MESO CHEMICAL SYMMETRY, DEFINITION BY MOLECULAR MODELLING AND APPLICATION TO INOSITOLS

ABSTRACT. Plane of symmetry is a physical chemical phenomenon and an instrument. Geometrical plane of symmetry indicates two identical achiral halves. In a slightly modified form, it is applied also in chemistry. In geometry it cuts a point or a line, while in chemistry it cuts a cloud of electrons (a bond) or one or more atoms, as railroad cuts a field. The second type, chemical plane of symmetry, named also mirror plane of symmetry, indicates two enantiomeric chiral halves uniformly linked with each other or uniformly linked on a suitable matrix. Compounds characterized by a mirror plane of symmetry have been designated meso. Meso compounds designated in this way by Cahn-Ingold-Prelog rules do not change the latter assertion: one can assert that molecules of this group are formed of two imaginary enantiomeric halves separated by an imaginary mirror plane of symmetry. From the definition of meso compounds one can infer, by molecular modelling, that alternative dimerization of the two enantiomeric halves, between them or on the initial matrix, would produce two chiral enantiomeric products. However, inositols, considered *meso* by numerous authors, present spectacular and unexpected surprisals.

Key words: meso; C_2 symmetrical; plane of symmetry; geometrical; mirror; homodimers; heterodimers; inositols;

1. INTRODUCTION

Systematization of a multitude formed of similar elements, regardless of its magnitude, is not the most difficult task, the most difficult is to find out a principle, a criterion, able to logically integrate all present and future component entities. In a tentative for systematization of natural micro molecular organic compounds, the elements of symmetry – mirror plane of symmetry, center of symmetry and (alternating) axis of symmetry have been considered as principles (criteria) for the aimed task. It has been constantly searched the capacity of organic compounds to exist in a symmetric form [1-11]. Symmetry is discussed in connection with planes of symmetry. Plane of symmetry is a physical chemical phenomenon and an instrument. Geometrical plane of symmetry indicates two identical achiral halves. It can be applied to regular geometrical figures (circle, square, rectangle, equilateral triangle, etc.) or to regular geometrical bodies (sphere, cube, cone, cylinder, etc.). In an equilateral triangle geometrical plane of symmetry cuts a point and a line, in a square two lines or two points, in a sphere or a cube it cuts an area, etc. In a slightly modified form, geometrical plane of symmetry can be applied also in chemistry. In the latter science it cuts a cloud of electrons (i.e. a bond) or one or more atoms (i.e. a nucleus or nuclei and their electronic clouds), as railroad cuts a field. In chemistry, geometrical plane of symmetry operates in this way: applied to cyclopropane it cuts an atom of C and two atoms of H, as well as a C-C bond, and what appears as two identical halves are the two methylene groups. There are two alternatives in cyclobutane: (a) geometrical plane of symmetry cuts two C-C bonds, and two ethylene groups appear as the two identical halves; (b) it cuts the two diagonal methylene group, and what appears as two halves are the other two methylene groups. Nonetheless that in chemistry, the geometrical plane of symmetry has the property to hide (or to mask) some chemical groups cut by it or situated in it. The second type, chemical plane of symmetry, named also mirror plane of symmetry, indicates two enantiomeric chiral halves uniformly linked with each other or uniformly linked on a suitable matrix. In heterodimeric compounds characterized by a mirror (or chemical) plane of symmetry, the cut

atoms are hidden (masked) of polarized light. E.g. xylitol, ribitol and numerous synthetic compounds [10,12].

Natural and synthetic organic compounds have been classified, in a tentative of their systematization, in three types [5,9-11]:

- (**A**) Symmetric, especially *meso* (**A1**) and *C_2 symmetric* (*C_2 symm.*) (**A2**). The molecule of *meso* compounds is formed of two enantiomeric halves, evidenced by a mirror plane of symmetry. *meso* Compounds designated in this way by Cahn-Ingold-Prelog rules do not change the latter assertion: one can assert that molecules of this group are formed of two imaginary enantiomeric halves separated by an imaginary mirror plane of symmetry. From the definition of *meso* compounds one can infer, by molecular modelling, that alternative dimerization of the two enantiomeric halves, between them or on the initial matrix, would produce two chiral *C_2 symm*. enantiomeric products; it should be stressed that the matrix, without being necessarily chiral has to satisfy the definition of C_2 symmetrical compounds [12]. Consequently, alternative uniform dimerization of his two halves produces two chiral enantiomeric *C_2 symm*. combinations. Hence, the molecule of *C_2 symm*. combinations is formed of two identical chiral halves uniformly linked with each other or on a suitable mono- or poly-atomic matrix.
- (**B**) Possible symmetry generators, i.e. compounds possessing a real or imaginary, but plausible, chemically symmetric correspondent: *irrechi* (from irregular distribution of chiral carbons) (**B1**) and *constitutional* (*constit*.) (**B2**).
- (**C**) *archaic* (or *primitive*) that are neither symmetric nor possible generators of chemical symmetry.

Symmetric compounds are a minority in organic chemistry. The three groups are (bio)chemically interchangeable. In preceding papers we have demonstrated that almost all natural micromolecular combinations [1,3-9] appear as *constit*., however they all are possible generators of chemical symmetry. *Archaic* (*primitive*) type is also represented in natural chemistry. On the other hand, it should be stressed that symmetric compounds, both *meso* and *C_2 symm*. have been found almost exclusively in plants and microorganisms, and they are usually produced from *constit*. precursors.

The term *meso*-inositol is as ubiquitous as a pollutant. It can be found in all textbooks and journals, inclusively in English Nature and in American Science. In this paper is demonstrated that no inositol *per se* is *meso*. All achiral inositols present a geometrical symmetry, like benzene and toluene. Comparatively, *meso* compounds of seven classes of combinations are presented (Figs. 1-9 and Table 1). Moreover, our aim is to identify as much as possible compounds possessing a real or possible degree of enantiomorphism in their molecule, both in natural realm and synthetic group, i.e. potential chemical symmetry generators.

2. CARBOHYDRATES

At the beginning of the nineteenth century, polarized light and optical activity have been discovered and polarimeter was invented. When Pasteur approached tartaric acid, two specimens of this acid were known: a dextrorotary type that had been discovered by Scheele (1770) in the sediment (tartar) deposited during the grape juice fermentation [14], and a specimen devoid of optical activity prepared by Kestner (1822) [15]. Pasteur (1848) separated two types of enantiomorphic crystals from a Kestner's sample (Fig. 1), and found out that their watery solutions were dextrorotary and levorotary, respectively. Hence, Kestner's specimen of tartaric acid was in fact a racemic mixture. When van't Hoff [16] and LeBel [17] invented steric molecular models, a question had to be raised concerning the correspondence between the

