



## Research Article

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# Conformational Studies on (+)-*epi-goniofufrone* and *Hirsutic Acid* Reveals Patterns of Conformer Populations in Triquinane Sesquiterpenes

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## Abstract

Cyclic compounds are frequently found in natural products, prevailing specially in alkaloids. Whether the choice of nature for these carbonic skeletal frameworks, is conformationally beneficial, has yet to be explored. In this paper we try to show how nature's choice of cyclic carbonic framework in two triquinane sesquiterpenes is responsible for populating specific conformers to provide bioactivity. Conformational analysis of *cis-octahdropentalenes* can provide a telltale sign that conformational preference may be a predesigned aspect of both (+)-*epi goniofufrone* and *hirsutic acid*. conformational analyses are done, using ωb97xd/6-311+G(d) level of theory. The model was then tested to analyze the stable conformers in, (+)-*epi-goniofufrone* and *hirsutic acid*, respectively. The results are in line with our previous findings on chondrosterin J, and further work is underway to find a comprehensive detailed conformational landscape for fused five membered rings.

**Keywords:** Bioactive conformers; *Cis-octahdropentalene*; (+)-*epi-goniofufrone*; *Hirsutic acid*; Triquinane sesquiterpenes

## Introduction

Hoffmann et al. [1] asked the pivotal question of whether nature is deliberately dictating conformational patterns for natural products or not. He suggested that cyclic compounds containing oxygen can attain conformational preferences that are of prime importance to bio activity Still et al. [2]. were among the pioneers to show these conformational preferences in oxygen containing six-membered rings can collectively determine the final shape of some natural products. Our new results seems to back up the idea of nature's deliberation in choosing fused cyclic carbonic skeletons to exploit their conformational space in sculpting bio active molecular shapes Lipnick et al. introduced a wheel model of a of up to 20 conformers [1,3,4] to show cyclopentane conformational mobility.

Further attempts [5-12] to classify these conformers mostly proved unsuccessful [13-15]. The concept of a spherical conformational landscape (see SI) decisively classified the conformers into so called bent and twist conformers arranged along two ring coordinates [16]. The model has then developed over the recent years to study the fused cyclic compounds [17]. Figure one shows such a conformational wheel model for *cis-octahdropentalene* (see SI for conformer legend), recently being studied along with other fused cyclic systems in our studies on conformational analysis Table 1. provides the relative energies of these conformers. Clearly the pseudorotational ring coordinates are not fully accessible in fused cyclic systems [16,17] (Figure 1 & Table 1).

**Table 1:** Relative energies and symmetry point groups for double envelope conformers in *cis-octahydropentalene*.

<i>cis-Octahydropentalene</i>		DFT $\omega$ b97xd/6-311+G*	
Conformer type	Conformer number	Symmetry	Erel (KCal/mol)
Double Bent Conformers	cEE1	C2v	1.2
	cEE2	C2	3.9
	cEE3	C2h	0
	cEE4	C2	2.1
	cEE5	C2	3.7
	cEE6	C1	4.2
	cEE7	C1	3.8
	cEE8	C1	3.9
	cEE9	C1	4.3
	cEE10	C1	4.2
	cEE11	C2v	1.7
	cEE12	C1	2.4
	cEE13	C2	2

