Catalysis Communications 86 (2016) 104–107

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Short communication

Selective oxidation of lupeol by iodosylbenzene catalyzed by manganese porphyrins

Dayse Carvalho da Silva Martins [a,*], Fernando César Silva [a], Alexandre Moreira Meireles [a], Érico Augusto Rodrigues Soares [a], Grácia Divina Fátima Silva [a], Sidney Augusto Vieira-Filho [b], Lucienir Pains Duarte [a], Júlio Santos Rebouças [c], Ynara Marina Idemori [a]

[a] Departamento de Química, Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte, MG, Brazil
[b] Escola de Farmácia, Universidade Federal de Ouro Preto, 35400-000 Ouro Preto, MG, Brazil
[c] Departamento de Química, Universidade Federal da Paraíba, 58051-900 João Pessoa, PB, Brazil

ARTICLE INFO

Article history:
Received 19 July 2016
Received in revised form 1 August 2016
Accepted 6 August 2016
Available online 7 August 2016

Keywords:
Porphyrin
Oxidation
Lupeol
Triterpene
Homogeneous catalyst

ABSTRACT

Manganese porphyrin-catalyzed oxidation of lupeol by iodosylbenzene was achieved under mild conditions with low isolated yields but with remarkable selectivity, depending on the catalyst of choice. Mn(III) *meso*-tetraphenylporphyrin and Mn(III) *meso*-tetrakis(4-carbomethoxyphenyl)porphyrin provided an entry for the preparation of 3β,30-dihydroxylup-20(29)-ene (6–14% yields), whereas Mn(III) β-octabromo-*meso*-tetrakis(4-carbomethoxyphenyl)porphyrin led to 20-oxo-3β-hydroxy-29-norlupeol (6% yield), as single products. Unreacted lupeol was recovered in quantitative yield. The oxidative transformations at lupeol C20 or C30 take place with no need for protection of C3 hydroxyl moiety.

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1. Introduction

Lupeol (Fig. 1), a lupane triterpene commonly isolated from various species of the Celastraceae family, has shown great pharmacological potential *in vitro* and/or *in vivo* studies on cancer, inflammation, arthritis, diabetes, and heart disease [1]. In cancer chemoprevention, for example, the non-derivatized, naturally occurring lupeol exerts multiple effects on biomarkers associated with carcinogenesis, resulting in antitumor activity [1].

Whereas the naturally occurring lupanes represent an abundant building block for the development of experimental therapeutics, they are usually little functionalized and of low polarity. Selective structural modifications of the lupane skeleton, such as functionalization of inert C—C and C—H bonds, are highly sought as a means to modulate solubility and bioavailability to yield products potentially more biologically active. The functionalised lupane compound labelled NVX-207, a lupeol-derived drug, improve radiotherapy effects on human malignant glioma cells [2].

It is worth noting that some of the new lupeol derivatives are more biologically active than the parent compound [3]. Semi-syntheses of lupeol derivatives have often relied on structural modification at the C3 hydroxyl group *via* esterification [3]. Less common transformations have been described at the olefin moiety at C20 [4,5] or at the lupeol rings [6], which are also usually preceded by protection of the C3 hydroxyl.

Whereas the biological/pharmacological activities of lupeol and lupeol-based therapeutics have been widely explored, little is known on the metabolism of these compounds. Xenobiotics usually undergo metabolism *via* oxidations catalyzed by the Cytochrome P450 enzymes. The first metabolic stability assessment of anti-HIV, lupane-based agents was recently carried out *in vitro* in pooled P450-containing human liver microsomes, but the metabolites were not described [7].

Cytochrome P450 reactions are primarily mixed-function oxidations carried out by a metalloporphyrin-based active site. The repertoire of substrates includes a wide variety of natural products ranging from terpenes in microorganisms to steroids in mammals. In the past years, the catalytic mechanisms involving P450 have been scrutinised in several reviews [8].