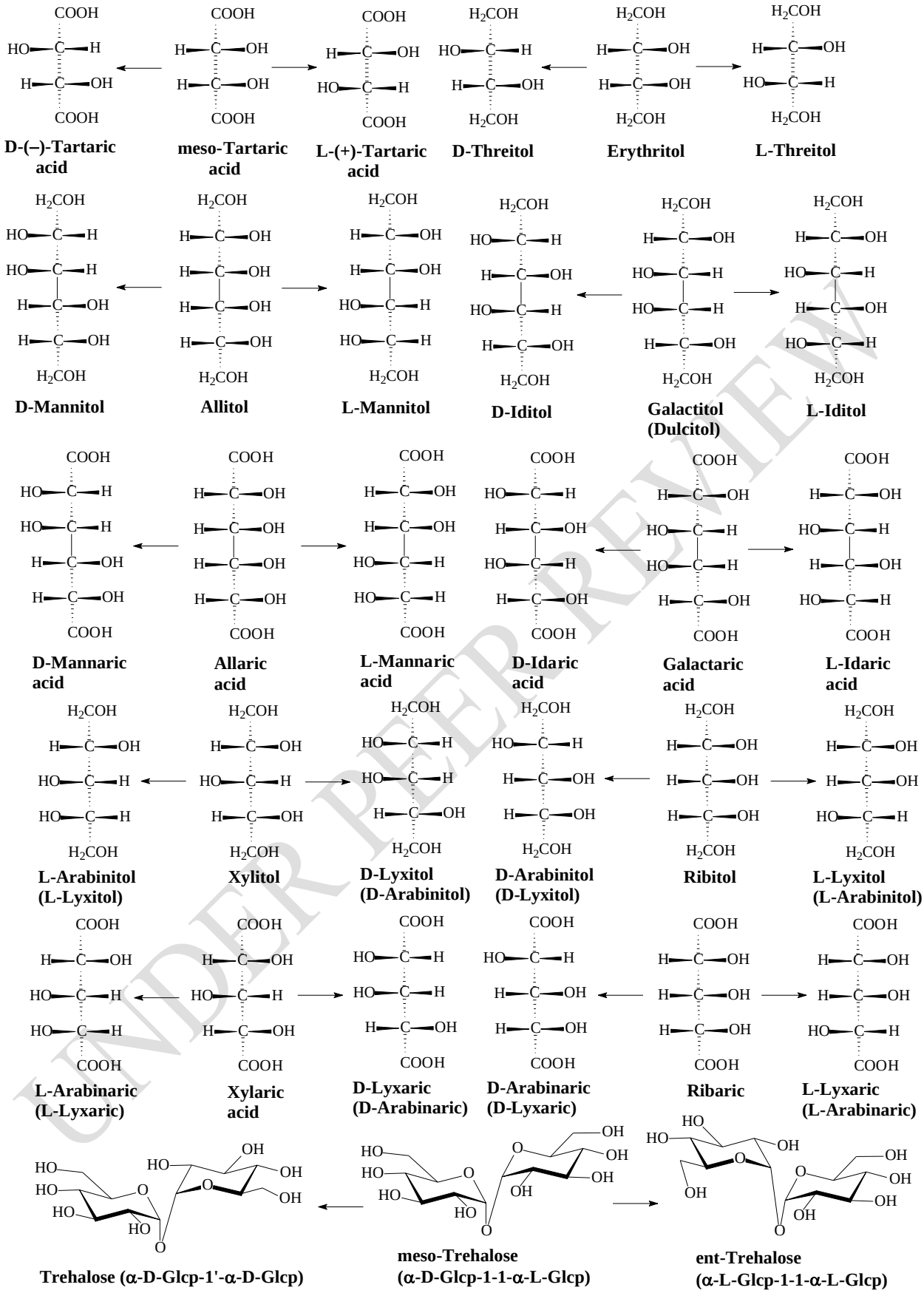


Figure 1. Stereochemistry relationship between *meso* carbohydrates and their C_2 *symm*. isomers.

samples of the enantiomeric tartaric acids and the two models elaborated by van't Hoff. Since [+]-tartaric acid had been the first discovered, it was selected as reference. Of all chemists faced

up with this dilemma, E. Fischer probabilistically solved it (Fig. 1) [18] and steadfastly followed it in the elaboration of the reasoning concerning structure elucidation of linear aldohexoses and their linear isomers [19,20]. The configuration of [+]-tartaric acid has been doubtlessly elucidated by Bijvoet et al., [21]. An important contribution to E. Fischer's biography was brought by showing that a preparative method elaborated by H. O. L. Fischer, his son, aiming at (+)- and (–)-glyceraldehyde [22,23], significantly facillitates the elucidation of configuration of C-2 of linear hexitols. By integration of finding of H. O. L. Fischer in the strategy of E. Fischer, a remarkable shortcut to structure elucidation of linear aldohexoses has been obtained [1].

meso-Tartaric acid has benn discovered also by Pasteur (1853) as an optically inactive compound, non-cleavable by chemical, physical or biological methods [24,25]. A series of structural relationsips between carbohydrates *meso* compounds and their C_2 *symm*. isomers are presented (Fig. 1). Concerning *meso* trehalose and ent-trehalose all experimental premises are fulfilled: Unreducing character of trehalose was inferred by Fischer [26] from the fact that this sugar did not react with phenylhydrazin. Trehalose doesn't reduce Fehling solution and its optical rotation is not influenced by time or temperature [27]. The two isomeris of trehalose have been prepared by synthetical methods. Fischer and Delbrück [28] obtained isotrehalose, i. e., the ββ-form, by condensing tetraacetyl glucosyl bromide in the presence of silver carbonate; isotrehalose is also a C_2 *symm*. compound, while the αβ one is *irrechi*. Moreover, since L-glucose was synthesized [29], the preparation of a *meso* isomer based on α-D-glucopyranose and α-L-glucopyranose is within our reach.

2.1. AMINO ACIDS

Linear aminoacids with dimeric structure – cysteine, lanthionine, α,ε-diaminopimelic acid (Figs. 2,3) [30-32], etc., and their higher homologues, present both types of isomers, *meso* and

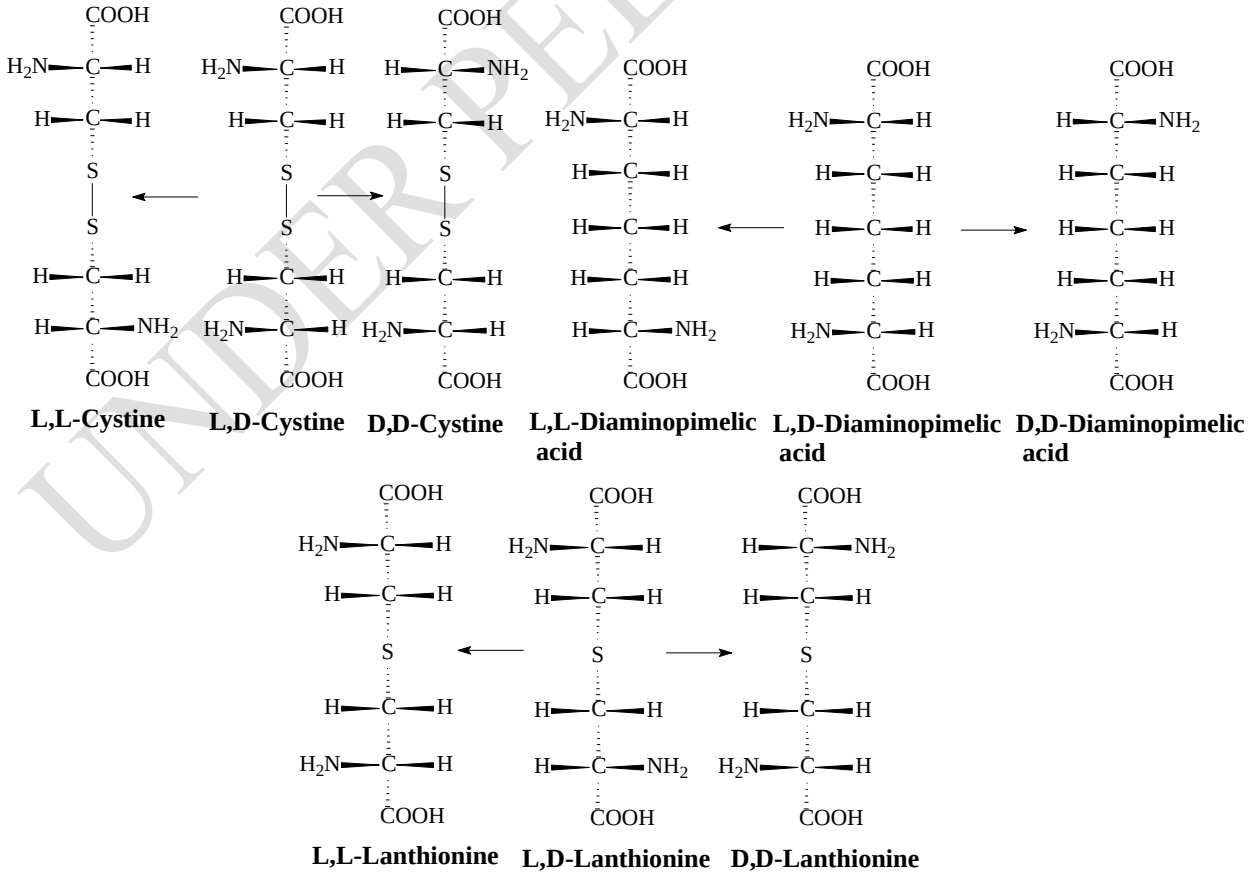


Figure 2. All linear isomers of natural symmetric isomers are known.

