55 dd (8.0; 1.5)	6.50 dd (8.0; 1.5)	6.50 d (8.0; 1.5)	6.48 d (8.0; 2.0)
13′	6.98 t (8.0)	6.95 t (8.0)[a]	6.95 m[a]	6.95m[a]
14′	6.41 brd (8.0)	6.39 brd (8.0)	6.39 brd (8.0)	6.37 brd (8.0)
3xα-CH_2	–	1.91 q (7.5)	1.88 t (7.5)	1.89 t (7.5)
		2.56 q (7.5)	2.52 t (7.5)	2.52 t (7.5)
		2.56 q (7.5)	2.53 t (7.5)	2.53 t (7.5)
$(CH_2)_n$	–	–	1.33 sext	1.07–1.42 m
			1.74 sext	1.69–1.79 m
			1.76 sext	
3xCH_3	–	0.82 t (7.5)	0.76 t (7.5)	0.81 t (7.5)
		1.22 t (7.5)	0.97 t (7.5)	0.83 t (7.5)
		1.27 t (7.5)	1.04 t (7.0)	0.94 t (7.5)

[a] Signals overlapped; α-CH_2 - methylene group next to ester moiety; $(CH_2)_n$ - other methylene groups of ester.

determined according to the shifted signals of H-3′ (δ_H 5.6), H-5′ (δ_H 6.6), H-10 (δ_H 7.3), and H-12 (δ_H 7.0) towards lower fields in comparison to marchantin A (Table 4). The signals of H-10 were shifted in all derivatives for 0.31, signal of H-12 for 0.12, signal of H-5′ for 0.16–0.17, while that of H-3′ for 0.42–0.44 ppm (Table S1, Supporting Information). Again, these changes of chemical shifts caused by the esterification were in accordance with the theoretical calculations [35]. In the ^{13}C NMR spectra of all triester derivatives novel signals in comparison to the ^{13}C NMR spectrum of marchantin A appeared at δ_C 170–172 ppm (ester carbonyls C) as well as below 40 ppm (aliphatic ester carbons) (Figs. S26, S27, S30, S31, S34, and S35, Supporting Information). The signals of C-2′, C-3′, C-4′ and C-5′ in all triester derivatives were shifted towards lower fields for 5–8 ppm confirming esterifications at C-1′ and C-6′ (Table S2, Supporting Information). Each position of the shifted carbons at the C-ring possess at least one ester moiety in *ortho* or *para* position, causing higher chemical shifts.

2.3. Cytotoxic effects

The cytotoxic effect (anti-proliferative activity) of synthesized compounds was tested on MRC-5 healthy human fibroblast, A549 human lung cancer, and MDA-MB-231 human breast cancer cell lines. The IC_{50} values were between 9 and 150 μM (Table 5). In general, monoesters displayed equal or slightly weaker activity than marchantin A, while cytotoxicity of pereserified products was negligible, presumably due to the blocked catechol group. Cytotoxicity of monoesters against healthy cells was also weaker, to the greater extent than against cancers cells, thus improving the selectivity of **ME3** (marchantin A monohexanoate) against MDA-MB-231 cells in comparison to that of marchantin A by 1.5-fold. From all esters, **ME3** derivative also showed the highest activity against lung cancer cell line A549 (Table 5). An interesting cytotoxic effect of **TE1** was noticed, when compared to **TE2** and **TE3**. Namely, it retained nearly the same activity in all three cell lines, and also a higher activity compared to other two peracylated products. To eliminate partial hydrolysis in the culture medium as the underlying cause of higher activity, **TE1** was subjected to conditions of the antiproliferative assay. A 100 mM solution of **TE1** in DMSO was added to the RPMI mediator and the mixture was kept at 37 °C for 48 h, under constant shaking (100 rpm). The NMR analysis of the resulting mixture showed no traces of hydrolysis products, therefore ruling out the initial hypothesis of partial hydrolysis of **TE1** in the culture medium.

It has been shown previously that marchantin-type bisbibenzyls exhibit anticancer activity. Marchantin A was cytotoxic against A256 breast cancer and against KB (derivative of HeLa) cell lines with IC_{50} values of 5.5 μM and 3.7 μM, respectively [8,20,21]. Recently it's cytotoxic effects against human melanoma cell line A375 were shown with IC_{50} values similar to ones obtained in our study [14].

Table 5
In-vitro cytotoxicity of marchantin A and synthesized derivatives against three cell lines (MRC-5, A549 and MDA-MB-231) following 48 h incubation time.