Biomimetic models based on synthetic metalloporphyrins have been used to achieve most of the known P450 reactions *via* high-valent metal-oxo oxidants derived from oxygen donors such as peracids or iodosyl compounds [9]. The use of metalloporphyrins as catalysts in the P450 biomimetic models for drug and pro-drug oxidation has allowed the synthesis, structure determination, and spectroscopic characterization of possible metabolites of interest to unravel the nature of these products, their involvement in the drug/pro-drug mode of action, and their toxicological and pharmacological properties. The oxidation of

* Corresponding author.
E-mail address: daysequimica@ufmg.br (D.C.S. Martins).

http://dx.doi.org/10.1016/j.catcom.2016.08.014
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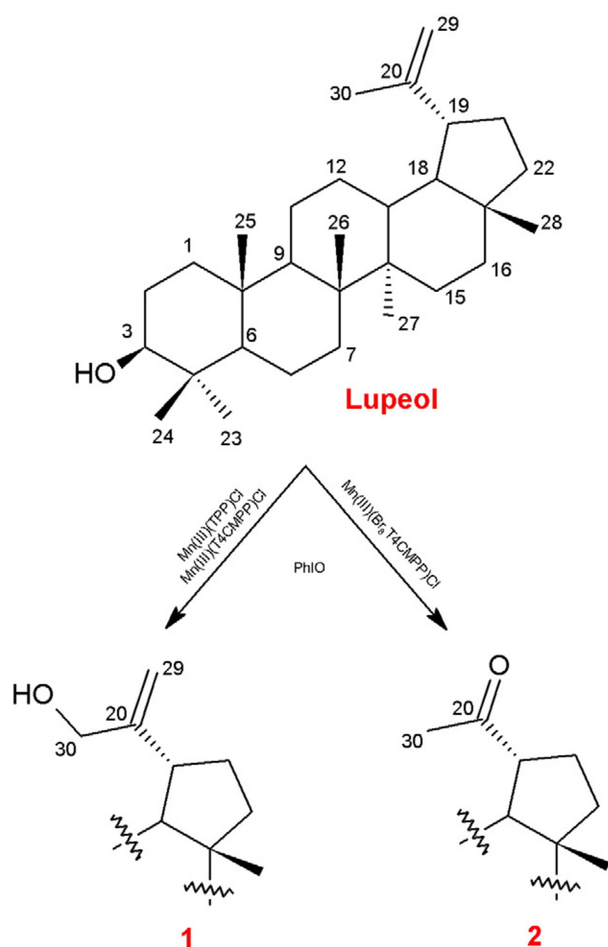

Fig. 1. Oxidation of lupeol by iodosylbenzene (PhIO) in 1,2-dichloroethane catalyzed by Mn-porphyrins. Chemoselectivity is achieved by the MnP of choice.

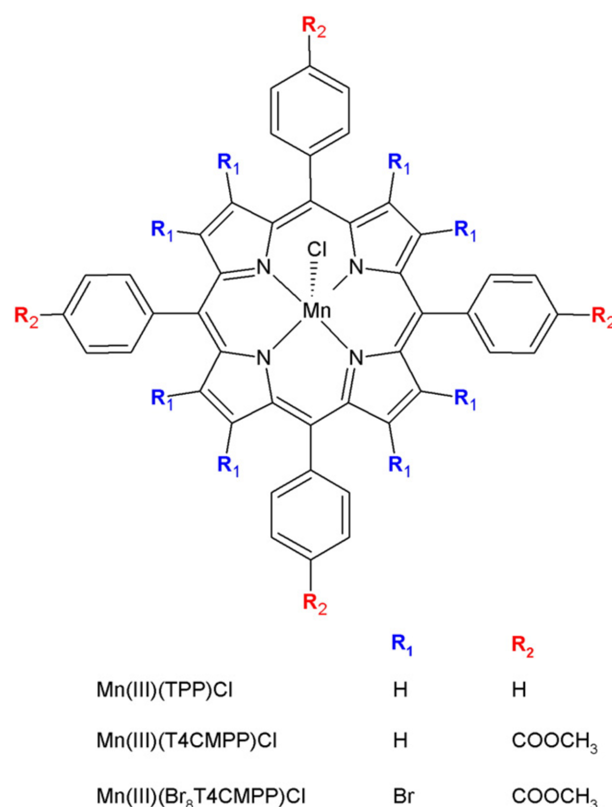

Fig. 2. Schematic structure of the Mn-porphyrins used in this study.

monoterpenes, such as limonene [10], by P450-based mimics is well established, but the development of metalloporphyrin-based P450-model systems to study the oxidation of triterpenes remains essentially neglected [11–13].