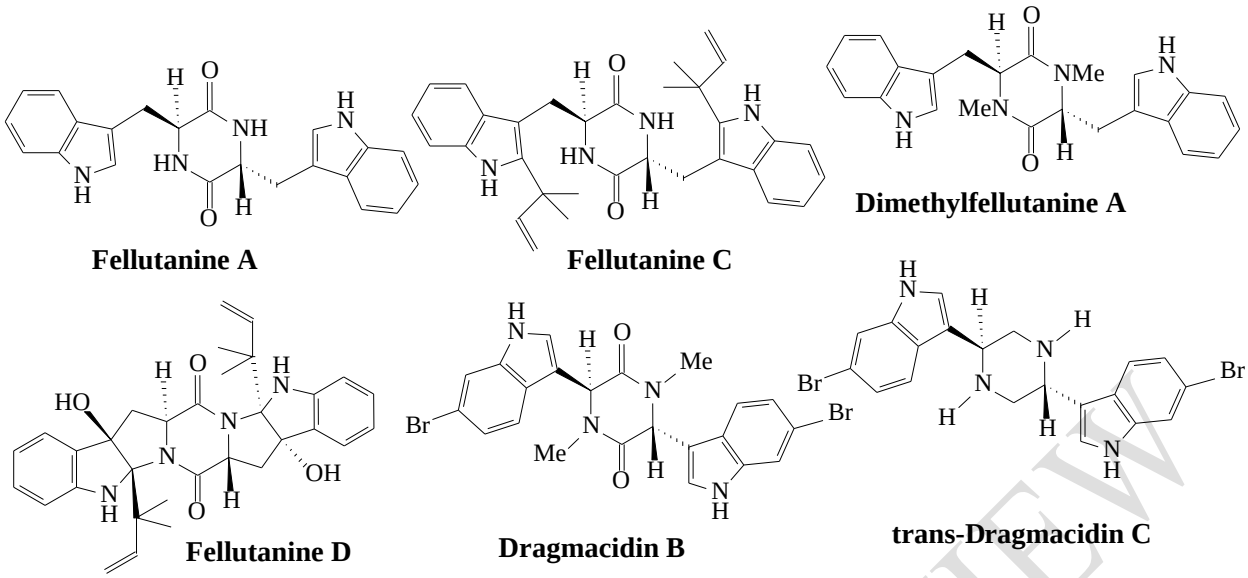


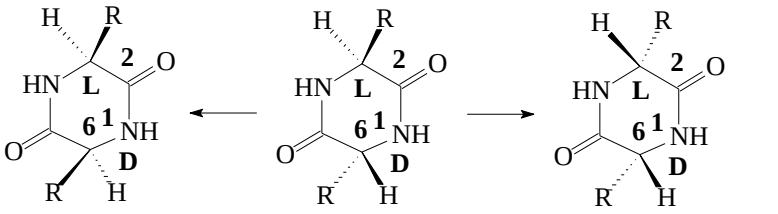
Figure 3. *meso* Derivatives related with *C_2 symm.* compounds.

C_2 symm. Vickery [33] included α,ε-L,L-diamminopimelic acid in the same category with threitol, tartaric acid and cystine. A series of representatives of linear synthetic diamino dicarboxylic acids (L/L or D/D) were synthesized and their biochemical activity investigated [34]. Lanthionine was discovered as a product of action of alkali on wool [35]. Subsequently, this amino acid was discovered in living matter and its isomers synthesized and characterized [31,36]. Lanthionine presents eight β-methyl derivatives, at least one of them found in nature [37], and structural analysis of these isomers showed that every *C_2 symm.* isomer has two β-methyl isomers while *meso* one alone has four. When *meso* isomer is naturally methylated, methyl group is found on D-moiety since this fragment come from L-Thr *via* a didehydro intermediate [38]. As expected, homolanthionine [32] presents also three linear isomers, two *C_2 symm.* and one *meso*. α,ε-Diaminopimelic acid was discovered in bacterial products. Even from its discovery this amino acid was compared with cystine and, as expected, three isomers were identified, two as a pair of externally compensated isomers (L,L- and D,D-) and the other one as a non-resolvable, internally compensated *meso* form (L,D-). To accomplish their separation, a synthetic mixture of the three forms was converted into diamides and treated with a hog kidney amidase-Mn^{2+}. The action of the L-directed enzyme led to the following mixture: the free L,L-diaminopimelic acid, the D,D-diamide and the L-diaminopimelic acid-D-monoamide. This mixture was then separated by ion-exchange chromatography [30]. At least L,L- and *meso* forms are natural compounds [39], and an epimerase converts L,L-diaminopimelic acid to the *meso*-isomer. An interesting biochemical equivalence of lanthionine and diaminopimelic acid has been noticed [40]. According to the same principle, at least three isomers are known for diketopiperazine of Pro: LL, LD, DD [41].

2.2. DIKETOPIPERAZINES AND THEIR DERIVATIVES

Of the 20 common aminoacids, 19 produce *C_2 symm.* diketopiperazines (DKPs) and derivatives (Table 1). 2,5-Diketopiperazines were discovered by E. Fischer [42]. All possible forms of homogenous (LL, DD) and mixed (D and L) as well as of different amino acids, were synthesized and/or discovered in natural materials [43]. Cyclo(L-Val-L-Val) and cyclo(L-Val-D-Val) were synthesized in view of their comparative oxidation with dioxiranes. Cyclodipeptide synthases were discovered as a novel enzyme family that employs aminoacyl-tRNAs as substrates for 2,5-diketopiperazine synthesis. A cyclodipeptide synthase of *Streptomyces noursei* AlbC, uses aminoacyl-tRNAs as substrates to catalyze the formation of cyclo(L-Phe-L-Leu) [44]. A number of 51 cyclodipeptide synthases were analyzed concerning their substrate

Table 1. Chemical modelling of 2,5-diketopiperazines.



2,5-Diketopyperazines of L/L aminoacids | **2,5-Diketopyperazines of L/D aminoacids** | **2,5-Diketopyperazines of D/D aminoacids**

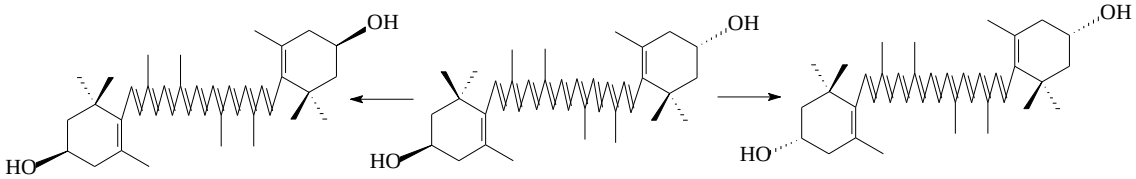
L/L-2,5-Diketopiperazine (*C_2 symm.*)	L/D-2,5-Diketopiperazine (*meso*)	D/D-2,5-Diketopiperazine (*C_2 symm.*)
Cyclo-L-Ala-L-Ala	Cyclo-L-Ala-D-Ala	Cyclo-D-Ala-D-Ala
Cyclo-L-Val-L-Val	Cyclo-L-Val-D-Val	Cyclo-D-Val-D-Val
Cyclo-L-Leu-L-Leu	Cyclo-L-Leu-D-Leu	Cyclo-D-Leu-D-Leu
Cyclo-L-Ile-L-Ile	Cyclo-L-Ile-D-Ile	Cyclo-D-Ile-D-Ile
Cyclo-L-Thr-L-Thr	Cyclo-L-Thr-D-Thr	Cyclo-D-Thr-D-Thr
Cyclo-L-Ser-L-Ser	Cyclo-L-Ser-D-Ser	Cyclo-D-Ser-D-Ser
Cyclo-L-Cys-L-Cys	Cyclo-L-Cys-D-Cys	Cyclo-D-Cys-D-Cys
Cyclo-L-Met-L-Met	Cyclo-L-Met-D-Met	Cyclo-D-Met-D-Met
Cyclo-L-Glu-L-Glu	Cyclo-L-Glu-D-Glu	Cyclo-D-Glu-D-Glu
Cyclo-L-Gln-L-Gln	Cyclo-L-Gln-D-Gln	Cyclo-D-Gln-D-Gln
Cyclo-L-Asp-L-Asp	Cyclo-L-Asp-D-Asp	Cyclo-D-Asp-D-Asp
Cyclo-L-Asn-L-Asn	Cyclo-L-Asn-D-Asn	Cyclo-D-Asn-D-Asn
Cyclo-L-Tyr-L-Tyr	Cyclo-L-Tyr-D-Tyr	Cyclo-D-Tyr-D-Tyr
Cyclo-L-Phe-L-Phe	Cyclo-L-Phe-D-Phe	Cyclo-D-Phe-D-Phe
Cyclo-L-His-L-His	Cyclo-L-His-D-His	Cyclo-D-His-D-His
Cyclo-L-Trp-L-Trp	Cyclo-L-Trp-D-Trp	Cyclo-D-Trp-D-Trp
Cyclo-L-Arg-L-Arg	Cyclo-L-Arg-D-Arg	Cyclo-D-Arg-D-Arg
Cyclo-L-Lys-L-Lys	Cyclo-L-Lys-D-Lys	Cyclo-D-Lys-D-Lys

specificity, and the conclusion was that they use 17 proteinogenic amino acids. Two such enzymes of *Nocardiopsis* sp., NozA and NcdA, catalyze cyclo(L-Trp-L-Trp) biosynthesis from tryptophanyl-tRNA, being outstandingly specific [45]. A few dozens of 2,5-diketopiperazines and their derivatives have been evidenced in marine organisms.