Compound	Cytotoxicity, IC_{50} (μM)		
	MRC-5[a]	A549[b]	MDA-MB-231[c]
MA	28 ± 2[d]	12 ± 1	9 ± 1
ME1	45 ± 3	25 ± 2	13 ± 2
TE1	45 ± 5	40 ± 4	40 ± 6
ME2	40 ± 2	25 ± 1	18 ± 2
TE2	80 ± 7	90 ± 5	40 ± 6
ME3	40 ± 1	18 ± 2	9 ± 1
TE3	150 ± 5	90 ± 3	65 ± 4
ME4	42 ± 2	20 ± 4	12 ± 2

[a] Healthy human fibroblast.
[b] Human lung cancer cell line.
[c] Human breast cancer cell line.
[d] IC_{50} values are the mean of three independent repetitions ± SD.

Despite the facts that neither synthesized derivatives showed significantly higher activity than marchantin A, nor there is a sufficient amount of data to establish firm conclusions, in order to gain better insight in SAR of investigated compounds, we decided to calculate some of the physically significant molecular descriptors and pharmaceutically relevant properties.

For that, we built all molecular structures using Maestro 11.9 from Schrödinger Suite 2019–1 (Maestro, version 11.9, Schrödinger, LLC, New York, NY, 2019.). From the table of properties and descriptors and activities of synthesized compounds and marchantin A (Table S3, Supporting Information), it seems that some of properties are in correlation with activities that compounds showed in biological tests. Most of them are obviously connected with permeability and solubility of investigated compounds. Even though this kind of analysis is based on rather small sample, and no firm conclusions are possible we are rather convinced that those properties are the most probably ones that should be taken into the account, when designing a molecule based on this scaffold, possessing higher activity than compounds tested in this article.

The table of calculated properties and descriptors correlated with activities and short description of significant properties has been given in Supporting Information as Table S3.

3. Conclusion

In summary, seven previously undescribed marchantin A esters were synthesized. Among these compounds, three peresterified bisbibenzyl products were obtained by chemical synthesis, while lipase-catalyzed regioselective synthesis afforded four monoester derivatives. In addition, the antiproliferative activities of all prepared derivatives of marchantin A were evaluated on MRC-5 healthy human lung fibroblast, A549 human lung cancer, and MDA-MB-231 human breast cancer cell lines. It is noteworthy that monoesters displayed higher cytotoxic activities than the corresponding peresterified products, presumably due to the presence of free catechol group. Monohexanoyl ester **ME3** exhibited the same activity against MDA-MB-231 cells and lower cytotoxicity against healthy cells in comparison to marchantin A which makes **ME3** more selective in this regard. This study provides strong evidence that marchantin A is a good structural platform for the further derivatization and finally possible application of its derivatives in the anticancer therapy.

4. Experimental section

4.1. General experimental procedures

Dry-flash chromatography was performed on SiO_2 (0.018–0.032 mm). Reaction progress was monitored by thin-layer chromatography (TLC Silica gel 60 F_{254} (Merck, Darmstadt)). IR spectra were recorded on a Thermo-Scientific Nicolet 6700 FT-IR Diamond Crystal instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield Avance III spectrometer (at 500 and 125 MHz, respectively) using $CDCl_3$ (unless stated otherwise) as the solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) on the (δ) scale. Chemical shifts were calibrated relative to those of the solvent.

Optical rotations were measured on a Rudolph Research Analytical Autopol IV automatic polarimeter with methanol as solvent, and the compound concentration used was in the range of 0.8–4.0 mg/mL. UV spectra were recorded on a GBC Cintra UV/vis spectrometer with methanol as solvent. HRMS spectra were data were obtained on an Agilent 6210 time-of-flight LC/MS system equipped with an ESI interface (ESI-TOF/MS). The solvent was methanol, and the mobile phase was 0.2% $HCOOH_{(aq)}/CH_3CN$, 1:1, 0.2 mL/min. The ESI was operated in a negative and a positive mode, and nitrogen was used as the drying gas