Allylic oxidations and epoxidations followed by lactonization of oleanane-type triterpenes with Fe-porphyrins have been described [11,12]. More recently, Ru-porphyrin-based oxidations of ursane-type triterpenes yielded ursolic acid-derivatives with cytotoxicity against rat glioma and human skin carcinoma cell lines [13]. To the best of our knowledge there has been no report on the biomimetic oxidation of lupane-type triterpenes.

Herein we describe the PhIO-oxidation of the lupane-type triterpene lupeol by Mn-porphyrin-based P450 biomimetic models (Fig. 2) under mild conditions to yield 3β,30-dihydroxylup-20(29)-ene (**1**) or 20-oxo-3β-hydroxy-29-norlupeol (**2**) (Fig. 1), which are of difficult access *via* conventional organic routes.

2. Experimental

2.1. General information

Meso-tetrakis(4-carbomethoxyphenyl)porphyrin (H_2T4CMPP), *meso*-tetraphenylporphyrin (H_2TPP) were purchased from MidCentury Chemicals and used as received. The Mn-porphyrin chloride complexes Mn(III)(TPP)Cl [14], Mn(III)(T4CMPP)Cl [15,16], and Mn(III)(Br_8T4CMPP)Cl [15,16] were synthesized as reported.

Reagent grade $NaHCO_3$, $Na_2S_2O_3$, and anhydrous Na_2SO_4 were obtained from Labsynth. Iodosylbenzene (PhIO) was prepared according to a literature procedure [17], stored in a freezer at −20 °C and periodically assayed by iodometric titrations. All other reagents and solvents of analytical grade were purchased from Aldrich, Sigma, Fluka or Merck and used without further purification, unless stated otherwise.

Lupeol was isolated from species of the Celastraceae family by successive column chromatography using silica gel as stationary phase and hexane/chloroform (7:3) as mobile phase. Crude lupeol was further purified by recrystallization in ethanol with a few drops of chloroform to yield a highly pure compound, whose physical and spectroscopic characteristics matched those of an authentic sample [18].

Thin-layer chromatography (TLC) was carried out in SiO_2 plates developed with a 1:1 perchloric acid:vanillin colorimetric reagent [19]. Ultraviolet–visible (UV–Vis) spectra (190–1100 nm) were recorded on HP-8453A diode-array spectrophotometer. One- (1D) and two-dimension (2D) ^{1}H and ^{13}C NMR data were obtained on a Bruker Avance DRX 400 using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Chemical shifts are reported in part per million (ppm). FT-IR spectra were recorded on a Perkin Elmer, Spectrum One spectrophotometer (ATR).

2.2. Oxidation reactions

Lupeol (0.33 mmol), Mn-porphyrin (0.0099 mmol), and PhIO (0.40 mmol) were weighed in a 10 mL glass vial, to which 1,2-dichloroethane (6.0 mL) was added. The vial was sealed with a screw cap and the mixture was magnetically stirred for 4 h at 0 °C. Then, the resulting mixture was treated with sat. $Na_2S_2O_3$(aq) and $NaHCO_3$(aq) to quench any remaining PhIO oxidant. The organic phase was extracted with ethyl acetate, dried with anhydrous Na_2SO_4, filtered and concentrated to minimum volume. The unreacted lupeol and the oxidation products were purified on a silica gel (70–230 mesh) column chromatography [11] eluted with a 7:3 hexane:ethyl acetate mixture. The isolated materials were characterized by melting point measurements, and 1D/2D

NMR and infrared spectroscopies. Lupeol oxidation runs in the absence of catalysts (blank/control reactions) showed no product formation.