Some diketopiperazines (especially based on L-Phe, L-Tyr and L-DOPA) and their derivatives, have antibiotic activity [43]. Cyclo(L-Phe-L-Phe) was isolated from *P. nigricans* and from a marine mangrove endophytic fungus. Cyclo(L-Tyr-L-Tyr) was isolated from the culture liquid of *Cordyceps sinensis* (Berk.) Sacc. Both these DKPs are *C_2 symm*. molecules. The Tyr DKP is converted into the DOPA analogue, that is also a *C_2 symm*. compound, by PC12 cell lysate, which produces high levels of tyrosine hydroxylase. In fact, both these DKPs are intermediates in the biosynthesis of the anticancer natural products. The dimethylanalogue of cyclo(L-Tyr-L-Tyr) was isolated from *Streptomyces griseus* [43]. Other *meso* derivatives (Fig. 3) can be submitted to the same test for their symmetry quality.

3. CAROTENOIDS

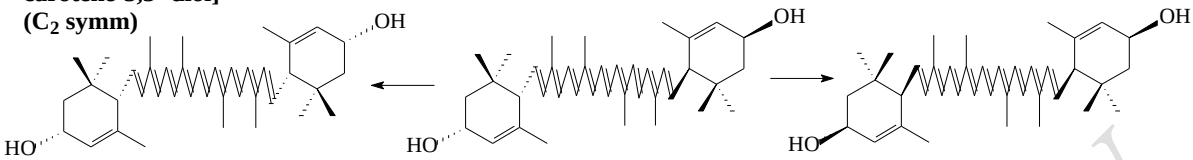
Carotenoid (polyprenyl, isoprenoid) compounds constitute one of the best and the most abundant illustration of *C_2 symm*. phenomenon (Fig. 4). They present a large structural variety and numerous outlines of relationships between *meso*, *C_2 symm*. *irrechi* and *constit*. because all their representatives (about 1000) are possible symmetry generators. Hence no carotene or



Zeaxanthin [(3R,3'R)-β,β-carotene-3,3'-diol] (C_2 symm)

meso-Zeaxanthin [(3R,3'S)-β,β-carotene-3,3'-diol]

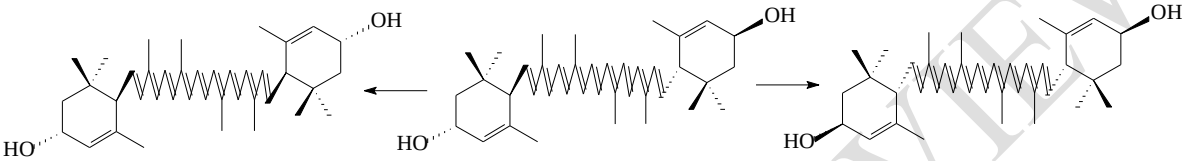
(3S,3'S)-Zeaxanthin [(3S,3'S)-β,β-carotene-3,3'-diol] (C_2 symm)



Tunaxanthin C [(3R,6S,3'R,6'S)-ε,ε-carotene-3,3'-diol] (C_2 symm)

Tunaxanthin D [(3R,6S,3'S,6'R)-ε,ε-carotene-3,3'-diol] (meso)

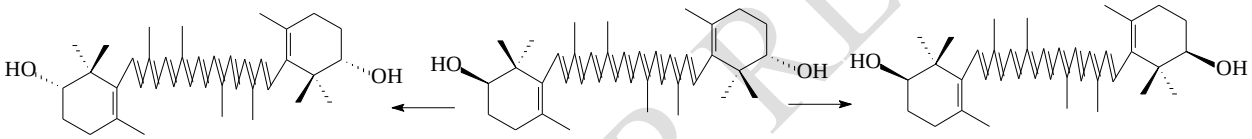
Tunaxanthin J [(3S,6R,3'S,6'R)-ε,ε-carotene-3,3'-diol] (C_2 symm)



Lactucaxanthin [(3R,6R,3'R,6'R)-ε,ε-carotene-3,3'-diol] (C_2 symm)

Tunaxanthin E [(3R,6R,3'S,6'S)-ε,ε-carotene-3,3'-diol] (meso)

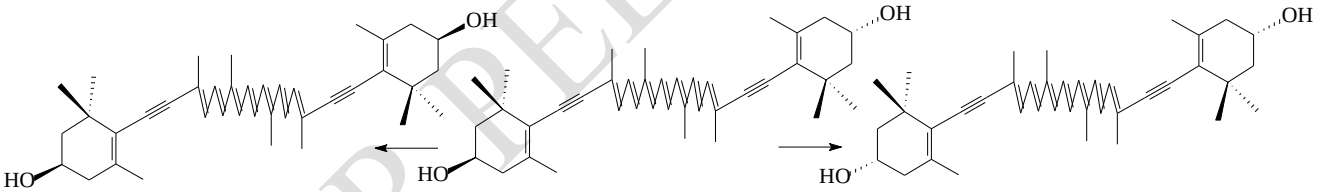
Tunaxanthin A [(3S,6S,3'S,6'S)-ε,ε-carotene-3,3'-diol] (C_2 symm)



(2S,2'S)-2,2'-Dihydroxy-β,β-carotene [(2S,2'S)-β,β-carotene-2,2'-diol] (C_2 symm)

(2R,2'S)-2,2'-Dihydroxy-β,β-carotene [(2R,2'S)-β,β-carotene-2,2'-diol] (meso)

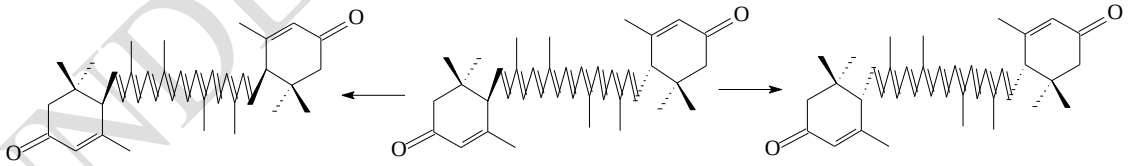
2,2'-Dihydroxy-β,β-Carotene [(2R,2'R)-β,β-carotene-2,2'-diol] (C_2 symm)



Alloxanthin [(3R,3'R)-7,8,7',8'-tetradehydro-β,β-carotene-3,3'-diol] (C_2 symm.)

(3R,3'S)-Alloxanthin [(3R,3'S)-7,8,7',8'-tetradehydro-β,β-carotene-3,3'-diol] (meso)

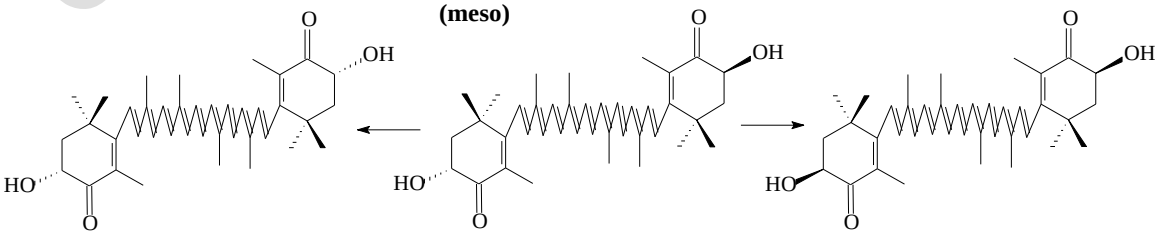
Alloxanthin [(3S,3'S)-7,8,7',8'-tetradehydro-β,β-carotene-3,3'-diol] (C_2 symm.)



3,3'-Diketo-ε-carotene [(6R, 6'R)-ε,ε-Carotene-3,3'-dione)] (C_2 symm.)

(6R,6'S)-3,3'-Diketo-ε-carotene [(6R,6'S)-ε,ε-Carotene -3,3'-dione)] (meso)

3,3'-Diketo-ε-carotene [(6S, 6'S)-ε,ε-Carotene-3,3'-dione)] (C_2 symm.)