(12 L/min) and nebulizing gas at 350 °C (45 psi). The OCT RF voltage was set to 250 V, and the capillary voltage was set to 4.0 kV. The voltages applied to the fragmentor and skimmer were 140 and 60 V, respectively. Scanning was performed from *m/z* 100 to 1500. All compounds used for biological assays are of ≥95% purity based on HPLC. The HPLC purity of Marchantin A, **ME1**-**ME4** and **TE1**-**TE3** was determined by Agilent 1200 HPLC system fitted with Quat Pump (G1311B), Injector (G1329B) 1260 ALS, TCC 1260 (G1316A) and Detector 1260 DAD VL+ (G1315C). Prior to purity determination and *in vitro* assays, the tested compounds were purified by semi-preparative HPLC. For this purpose a C18 reversed-phase column (Zorbax ODS Semi-Preparative 5 μm 9.4 × 250 mm) was used. Gradient elution was performed, using 0.2% $HCO_2H_{(aq)}$ (A)/CH_3CN (B): 0–12 min 70% A → 50% A, 12–14 min 50% A → 0% A, 14–19 min 0% A. The flow rate was set to 4 mL/min. The purity of reported compounds was tested with two HPLC methods:

Method A. The LC system was fitted with a C18 reversed-phase column (Poroshell 120 SB-C18, 2.7 μm, 4.6 × 50 mm) and gradient elution was performed using H_2O (A) and CH_3CN (B) as solvents, in the following manner: 0–1 min 95% A, 1–6 min 95% A → 5% A, 6–22 min 5% A, 22–25 min 5% A → 95% A. The flow rate was set to 0.7 mL/min.

Method B is identical to Method A, apart from MeOH being used as solvent B.

4.2. Reagents and chemicals

Marchantin A was isolated from *Marchantia polymorpha* by a previously reported procedure [7]. Novozym® 40,086 was a gift from Novozymes A/S (Bagsværd, Denmark). Unless stated otherwise, solvents and other reagents were obtained from commercial sources and used without further purification.

4.3. Computational methods

All molecular structures were built using Maestro 11.9 from Schrödinger Suite 2019–1 (Maestro, version 11.9, Schrödinger, LLC, New York, NY, 2019.).All structures were submitted to Conformational search from the MacroModel module (MacroModel, version 12.3, Schrödinger, LLC, New York, NY, 2019.). The OPLS_2005 force field, with water as the solvent were used. For the conformational search method we used mixed MCMM/low-mode [25], were the set parameters. Conformations were minimized using the Polak–Ribiere conjugate gradient method [34], with 25,000 maximum iterations or until a 0.05 convergence threshold was obtained. Duplicates were removed and all structures within energy window of 10.5 kJ/mol were saved. Best conformers were selected and calculation of physically significant molecular descriptors and pharmaceutically relevant properties was performed using QikProp (QikProp, version 5.9, Schrödinger, LLC, New York, NY, 2019.).

4.4. General procedure for the peracylation of marchantin A

A previously reported procedure for the *O*-acylation of phenols was modified and employed in this work [45]. A reaction vial was charged with marchantin A (35 mM), Na_2CO_3 (4.8 mg, 45 mmol), and MeCN (1.3 mL). The appropriate vinyl-ester was added dropwise (final concentration 420 mM) to the reaction mixture under constant magnetic stirring. The vial was crimped and heated at 120 °C for 24 h. The reaction mixture was filtered, washed with MeCN (5 mL) and the solvents were removed under reduced pressure. The crude product was dried under high-vacuum, and NMR analysis confirmed that no further purification was necessary. All products **TE1**, **TE2**, and **TE3** were obtained in quantities of 26.4, 28.0, and 28.1 mg, respectively and their HPLC purities were over 95%.

4.5. General procedure for the lipase-catalyzed acylation of marchantin A

A reaction vial was charged with marchantin A (23 mM), Novozym® 40,086 (1.6 g/mmol of substrate), and *i*-Pr_2O (44.4 mL/mmol of substrate). The appropriate vinyl-ester was added dropwise (final concentration 460 mM) to the reaction mixture under constant magnetic stirring. The vial was crimped and heated at 45 °C for 24 h. The enzyme was separated from the reaction mixture by filtration and washed with CH_2Cl_2 (10 mL). The filtrate was collected and concentrated under reduced pressure. The crude products were purified by Dry-flash chromatography (SiO_2, Hex/EtOAc 7:3 *v*/v) or preparative Thin-layer chromatogaphy (SiO_2, CH_2Cl_2/MeOH 97:3 v/v).

All products **ME1**, **ME2**, **ME3**, and **ME4** were obtained in quantities of 8.1, 10.1, 32.0, and 1.5 mg, respectively and their HPLC purities were over 95%.