## Methods

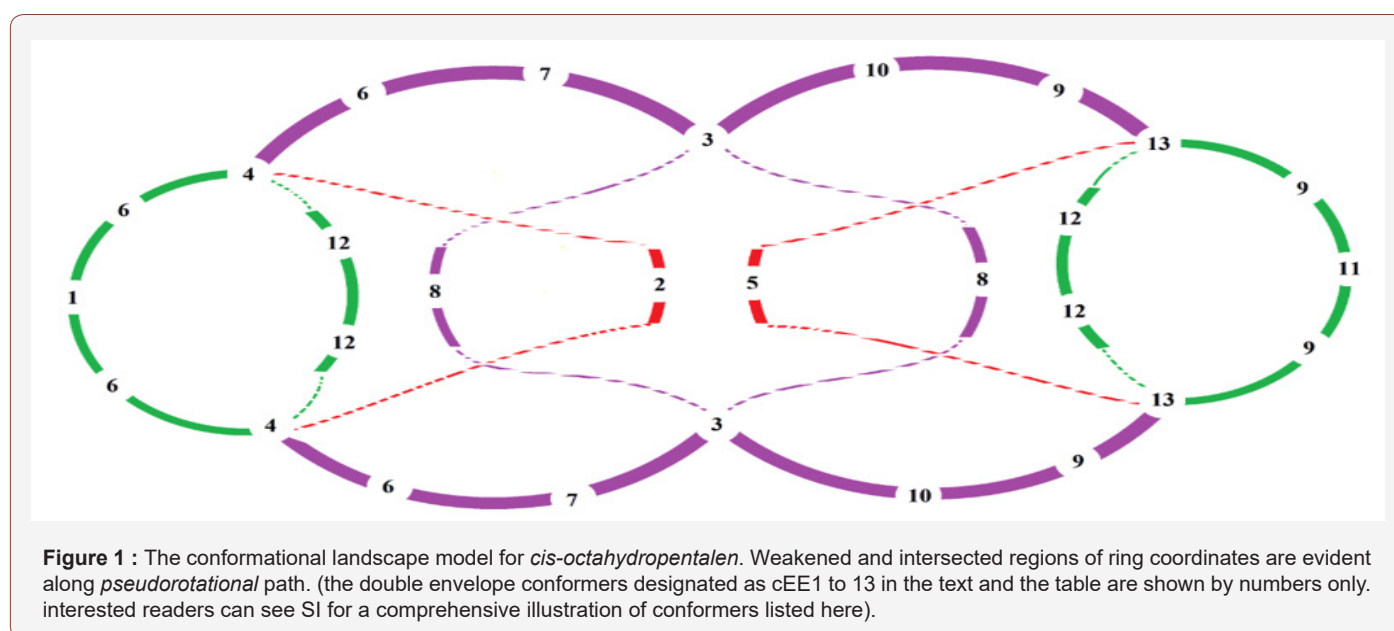
To study conformational forms in *cis-octahydropentalenes* as well as *hirsutic acid* and goniofufrone, density functional methods like  $\omega$ b97xd, in particular yield results similar, if not close, to those obtained via correlational methods like MP2. Most local density functional methods, slightly overestimate barriers due to their inability to account for van der Waals attractions in some strained conformers [18,19]. The  $\omega$ b97xd basis set can reliably result in accurate van der Waals modifications. The geometries computations were done at  $\omega$ b97xd/6-311+G(d) level [20-22], using Gaussian g09 package [23]. Larger basis sets like 6-311+G(d,p) proved no better accuracy.

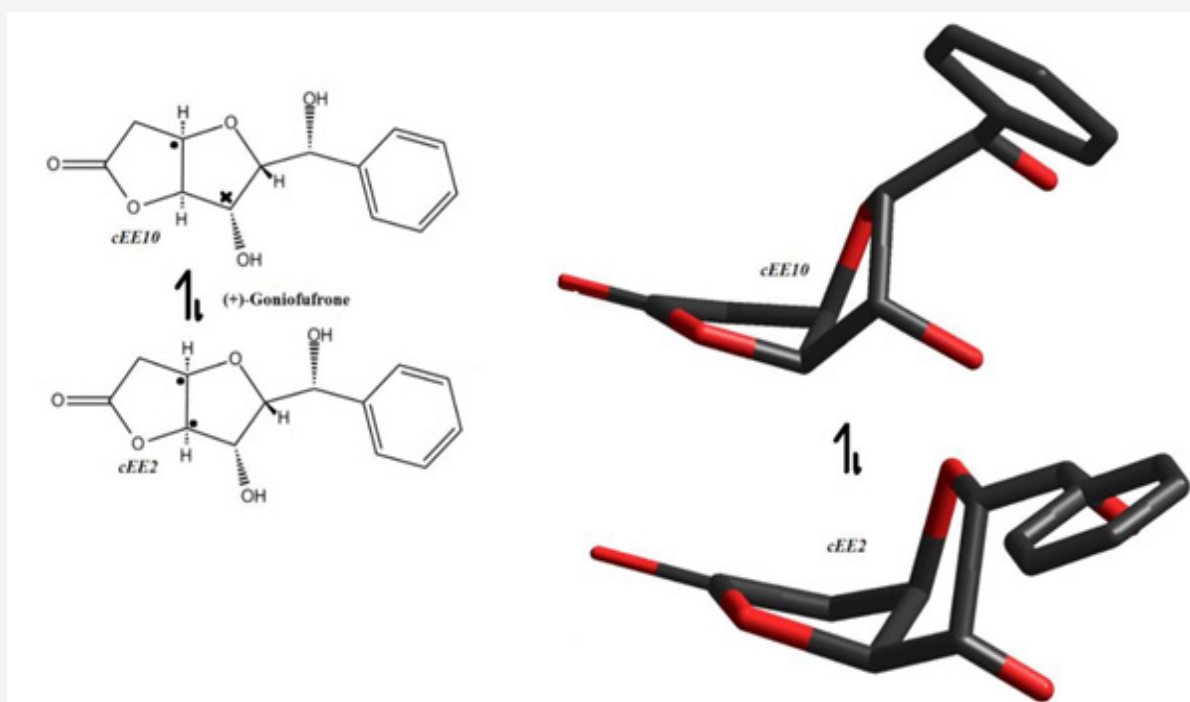
## Results and Discussion

(+)-*epi-goniofufrone* [24] is one of herbal pharmaceutical polyketide components found in plant family *Annonaceae* with about 2000 species and have been historically important. This marine natural product is a triquinane sesquiterpene with a