(3R,3'R)-Astaxanthin [(3R,3'R)-3,3'-dihydroxy-β,β-carotene-4,4'-dione] (C_2 symm.)

(3R,3'S)-Astaxanthin [(3R,3'S)-3,3'-dihydroxy-β,β-carotene-4,4'-dione] (meso)

(3S,3'S)-Astaxanthin [(3S,3'S)-3,3'-dihydroxy-β,β-carotene-4,4'-dione] (C_2 symm.)

Figure 4. Chemical modelling of *meso* carotenoids.
carotenoid is archaic [46].

Chemical representations of perhydro polyprenyl compounds – squalane, lycopane, carotane, isorenieratane, renierapurpurane, 1,10-bis(2',2',6'-trimethylcyclohexyl)-3,8-dimethyldodecane – are presented in an equivocal way concerning their chirality [47,48], and this allow us to hypothesize that the isomers of these compounds can belong to the three types: *meso*, C_2 *symm*. and *constit*.

As expected, carotenoids possessing two asymmetric carbons present only two types of optical isomers, *meso* and C_2 *symm*. C_{40} carotenoids with two chiral centers are represented by β-carotene-2,2'-diol [49], β-carotene-3,3'-diol (zeaxanthin), β-carotene-4,4'-diol (isozeaxanthin), astaxanthin [50], alloxanthin, tetrahydrozeaxanthin dione, tetradehydroastaxanthin [51]. At least in case of zeaxanthin, β-carotene-2,2'-diol, alloxanthin [52], (6,6'S)-ε,ε-Carotene-3,3'-dione [53,54] and astaxanthin, all three isomers – two enantiomeric C_2 *symm*. and one *meso*, are known [51]. *meso*-Zeaxanthin [(3R,3'S)-β,β-carotene-3,3'-diol] (Fig. 4) is largely distributed in nature, usually mixed with other isomers, especially (3R,3'R)- and (3S,3'S)-. Separation was made chromatographically, e.g. via the dicarbamates of (S)-(+)-α-(1-naphthyl) ethyl isocyanate. After the first isolation of *meso*-zeaxanthin in nature [55], it was found in shellfishes, human retina (as a major carotenoid), shrimp, fish and turtle [55]. *Meso*-zeaxanthin was synthesized by asymmetric hydroboration. *Meso*-dihydroxy-β-carotene [(2R,2'S)-β,β-carotene-2,2'-diol] has been isolated from the stick insect *Ectatosoma tiaratum* as a mixture with the other two isomers [56].Tunaxanthin D [(3R,6S,3'S,6'R)-ε,ε-carotene-3,3'-diol] was isolated as a major carotenoid from the yellow-tail rockfish *Sebastes flavidus* [57] and the fresh-water fish *Siniperca scherzeri* [58]. A HPLC chiral colum was used for its purification.Tunaxanthin E [(3R,6R,3'S,6'S)-ε,ε-carotene-3,3'-diol] was isolated as a minor carotenoid from the fishes *Chaenogobius isaza* and *Siniperca scherzeri* [58]. Five *meso* compounds – (3R,3'S)-astaxanthin, (3R,3'S)-zeaxanthin, (6R,6'S)-3,3'-diketo-ε-carotene, tunaxanthin D, tunaxanthin E – are linked in *Siniperca scherzeri* by a reductive metabolic pathway from astaxanthins to tunaxanthins (Fig. 4). *Meso*-astaxanthin is distributed in natural materials in the crab *Paralithodes brevipes*, shellfishes [59], northern circumpolar shrimp *Pandalus borealis* (Crustaceae Malacostraca, order Decapoda), as well as in other aquatic animals [58]. *Meso*-3,3'-diketo-ε-carotene [(6R,6'S)-ε,ε-carotene-3,3'-dione] has been isolated from the yellow-tail rockfish *Sebastes flavidus* [57] in a mixture with its optical isomers, (6R,6'R) and (6S,6'S). They were separated by HPLC on a chiral column. Some aquatic organisms contain abundantly alloxanthin, all three isomers. The structure of *meso*-alloxanthin was checked also by chemical synthesis [60]. C_{40} carotenoids with four or more chiral centers present the four types of isomers, C_2 *symm*., *meso*, *irrechi*, *constit*. e. g., capsorubin [(3S,5R,3'S,5'R)-3,3'-dihydroxy-κ,κ-carotene-6,6'-dione] [61], auroxanthin-(3S,5R,8R,3'S,5'R,8'R), auroxanthin-(3S,5R,8S,3'S,5'R,8'S), [62]. Of C_{50} carotenoids, sarcinene, decaprenoxanthin, okadaxanthin and sarcinaxanthin possess four chiral carbon while flavuxanthin, C. p. 450, bacterioruberin, bisanhydrobacterioruberin, tetrahydro bisanhydrobacterioruberin has two.

4. LIGNANS

Discovery of phenylpropanoids, lignans (Fig. 5) and neolignans, is due to three criteria: (i) the need to increase the therapeutic efficiency of plants, used as remedies for millennia, determined the knowledge of their chemical composition, and sometimes even the recognition of chemicals as the active biological components; (ii) the elaboration and practice of biological or biochemical tests, the so called bioasays i. e., the quality of some compounds to regulate biochemical or biological parameters: the activity of enzymes, the level of hormones, the life of culture cells, etc.; (iii) systematic chemical inquiry of biological material, its relative abundance of some principles being important.

The word lignan was coined by Haworth [63] as an unequivocal term concerning the vegetable origin of these compounds. Lignans and neolignans have a wide distribution in plants

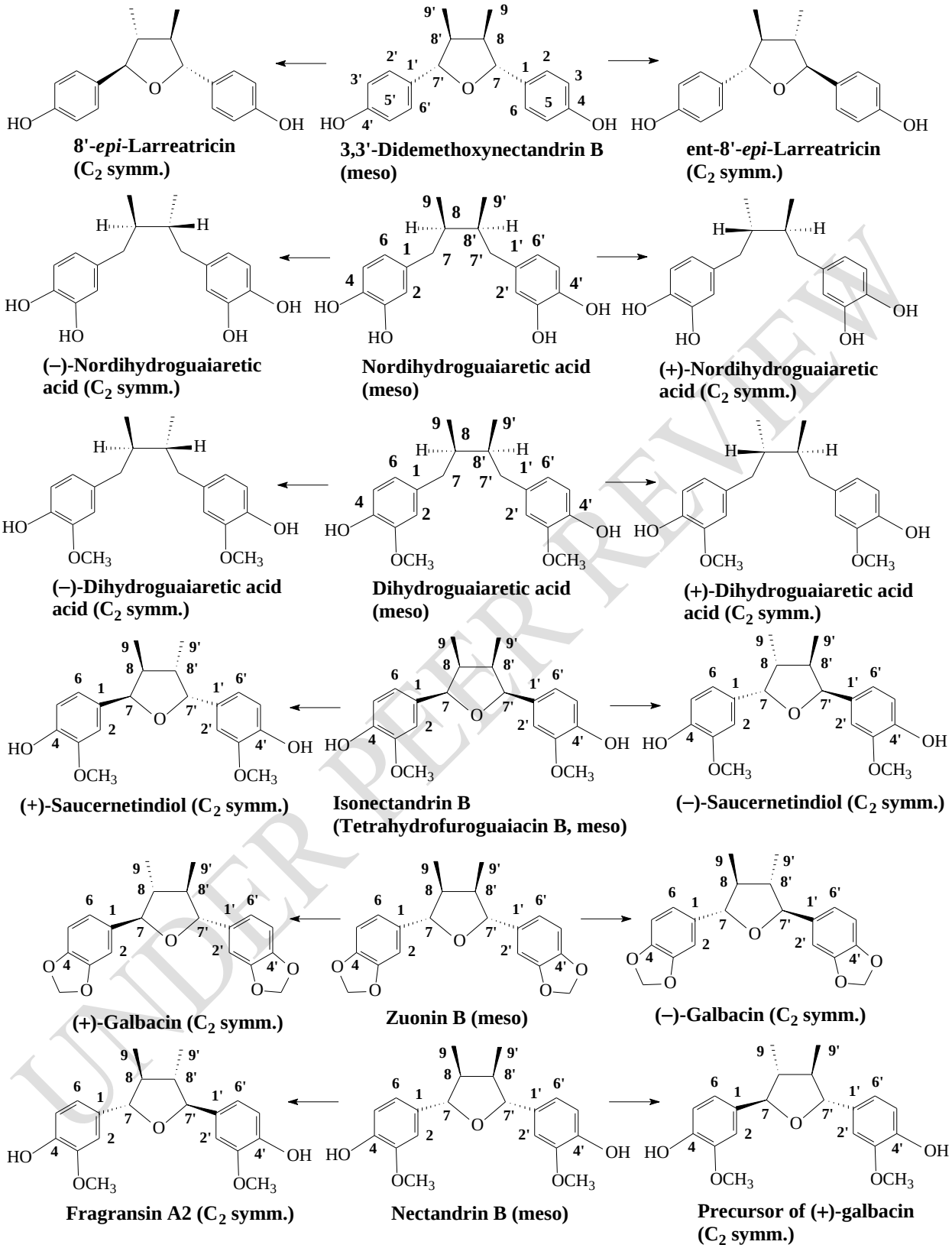


Figure 5. Relationship between *meso* lignans and their *C₂ symm*. isomers.

kingdom, and in the same plant they are usually found in all its organs. Lignans are typically dimerization products of phenylpropanoids, which are called monolignols in this instance.