3. Results and discussion

The oxidation of the lupane-type triterpene lupeol catalyzed by the simplest, commercially available Mn-porphyrin Mn(III)(TPP)Cl using PhIO as oxidant led to the formation of **1** (Fig. 1), which was chromatographically isolated in 6% yield, based on the starting lupeol (Table 1). The isolated triterpene lupeol derivative **1** showed physical and spectroscopic characteristics that matched those of an authentic sample [20–23]. The formation of **1** corresponds to an allylic oxidation at C30 (Fig. 1), but no epoxide, which is normally observed in Mn-porphyrin-based oxidations [15,24], was found. In fact, all attempts to detect triterpenic products other than **1** by TLC were unsuccessful. Mn(III)(TPP)Cl is, however, unstable toward PhIO-degradation; full catalyst decomposition limited lupeol conversion.

The introduction of electron-withdrawing groups onto the metalloporphyrin periphery has been used as a strategy to yield more robust catalysts [25]. The use of a carbomethoxy-substituted TPP, Mn(III)(T4CMPP)Cl (Fig. 2), as catalyst for PhIO-oxidation of lupeol, resulted in the selective formation of **1** in higher yield than that obtained with the parent Mn-porphyrin Mn(III)(TPP)Cl (Table 1). Mn(III)(T4CMPP)Cl was more stable toward oxidative degradation (~30% bleaching) than the parent Mn(III)(TPP)Cl.

The use of the highly electron-deficient Mn-porphyrin Mn(III)(Br_8T4CMPP)Cl (Fig. 2) resulted in the formation of compound **2** (Fig. 1) with high selectivity; remarkably, Mn(III)(Br_8T4CMPP)Cl-based lupeol oxidation yields no **1**, as indicated by TLC analysis. Compound **2** was chromatographically isolated in 6% yield (Table 1). Unexpectedly, the octabrominated complex and Mn(III)(TPP)Cl shared similar low stability toward PhIO-degradation. Both catalysts were completely destroyed during the reaction, limiting product yield. Unreacted lupeol was recovered in >90% yield.

The usual reaction pattern of Mn-porphyrin-based oxidations indicates that the likely sites of reaction within lupeol would be the C20—C29 olefin and/or the C3 alcohol moieties to yield the corresponding epoxide and/or ketone [15,24,26], these products, however, were not observed in the present systems. In the Mn-porphyrin systems studied, the lupeol oxidation takes place at its side-chain moiety *via* allylic hydroxylation at C30 to yield **1** (with Mn(III)(TPP)Cl and Mn(III)(T4CMPP)Cl catalysts), or, more remarkably, *via* selective C20═C29 bond cleavage (with loss of the methylene carbon C29) to yield **2** (with Mn(III)(Br_8T4CMPP)Cl catalyst).

The oxidative cleavage of alkenes to ketones is a very useful reaction in organic synthesis [27,28]. The most common routes to carry out a C═C oxidative cleavage involve either the conversion of olefins to vicinal diols followed by cleavage with $NaIO_4$, oxone, OsO_4 *etc.*, or ozonolysis, in which the olefin is directly cleaved into the functionalized products [28]. Ozonolysis is quite reliable, but a major issue is related to safety concerns, as ozone gas is highly toxic and its generation requires special instrumentation. The oxidative cleavage of alkyl olefins by standard OsO_4 route suffers from the high volatility and toxicity of this agent [27]. The use of Mn(III)(Br_8T4CMPP)Cl as catalyst for the PhIO-oxidation of lupeol to yield **2**, appears, thus, as a highly selective route to the oxidative cleavage of this lupane under mild conditions; this transformation represents an elegant entry to future investigations on exploring metalloporphyrins as P450 biomimetic model on lupane triterpene oxidation.

Table 1
Lupeol oxidation by PhIO, in 1,2-dichloroethane, catalyzed by Mn-porphyrins.