4.6. In vitro antiproliferative assays

For the determination of cytotoxicity of synthesized compounds and Marchantin A, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric assay was used. The compounds were tested against MRC-5, A549 lung cancer and MDA-MB-231 breast cancer cell lines. The cells were incubated for 24 h in an RPMI-1640 medium with 10^4 colonies per well. The assay was done in 96 well flat-bottom microtiter plates (Sarstedt, Germany). After incubation, cells were treated with marchantin A and corresponding esters (dissolved in DMSO ((100 mM), filtered through a 0.2 μm filter, EMD Millipore, Billerica, USA) with final concentrations ranging from 0.5–250 μM. DMSO was used as a negative control. The cells were treated with the mentioned compounds for 48 h, and MTT (Sigma Aldrich, St. Louis, MO, USA) dissolved in RPMI medium (0.5 mg/mL) was added to each well subsequently. After an incubation time of 30 min at 37 °C, the medium was carefully removed by pipetting and DMSO (50 μL, 100%) was added to the adherent cells with formazan crystals in order to dissolve the formazan crystals. The absorbance of resulting solutions was measured with a *Tecan Infinite 200 pro multiplate reader* at a wavelength of 540 nm. The results were presented relative to the DMSO negative control. The cytotoxicity was presented as the IC_{50} value, the compound concentration value causing survival of 50% of the cells.

4.6.1. 1′,6′,13-n-tripropanoylmarchantin A (TE1)

Viscous colorless oil; $[\alpha]_D^{22}$ +5.0 (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ε): 274 (3.23), 238 (3.99), 229 (4.19) nm; IR (ATR) ν_{max}: 2983, 2941, 1769, 1593, 1505, 1461, 1351, 1318, 1268, 1213, 1187, 1138, 1079, 1040, 907, 859, 781, 736, 697; ESI-HRMS *m/z* 567.2741 $[M + H]^+$ (calcd. for $C_{36}H_{39}O_6$ 567.2747); ^1H NMR (500 MHz, $CDCl_3$) 7.34 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.93–6.97 (m, 3H), 6.64 (d, *J* = 1.5 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 2H), 6.50 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.43 (brs, 1H), 6.39 (brd, *J* = 8.0 Hz, 1H), 5.58 (d, *J* = 1.5 Hz, 1H), 3.00–3.10 (m, 4H), 2.86–2.90 (m, 2H), 2.70–2.77 (m, 2H), 2.52–2.56 (m, 4H), 1.91 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H), 1.22 (*J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) 171.9, 171.6, 171.4, 157.4, 152.9, 151.5, 143.9, 143.1, 142.5, 141.5, 138.6, 138.4, 136.6, 129.6, 128.6, 128.1, 124.7, 122.3, 121.6, 121.3, 115.9, 115.1, 114.0, 113.1, 36.1, 34.9, 34.3, 30.0, 27.5, 27.2, 27.0, 9.3, 9.2, 8.4.

4.6.2. 1′,6′,13-n-tributanoylmarchantin A (TE2)

Viscous colorless oil; $[\alpha]_D^{22}$ +6.0 (*c* 0.8, MeOH); UV (MeOH) λ_{max} (log ε): 274 (3.43), 238 (4.10), 231 (4.33) nm; IR (ATR) ν_{max}: 3510, 3033, 2966, 2934, 2875, 1767, 1594, 1505, 1463, 1349, 1311, 1268, 1244, 1213, 1183, 1142, 1097, 1038, 915, 850, 777, 733, 695; ESI-HRMS *m/z* 651.2954 $[M + H]^+$ (calcd. for $C_{40}H_{43}O_8$ 651.2958); ^1H NMR (500 MHz, $CDCl_3$) 7.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.93–6.97 (m, 3H), 6.65 (d, *J* = 1.5 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 2H), 6.50 (dd, *J* = 8.0,

1.5 Hz, 1H), 6.43 (brs, 1H), 6.39 (brd, J = 8.0 Hz, 1H), 5.58 (d, J = 1.5 Hz, 1H), 3.01–3.10 (m, 4H), 2.87–2.91 (m, 2H), 2.73–2.77 (m, 2H), 2.50–2.54 (m, 4H), 1.88 (t, J = 7.5 Hz, 2H), 1.76 (sext, 2H), 1.74 (sext, 2H), 1.33 (sext, 2H), 1.04 (t, J = 7.5 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H), 0.76 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) 171.1, 170.8, 170.6, 157.3, 152.8, 151.5, 143.9, 143.1, 142.5, 141.5, 138.6, 138.4, 137.7, 130.0, 129.6, 128.6, 128.1, 124.7, 122.3, 121.6, 121.3, 115.9, 115.2, 114.0, 113.0, 36.1, 35.9, 35.6, 35.4, 34.9, 34.3, 30.1, 18.5, 18.4, 17.7, 13.6, 13.5, 13.4.