Dimerization reaction is accomplished in such a manner to block it at this stage, completely different from lignin biosynthesis. Lignans are optically active. Lignans are formed by the fusion of two phenylpropane units through the center carbon atoms (C-8/C-8′) of their sidechains. Systematization of lignans used in this paper is based on Lignan Nomenclature [64], the work of Hearon and MacGregor [65] and Tepono et al., [66].

8'-epi-Larreatricin and its isomer 3,3'-didemethoxynectandrin B have been found as products of biosynthesis from anol [67]. ent-8'-epi-Larreatricin can be found in a series of natural compounds: fragransins (A2, B2, C2), (–)-talaumidin, (–)-galbelgin, (–)-galbacin, etc., [68]. Nordihydroguaiaretic and dihydroguaiaretic acid are also biosynthesized from anol via larreatricin and 3,3'-dihydroxylarreatricin in creosote bush [67]. C_2 *symm*. isomers of nordihydroguaiaretic [69] and dihydroguaiaretic acid [70] are also known.

Under the title 1,4-diaryl-2,3-dimethylbutane (2,3-dibenzylbutane) derivatives have been included guaiaretic acid, dihydroguaiaretic acids, nordihydroguaiaretic acids and their derivatives. This type of lignans contains usually two chiral centers, hence they present only two types of isomers, C_2 *symm*. and *meso*. Guaiaretic acid was isolated from the resin of *Guaiacum officinale* L. or *G. sanctum* L. as insoluble potassium salt in alcoholic solution [65]. Its structure was elucidated by Schroeter et al [71] and confirmed by Haworth et al [72]. Guaiaretic acid has been a key compound in the elucidation of the absolute configuration of lignans. As expected, its hydrogenation leads to two isomers, *meso*-dihydroguaiaretic acid and (–)-dihydroguaiaretic acid. Rao and Chattopadhyay [73] discovered (–)-dihydroguaiaretic acid in the plant *Saururus cernuus*, and in order to prove its structure they synthesized (–)-dihydroguaiaretic acid from (–)-austrobailignan-5. The other isomers are also known: (+)-dihydroguaiaretic acid (C_2 *symm*.), *meso*-dihydroguaiaretic, (+)-and (–)-nordihydroguaiaretic (both C_2 *symm*.) [69] and *meso*-nordihydroguaiaretic acid.

Tetrahydrofuroguaiacin B (isonectandrin B) has been isolated from *Myristica fragrans* (nutmeg); its structure was elucidated by chemical and spectroscopical methods (^{1}H and ^{13}C NMR spectra) [74]. (+)-Saucernetindiol has been isolated and characterized of the same material [75], while (–)-saucernetindiol has been found in *Hippophae rhamnoides* fruits [76]. Zuonin B, has been separated from the stem bark of *Machilus thunbergii* [77]. (+)-Galbacin is of the same group with 8-*epi*-larreatricin. (+)-Galbacin was isolated from the bark of *Machilus thunbergii* [78], was found in *Aristolochia triangularis* Chamisso [79], in *Virola surinamensis* (accompanied by (+)-galbelgin, 5-methoxygalbelgin and grandisin) [80], in *Machilus japonica* Zieb. et Zucc., (accompanied by (+)-galbelgin) [81]. For structure elucidation, the latter authors combined chemical methods (permanganate oxidation) with physical ones (NMR and MS). The main and significant products of potassium permanganate oxidation were veratric acid (3,4-dimethoxybenzoic) and piperonylic acid (3,4-methylenedioxybenzoic acid). Both (+)-galbacin and (+)-galbelgin have been prepared by chemical synthesis [82]. (–)-Galbacin was isolated from *Myristica fragrans* (nutmeg). Nectandrin B was also found in *Myristica fragrans* and fragransin A2 in the seeds of Vietnamese nutmeg *Myristica fragrans* [83].

5. PHENOLS

meso Phenols are also represented among natural compounds (Fig. 6). Hybocarpone [6,6'-bis(3-ethyl-2,7-dihydroxynaphthazarin)] (C_2 *symm*.) was isolated from the cultured mycobiont of *Lecanora hybocarpa* (Tuck.) Brodo [84]. Natural hybocarpone and some of its isomers have been synthesized, by an oxidative dimerization of hydroxynaphthoquinone by a technique of single electron transfer, and studied by Nicolaou and Gray [85]. Some isomers were compared about their relative thermodynamic stability: (2S,3S,4S,5S) (natural compound; C_2 *symm*.), (2S,3R,4S,5S) (*irrechi*), (2S,3S,4S,5R) (*irrechi*), (2S,3R,4S,5R) (*meso*), (2R,3S,4S,5R) (C_2 *symm*.), (2R,3R,4S,5S) (*meso*) [85]. The following conclusions could be drawn: the most stable isomer proved to be the natural one, followed by a *meso* isomer, and the least stable was a *meso* isomer, i. e., the all-cis one. These results are in agreement with a study about lignans: grandisin,

a *C₂ symm.* compound, proved to be more stable by 6.5 kcal·mol^{-1} than its all-cis isomer (*meso*), [rel-(7R,8S,7'S,8'R)-3,4,5,3',4',5'-hexamethoxy-7,7'-epoxylignan], due to the hydrogen bonds