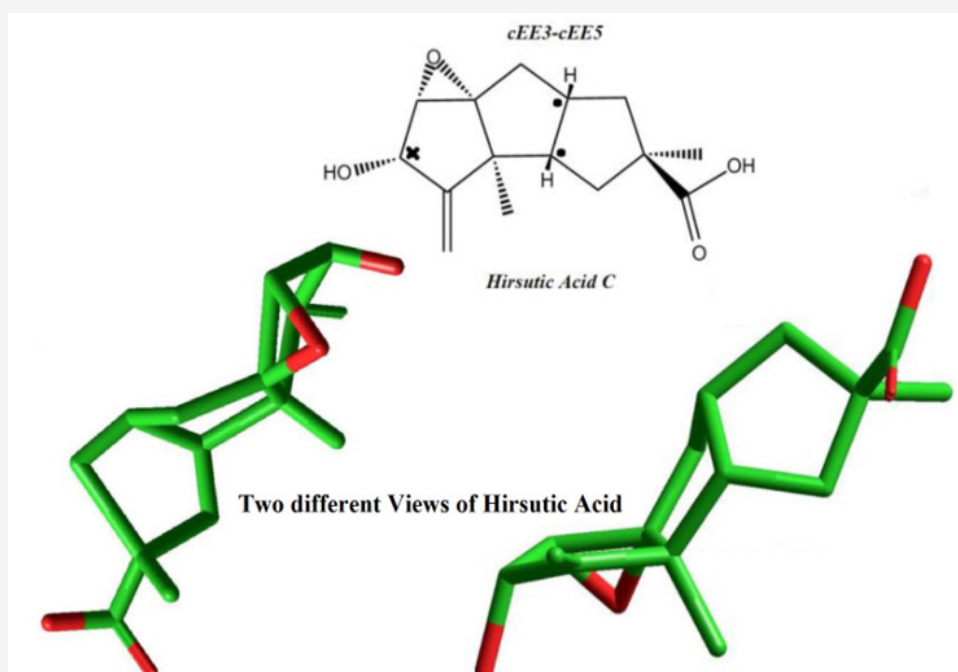
main *cis-octahydropentalene* framework. The molecule switches between conformational forms cEE2 and cEE10, with latter being more fluxional and dynamic in ring coordinate, while cEE2 is rather a trapped conformer with minimal fluxional nature. The two conformers are believed to cooperatively populate the cEE10 in the conformational landscape (Figure 1). It is also noteworthy that more axial/equatorial character is given to hydroxy substituent in cEE10 compared to cEE2, as the substituents are closer the puckered tip of the envelope rather its terminal planar carbons. This more axial/equatorial character may well suggest how nature uses fused cyclic rings to its benefit (Figure 2).

*Hirsutic acid* is an antibiotic isolated from a fungus, *Stereum Hirsutum*, with the main skeleton of three successive fused cyclopentane rings. *Hirsutic acid* is also a triquinane sesquiterpene that has three five membered rings fused together in two *cis* configurations, here a mobile cEE3 part of the molecule seems to balance the other end of the molecule to attain a trapped cEE5 conformation (Figure 3) (Figure S1, S2 & S3).





**Figure 2 :** Conformational preference in (+)-*epi goniofufrone* localizing the framework to cEE10 and cEE2 conformers populating the cEE10 mostly. In cEE10 both benzylic and hydroxy substituents gain maximum axial/equatorial character..



**Figure 3 :** Conformational preference in hirsutic acid, where the stable cEE3 moiety helps lock the other end into a restricted cEE5 conformer, in which the acidic functional group can have a minimal degree of freedom and thus maximum directionality.

## Conclusion

In Conclusion, two triquinane sesquiterpenes have been shown two adopt pseudorotationally localized conformers, in which their functional substituents can attain maximum axial/equatorial characters. Both compounds possess a *cis-octahydropentalene* carbonic backbone. Our results show *cis-octahydropentalene* frameworks can populate desired conformers mainly because of if the intersected ring coordinates in their conformational landscape

model. The conformational landscape shown here, successfully explains the bioactive conformers in these two triquinane sesquiterpenes. Further ongoing research is underway to explore a more in depth understanding of such conformational landscapes in cyclic and cyclic fused compounds.

## Acknowledgement

None

## Conflict of Interest

No conflict of interest.

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