4.6.3. 1′,6′,13-n-trihexanoylmarchantin A (TE3)

Viscous colorless oil; $[\alpha]_D^{22}$ +5.0 (c 1.0, MeOH); UV (MeOH) λ_{max} (log ε): 271 (3.34), 238 (4.05), 233 (4.01) nm; IR (ATR) ν_{max}: 3472, 3033, 2957, 2931, 2864, 1768, 1593, 1505, 1463, 1348, 1315, 1268, 1212, 1140, 1098, 1041, 912, 851, 776, 733, 695; ESI-HRMS m/z 735.3892 [M + H] $^+$ (calcd. for $C_{46}H_{55}O_8$ 735.3897); ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (dd, J = 8.0, 1.5 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 6.99 (dd, J = 8.0, 1.5 Hz, 1H), 6.93–6.97 (m, 3H), 6.64 (d, J = 1.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 2H), 6.48 (dd, J = 8.0, 1.5 Hz, 1H), 6.43 (brs, 1H), 6.37 (brd, J = 8.0 Hz, 1H), 5.56 (d, J = 1.5 Hz, 1H), 3.02–3.09 (m, 4H), 2.85–2.89 (m, 2H), 2.73–2.78 (m, 2H), 2.48–2.56 (m, 4H), 1.89 (t, J = 7.5 Hz, 2H), 1.69–1.79 (m, 4H), 1.24–1.41 (m, 10H), 1.06–1.20 (m, 4H), 0.94 (t, J = 7.5 Hz, 3H), 0.78–0.87 (m, 6H); ^{13}C NMR (125 Hz, $CDCl_3$) 171.2, 171.0, 170.8, 157.4, 152.8, 151.5, 143.9, 143.1, 142.6, 141.4, 138.6, 138.4, 136.7, 129.6, 128.5, 128.1, 124.7, 122.4, 121.6, 121.3, 115.9, 115.1, 114.0, 113.0, 36.1, 35.0, 34.3, 34.0, 33.7, 33.6, 31.2, 31.1, 31.0, 29.9, 24.7, 24.6, 23.8, 22.3, 22.2, 22.1, 13.9, 13.8, 13.7.

4.6.4. 13-n-propanoylmarchantin A (ME1)

Viscous colorless oil; $[\alpha]_D^{22}$ +4.5 (c 0.9, MeOH); UV (MeOH) λ_{max} (log ε): 274 (3.26), 238 (3.94), 231 (4.17) nm; IR (ATR) ν_{max}: 3443, 3033, 2922, 2854, 1763, 1604, 1508, 1461, 1353, 1268, 1213, 1140, 1077, 1027, 993, 961, 906, 847, 786, 735, 697, 458; HRESIMS m/z 495.1828 [M - H] $^-$ (calcd. for $C_{31}H_{27}O_6$ 495.1808); ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (dd, J = 8.0, 1.5 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.98 (m, 3H), 6.92 (t, J = 7.5 Hz, 1H)), 6.59 (d, J = 8.5 Hz, 2H), 6.48 (dd, J = 8.0, 1.5 Hz 2H), 6.46 (d, J = 1.5 Hz, 1H), 6.38 (brd, J = 7.5 Hz, 1H), 5.26–5.31 (m, 2H), 5.21 (d, J = 1.6 Hz, 1H), 3.02–3.10 (m, 4H), 2.72–2.82 (m, 4H), 1,90 (q, J = 7.5 Hz, 2H), 0,82 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ: 171.6, 157.3, 152.9, 146.1, 144.1, 144.0, 142.4, 142.2, 138.4, 136.5, 132.5, 130.6, 129.7, 128.3, 128.1, 124.6, 122.5, 121.7, 121.1, 115.3, 112.8, 109.3, 107.8, 36.1, 35.4, 34.3, 30.1, 27.0, 8.4.