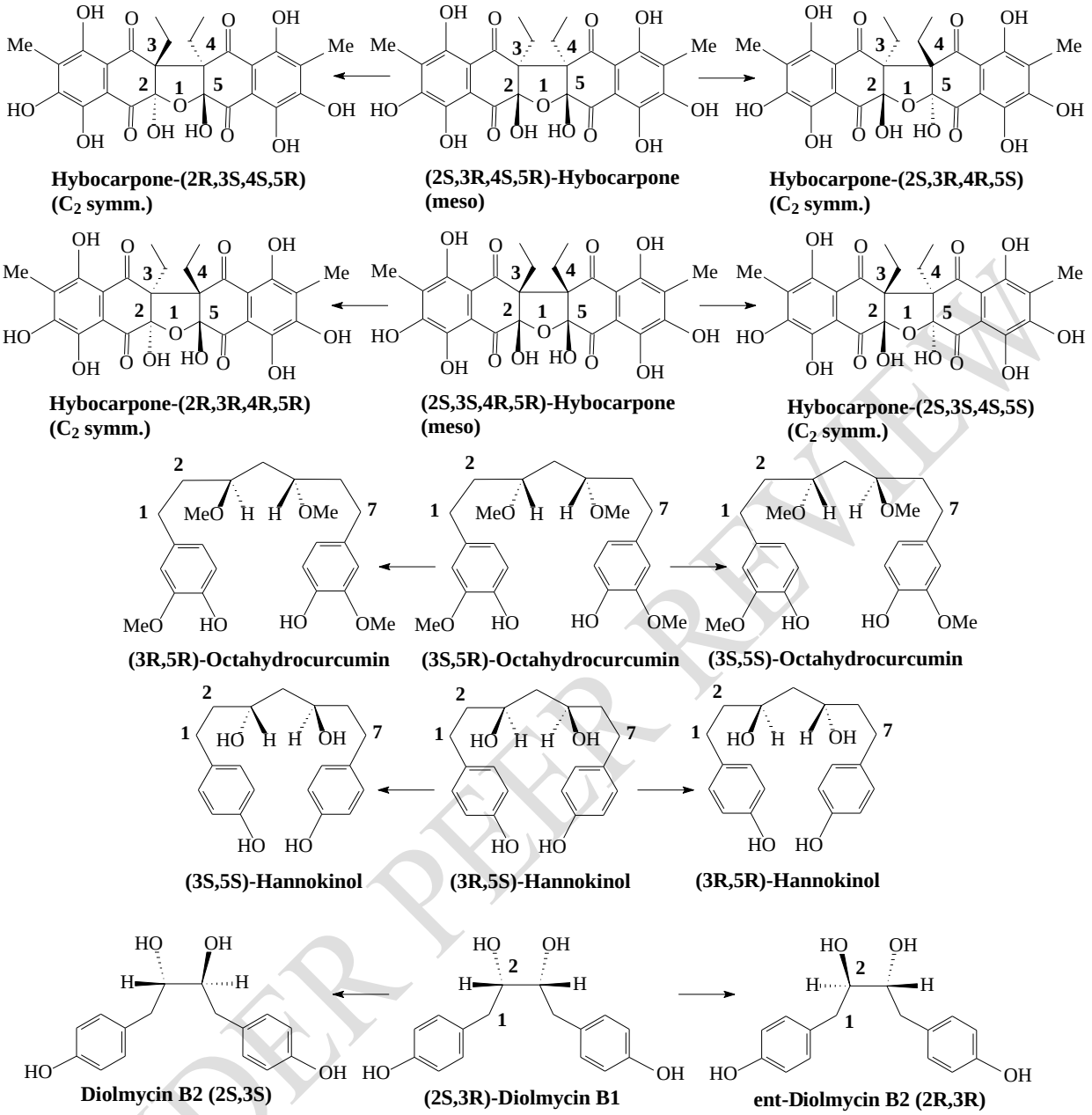


Figure 6. Isomerism of natural phenols.

between methoxy groups in trimethoxyphenyl rings [86].

Five diarylheptanoids including a *C₂ symm.* compound have been isolated from the rhizomes of *Curcuma xanthorrhiza* (Zingiberaceae) [87]. Its structure was determined to be octahydrocurcumin [(3S,5S)-1,7-bis(4-hydroxy-3-methoxyphenyl)-heptane-3,5-diol], while the structure of a similar chiral compound (a biosynthesis precursor, probably) was concluded as (3R,5R)-l-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol. Catalytic hydrogenation of curcumin led to three isomers, two *C₂ symm.* and one *meso*: (3S,5S)-, (3R,5R)- and (3R,5S)-octahydrocurcumin [87]].

A diol, hannokinol [3,5-dihydroxy-1,7-di-(p-hydroxyphenyl)-heptane], has been isolated from vegetable tissue in all three forms: *meso*, (+), (–) [88]. Its enantiomers are (3S,5S)-hannokinol and (3R,5R)-hannokinol, both *C₂ symm.*

Gordonia sp. 647W.R.1a.05, a bacterium isolated from the venom duct of the cone snail, *Conus circumcises,* produces two *C₂ symm.* molecules with the same configuration of their chiral

centers, (2S,3S)-1,4-diphenyl-(+)-2,3-butanediol and diolmycin B2 [(2S,3S)-1,4-di-(p-hydroxyphenyl)-(+)-2,3-butanediol] [89]. Four other compounds, circumcins A-C and kurasoin, found in the same material, suggest a strong metabolic relationship between these compounds. Intermediates of benzoin type (circumcins B and C, kurasoin) show that their biosynthesis is similar to 2,3-butanediols. A *meso* isomer, diolmycin B1, was isolated from the fermentation broth of *Streptomyces* sp. WK-2955 [90].

6. ALKALOIDS

meso Isomers of the spectacular group of alkaloids are not abundantly represented (Fig. 7). Monomeric unit of pyrrolidinoindoline alkaloids is hexahydropyrrolo[2,3,-b]indole (HPI) ring [91]. Its dimerization, preceded by partial and specific N-methylation, produces dimeric isomers (Fig. 7). Oxidative dimerization of a natural product (dipterin; N-methyltryptamine)

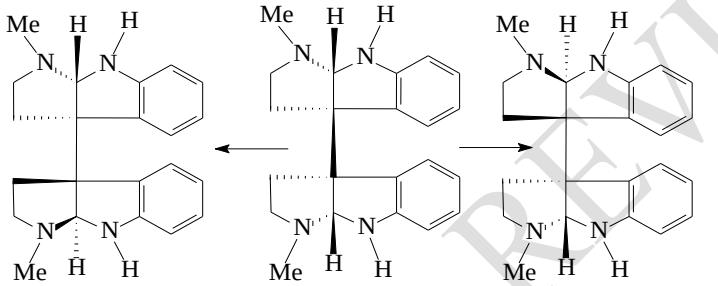


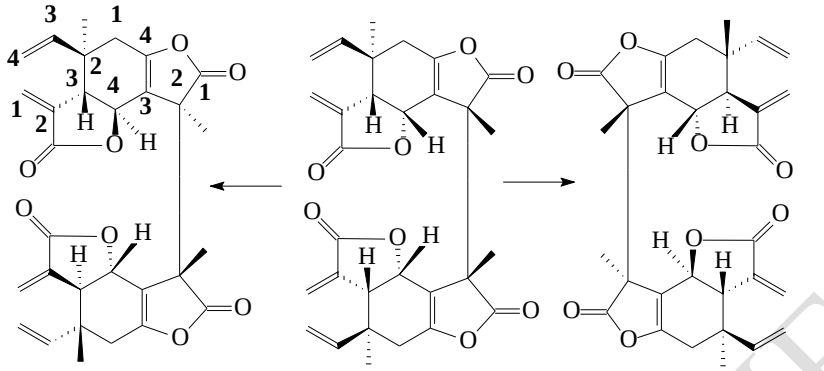
Figure 7. Three isomeric chimonanthines: one *meso* and two C_2 *symm*.

suggested a biochemical pathway to chimonanthine [92]. The indole alkaloid family of chimonanthines includes all three possible isomers – *meso*, levo, dextro, (the latter two, C_2 *symm*.) and all three have been found in nature: *meso*- and (–)-chimonanthine in plants as *Psychotria colorata* flowers, [93,94], (+)-chimonanthine in a dendrobatid frog and in plants [95]. *Psychotria colorata* (Willd., ex R & S.) Muell. Arg. is a medicinal plant used by some Amazon tribes in the treatment of earache (flowers) and to alleviate abdominal pain (roots and fruits). Chemical analysis indicated that these vegetable materials contained alkaloids and its fractionation, monitored by bioassay, led to an alkaloid with molecular formula $C_{22}H_{22}N_4$. ^1H and ^{13}C NMR spectra disclosed a C_2 *symm*. compound, chimonanthine. Polarimetry indicated a levorotary combination [93]; *meso* chimonanthine was found in the same source [94]. The chimonanthine isomers are both C_2 *symm*., a result provided by ^{13}C NMR analysis [96]. Absolute configuration of chimonanthine C_2 *symm*. enantiomers has been elucidated by circular dichroism comparison with their isomer, (+)-calycanthine. In acidic conditions, the latter is in equilibrium with (–)-chimonanthine. It was easy to conclude that the frog alkaloid was very similar to the alkaloid from plants; however the optical rotation of the first was levorotary, while the second was dextrorotary.

7. SESQUITERPENOIDS

Meso terpenoides are less numerous than other isomers of this group. Well known and characterized are daibudilactone C (*meso*) and daibudilactone D (C_2 *symm*.) (Fig. 8). Daibudilactones B and C have been isolated from the stem of *Neolitsea daibuensis* Kamikoti by bioassay-guided fractionation. Their structures were elucidated by spectral analysis and single-

crystal X-ray diffraction. Both daibudilactones presented potent anti-inflammatory activity using an inducible enitric oxide synthase (iNOS) assay [97,98]. ent-Daibudilactone B is a hypothetical compound for the time being.



Daibudilactone B **Daibudilactone C** **ent-Daibudilactone B**

Figure 8. Three isomeric sesquiterpenoides: *meso* (daibudilactone C) and C_2 *symm*. (daibudilactone B and ent-daibudilactone B).