Catalyst	Yield of oxidation product (%)	
	1	**2**
Mn(III)(TPP)Cl	6	–
Mn(III)(T4CMPP)Cl	14	–
Mn(III)(Br_8T4CMPP)Cl	–	6

To the best of our knowledge, the present work is the first example of selective oxidative cleavage of C═C bond on lupane skeleton by metalloporphyrin-based catalysis. The oxidations of lupeol using conventional methods are already described in literature. The oxidation of lupeol with pyridinium chlorochromate (PCC) yields lup-20(29)-en-3-one (lupenone) [29]. Allylic oxidation of lupeol with SeO_2 gave the aldehyde in C30 [30]. The treatment of lupeol with lead tetraacetate followed by immediate reduction with $LiAlH_4$ led to a product from the cleavage of C3—C4 bond [31]. The oxidation of lupeol with dimethyldioxirane yields compound **2**, but to maintain intact the C3 hydroxyl moiety is necessary to use protecting group [32]. In early studies on alkene oxidation by Mn(III)(TPP)Cl [33], Mn(III)(T4CMPP)Cl [34], and Mn(III)(Br_8T4CMPP)Cl [34] we observed the cleavage of C═C bonds to yield aldehyde, as side-product, along with epoxide (major product), which contrasts markedly with the high selectivity observed for the lupeol system.

It is worth noting that selective oxidation at lupeol C20, *via* C20═C29 cleavage, takes place without the need for protection of the hydroxyl group at C3. A lupeol-derived compound related to **2** has been recently described by Kazakova et al. [5] using a multi-step procedure by which lupeol was first protected by acetic anhydride acetylation of the hydroxyl group at C3 and then subjected to ozonolysis, which resulted in the elimination of the methylenic C29 and with subsequent formation of the carbonyl at C20 [5]. Under such conditions, at least three steps (*i.e.*, protection, ozonolysis, deprotection) would be needed to obtain **2** from lupeol, whereas this transformation can be selectively achieved in a one-pot procedure *via* the PhIO-oxidation of lupeol catalyzed by Mn(III)(Br_8T4CMPP)Cl; the association of the high selective process with the reduced number of steps represents a clear advantage on the direct synthesis of C20 modified lupeol derivatives with no need for C3 hydroxyl protection. Noteworthy is that Arciniegas and coworkers [35] showed that lupeol derivatives with structural modification at C20 and free hydroxyl group at C3 show higher anti-inflammatory activity than that of lupeol and its C3 protected analogue. This method for selective preparation of products **1** and **2** allows further investigations on their potential biological activities. In some cases, the lupeol derivatives show better activity than the parent compound [3,4,29,32,35].

4. Conclusions

The PhIO-oxidation of lupeol catalyzed by Mn-porphyrins as Cytochrome P450-based metabolism reaction models was investigated. Despite low lupeol conversions, the reactions achieved 100% selectivity toward either product **1** or **2**, with unreacted lupeol being recovered chromatographically at 94, 86, and 94% yield for Mn(III)(TPP)Cl, Mn(III)(T4CMPP)Cl, and Mn(III)(Br_8T4CMPP)Cl reactions, respectively. Lupeol allylic oxidation to yield **1** is accomplished by choosing either Mn(III)(TPP)Cl or Mn(III)(T4CMPP)Cl as catalysts, whereas the use of β-octabrominated Mn-porphyrin Mn(III)(Br_8T4CMPP)Cl leads to an unusual side-chain C═C cleavage yielding compound **2**. The results of this work introduce an alternative, selective route to semi-synthetic derivatives of lupeol with no need to prior protection of the hydroxyl group at C3. These Cytochrome P450-based catalytic model systems may contribute to the prospection, identification, and quantification of likely metabolites of lupeol in biological systems. Overall, the results suggest that (a) lupeol can be considerably resistant to oxidative transformations (and possibly of difficult metabolism) and (b) it may be selectively oxidised to just a few products *in vivo*.

The side-chain cleavage that accompanies the formation of **2** from lupeol represents an entry to a P450 reaction model and introduces a promising use of Mn(III)(Br_8T4CMPP)Cl for the oxidative cleavage of other natural products of biological interest.

Acknowledgments

This study was funded by the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2016.08.014.

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