4.6.5. 13-n-butanoylmarchantin A (ME2)

Viscous colorless oil; $[\alpha]_D^{22}$ + 1.0 (c 4.0, MeOH); UV (MeOH) λ_{max} (log ε): 282 (3.43), 272 (3.55), 240 (4.01); IR (ATR) ν_{max}: 3421, 2929, 2858, 2155, 1763, 1662, 1604, 1509, 1462, 1342, 1268, 1246, 1215, 1141, 1099, 1031, 850, 772; ESI-HRMS m/z 509.1977 [M - H] $^-$ (calcd. for $C_{32}H_{29}O_6$ 509.1964); ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (dd, J = 8.0, 1.5 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.98 (m, 3H), 6.92 (t, J = 7.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 2H), 6.43–6.48 (m, 3H), 6.38 (brd, J = 7.5 Hz, 1H), 5.26–5.31 (m, 2H), 5.21 (d, J = 1.5 Hz, 1H), 3.03–3.09 (m, 4H), 2.71–2.81 (m, 4H), 1.87 (t, J = 7.5 Hz, 2H), 1.30–1.33 (m, 2H), 0.76 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) 170.9, 157.3, 153.0, 146.2, 144.2, 144.0, 142.5, 142.3, 138.5, 136.6, 132.5, 130.7, 129.6, 128.3, 128.1, 124.7, 122.5, 121.6, 121.1, 115.4, 112.8, 109.3, 107.9, 36.1, 35.5, 35.4, 34.3, 30.1, 17.9, 13.5.

4.6.6. 13-n-hexanoylmarchantin A (ME3)

Viscous colorless oil; $[\alpha]_D^{22}$ +4.0 (c 1.0, MeOH); UV (MeOH) λ_{max} (log ε): 280 (3.37), 274 (3.48), 238 (4.16), 227 (3.98); IR (ATR) ν_{max}: 3436, 3033, 2930, 2860, 1763, 1605, 1508, 1462, 1343, 1268, 1214, 1142, 1101, 1028, 995, 961, 910, 848, 774, 733, 694; ESI-HRMS m/z 539.2428 [M + H] $^+$ (calcd. for $C_{34}H_{35}O_6$ 539.2434); ^{1}H NMR (500 MHz, $CDCl_3$) 7.32 (brd, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.95–6.98 (m, 3H), 6.91 (t, J = 7.5 Hz, 1H)), 6.59 (d, J = 8.5 Hz, 2H), 6.43–6.48 (m, 3H), 6.36 (brd, J = 7.5 Hz, 1H), 5.26–5.31 (m, 2H), 5.18 (d, J = 1.5 Hz, 1H), 3.02–3.09 (m, 4H), 2.70–2.80 (m, 4H), 1.89 (t, J = 7.5 Hz, 2H), 1.09–1.34 (m, 6H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) 171.0, 157.3, 152.9, 146.1, 144.1, 144.0, 142.6, 142.2, 138.5, 136.6, 132.5, 130.6, 129.6, 128.3, 128.1, 124.7, 122.5, 121.6, 121.2, 115.4, 112.7, 109.3, 107.8, 36.1, 35.5, 34.4, 33.6, 31.1, 30.1, 23.8, 22.1, 13.8.

4.6.7. 13-n-octanoylmarchantin A (ME4)

Viscous colorless oil; $[\alpha]_D^{22}$ +3.0 (c 1.0, MeOH); UV (MeOH) λ_{max} (log ε): 282 (3.46), 274 (3.64), 238 (4.13), 233 (4.15); IR (ATR) ν_{max}: 3433, 3033, 2927, 2856, 1764, 1606, 1506, 1463, 1343, 1246, 1215, 1207, 1141, 1103, 1029, 960, 909, 847, 770, 730, 694; ESI-HRMS m/z 567.2741 [M + H] $^+$ (calcd. for $C_{36}H_{39}O_6$ 567.2747); ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (dd, J = 8.0, 1.5 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 6.99 (m, 3H), 6.92 (t, J = 7.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 2H), 6.45–6.48 (m, 3H), 6.36 (brd, J = 7.5 Hz, 1H), 5.30 (s, 2H), 5.18 (d, J = 1.5 Hz, 1H), 3.03–3.09 (m, 4H), 2.71–2.81 (m, 4H), 1.89 (t, J = 7.5 Hz, 2H), 1.09–1.28 (m, 10H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) 171.0, 157.3, 152.9, 146.2, 144.1, 144.0, 142.6, 142.2, 138.5, 136.6, 132.5, 130.6, 129.7, 128.3, 128.1, 124.7, 122.5, 121.6, 121.2, 115.4, 112.8, 109.3, 107.8, 36.1, 35.5, 34.4, 33.7, 31.5, 28.9, 28.8, 24.2, 22.6, 14.0.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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