8. ARCHAIC (PRIMITIVE) COMBINATIONS AND GEOMETRICAL SYMMETRY

Archaic (primitive) combinations have been defined as a distinct group devoid of chemical symmetry and of an imaginary partner possessing chemical symmetry. Many of them are in an advanced degree of oxidation [9]. However, they are characterized by a geometrical symmetry (Fig. 9). Benzene has six planes of symmetry, and toluene one. The symmetry parts of

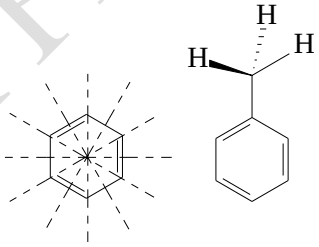


Figure 9. Symmetry planes of benzene and toluene.

benzene depend of the plane of symmetry, whether it cuts two =CH- or two bonds. Symmetry plane of toluene cuts a C, a CH (of methyl groups) and an =CH- (C-4 of benzene ring). Important combinations belong to archaic group: alkanes (C_1-C_7. C_7 is the first alkane presenting optically active isomers), alkenes (C_2-C_4), alkynes (alkadienes) (C_2-C_6), arenes (benzene, toluene, naphthalene, anthracene, phenanthrene, diphenyl, etc.), alcohols (C_1-C_8), aldehydes (ketones) (C_1-C_4), saturated organic acids (C_1-C_2). Other combinations also belong to archaic group: fumaric/maleic acids, benzoic acid, phthalic acid, nucleic bases, sepiapterine, niacin (nicotinic acid, nicotinamide), xanthopterin, leucopterin, pyrrole, imidazole, choline, indole, glycerol, salicylic acid, etc.

9. IS THERE ANY INOSITOL A MESO DERIVATIVE?

When the same reasoning is applied to inositols, the following results are obtained. cis-Inositol, a compound formed of six equivalent carbons and characterized by six geometrical planes of symmetry, and epi-inositol give neo-Inositol (Fig. 9a and b). myo-Inositol gives muco-inositol and the latter gives scyllo-inositol, a centrosymmetric molecule with three geometrical

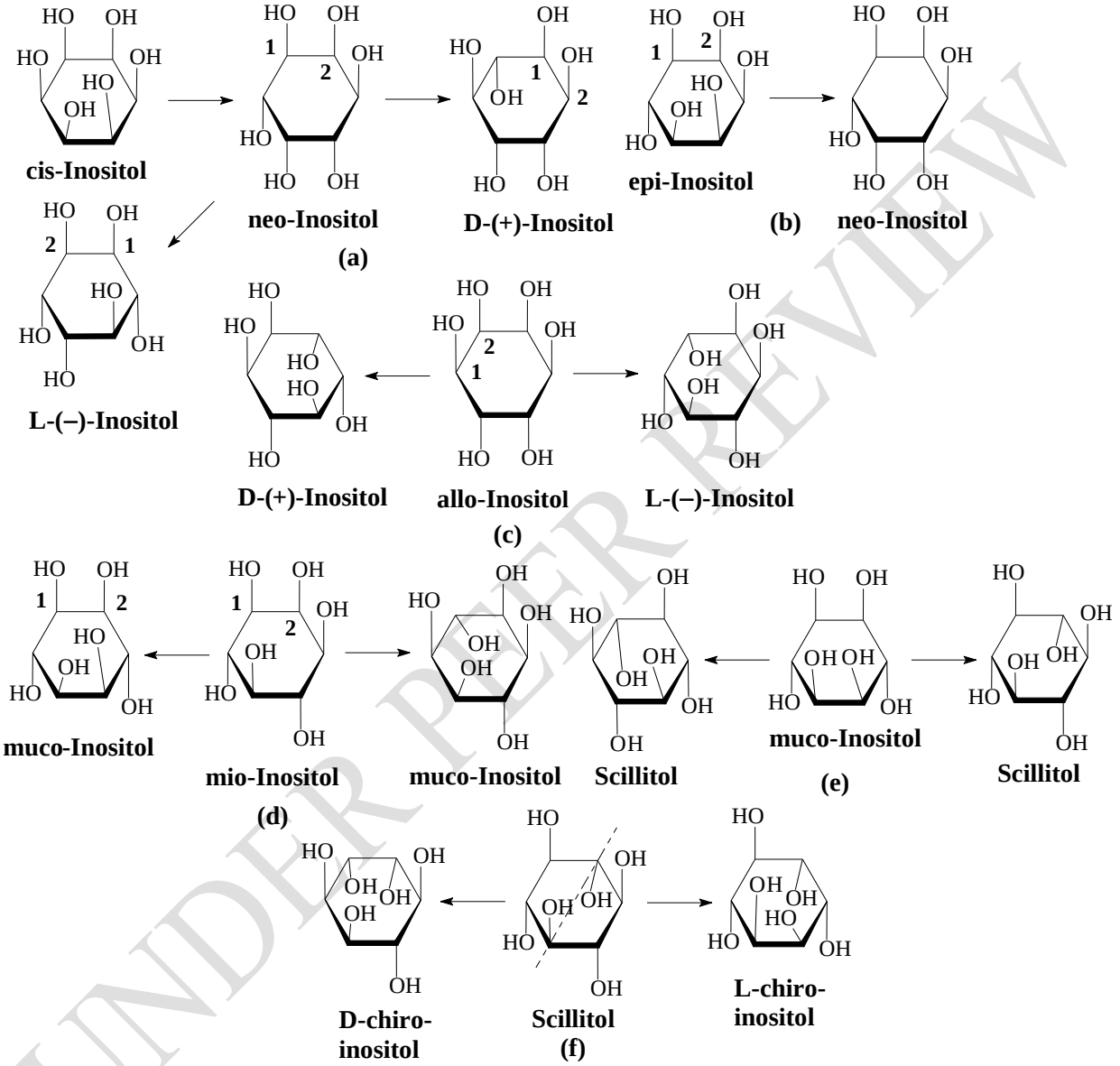


Figure 10. Symmetry properties of inositols.

planes of symmetry. Geometrical symmetry is clearly broken in case of neo- allo- and scyllo-inositol: all three compounds produce (+)- and (–)-inositol (Fig. 9). Hence inositols behave completely different of typical *meso* compounds in the sense that dimerization of their halves fails to produce C_2 *symm*. derivatives, and from this behaviour we have concluded that they are not *meso*.

Disubstituted derivatives instead (usually phosphorylated or methylated) are clearly *meso* (Fig. 10). An interesting behaviour has 1,3-dideoxy-1,3-diguanidyl-scyllo-inositol, a constituent of streptomycin (Fig. 11). It is neither *meso* nor C_2 *symm*. However, 1,3-dideoxy-1,3-diguanidyl-2,5-diketo-scyllo-inositol is clearly *meso* (Fig. 11).

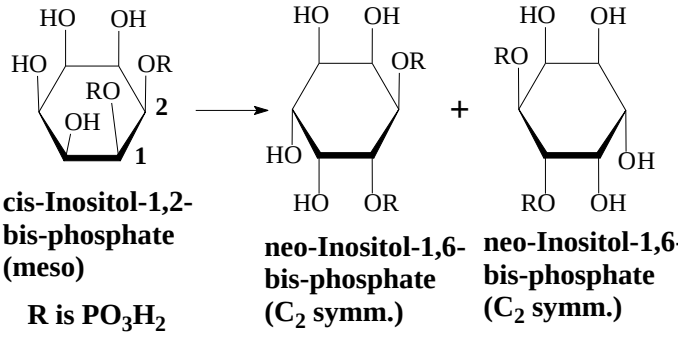


Figure 11. cis-Inositol-1,2-bis-phosphate is a *meso* compound.

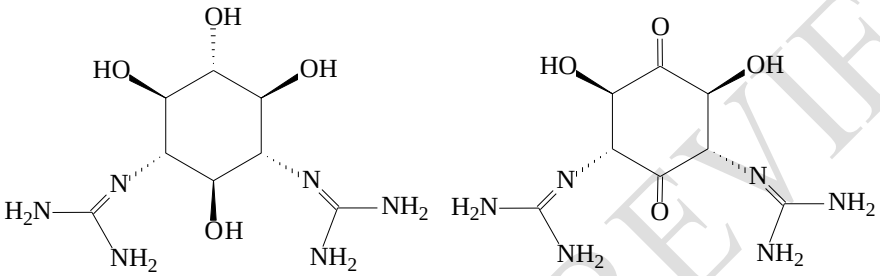


Figure 12. Symmetry comparison of two disubstituted derivatives of scyllo-inositol.

10. CONCLUSIONS

1. *meso* Isomers are exemplified in seven classes of natural compounds: carbohydrates, amino acids, carotenoids, lignans, phenols, alkaloids, terpenoids.
2. Two types of symmetries can be distinguished to chemical combinations: geometrical and chemical (the latter characterized by the mirror plane of symmetry).
3. Alternative dimerization of the two halves of a *meso* combination produced two enantiomerical *C_2 symm.* compounds.
4. All the achiral inositols behaved in a different manner at this modelling. It has has been concluded that no inositol *per se* is a *meso* compound; they present a geometrical symmetry instead.

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