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Biochemical Symmetrization/ Desymmetrization of Organic Compounds: Dendrimeric Relationship with Molecular Formulas

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

A criterion for systematization of organic compounds is described. Organic compounds (estimated to 16-20 millions) are of three types: (A) symmetric (especially *meso* and *C2 symmetric*), (B) possible symmetry generators, i.e. compounds possessing a real or imaginary, but plausible, symmetric correspondent: *irrechi* (from irregular distribution of chiral carbons) and *constitutional*), and (C) *archaic* (or *primitive*) that are neither symmetric nor possible symmetry generators. 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

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combinations are either symmetric or possible symmetry generators; *archaic* (*primitive*) type is also represented in natural chemistry. On the other hand, it should be stressed that symmetric compounds, both *meso* and *C2 symmetrical* (*C2 symm.*) have been found almost exclusively in plants and microorganisms, and they are usually produced from *constitutional* (*constit*.) precursors. A series of symmetrization/desymmetrization reactions are presented, and the proof is evidenced that they can establish a new and coherent concept in biochemistry and organic chemistry. Symmetrization reactions can be followed according to chemical type involved: oxidation, cyclization, esterification, glycosylation, methylation, etc. This approach is valid to all major classes of compounds. A dendrimeric relationship is presented within molecular formulae.

Keywords: Isomers; meso; C2 symmetrical (C2 symm.); irrechi; constitutional; archaic; symmetrization; desymmetrization; dendrimeric relationship.

1. INTRODUCTION

The systematization of organic compounds (evaluated to 16-20 million at present time) is a difficult task, and this task belongs nonetheless to chemistry. The act is quite familiar in other sciences – mathematics [1], physics [2], biology (Linnaeus, 1753, 1758, cited by [3]). 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 [4-11].

Organic compounds can be classified as follows: (A) Symmetric (symmetry in chemistry includes chirality [12-16]). Symmetric compounds constitute a minority in organic chemistry. The most studied symmetric compounds are in two groups: (A1) *meso* and (A2) *C2 symmetrical* (*C2 symm*.).

(B) Potential symmetry generators; in other words, the investigated combination possesses a correspondent symmetric isomer, real or imaginary, but plausible. Potential symmetry generators are of two types: (B1) *irrechi* (from irregular distribution of chiral carbons); they have an identical skeleton with the *C2 symm*., and *meso* but they differ only by configuration of component chiral carbons. The phenomenon can be named isoskeletomeric relationship [16]. (B2) The forth type of isomers possibly possessing a different skeleton from the aforementioned three have been defined as constitutional (*constit*.) and they are either chiral or achiral [14-16].

(C) Archaic (or primitive) are combinations that are neither symmetric nor potential symmetry generators.

The demanded conditions for every type have been described in previous papers [5,6,17,18].

2. BIOCHEMICAL SYMMETRIZATION / DESYMME-TRIZATION OF ORGANIC COMPOUNDS

Transformation of a *constit*., compound in either *meso* or *C2 symm*., means symmetrization; the reverse is desymmetrization. The two transformations are exemplified to different classes of compounds.

2.1 Mono- and Disaccharides

Plants, especially higher plants, produce all three stereoisomeric forms of tartaric acid [19] (Fig. 1.a). It should be noticed that dimerization of the lower part of *meso*-tartaric acid leads to (2S,3S)-(–)-tartaric acid, while the upper part gives (2R,3R)-(+)-tartaric acid. Numerous other similar examples can be presented, and their significance is that *C2 symm*. compounds (homodimers) are, in theoretical terms, derivatives of *meso* ones [20].

The direct precursor of tartaric acid is L-ascorbic acid [21] (Fig. 1.b), and ascorbic acid is produced from D-glucose. The latter is transformed to D-Man 1-P, via D-Glc 1-P and D-Fru 6-P. Ascorbate is biosynthesized from D-Man 1-P (Fig. 1.c).

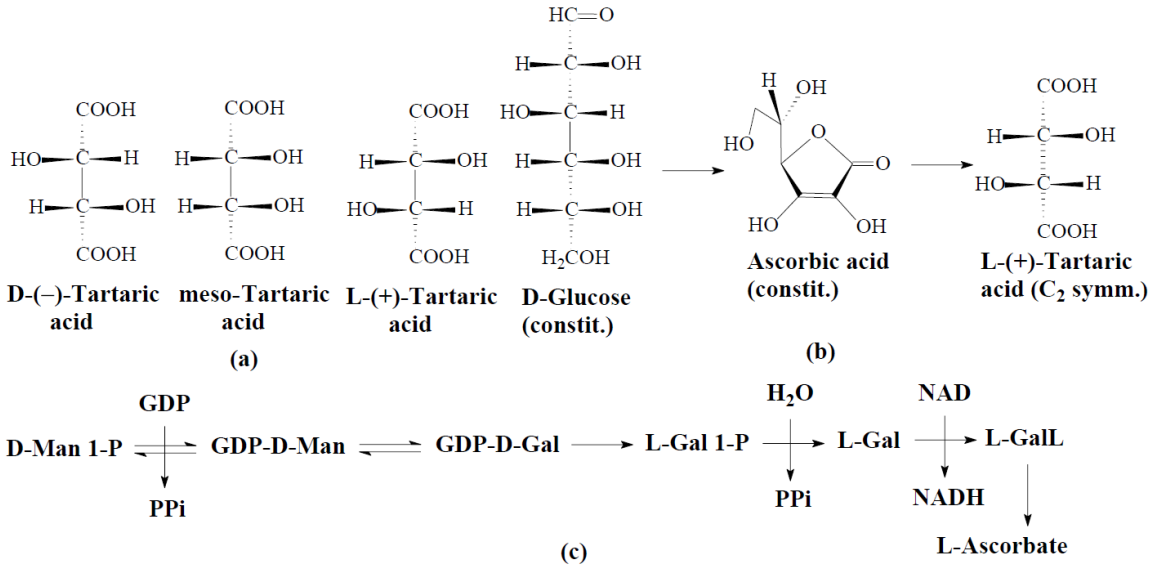


Fig. 1. Isomers of tartaric acid (a), biosynthesis of (R,R)-(+)-tartaric acid (L-tartaric) from D-Glc (b), biosynthesis of L-ascorbate from D-Man 1-P (c)

Vitaceae and Geraniaceae give (+)-tartaric acid, and *Bauhinia reticulata* (–)-tartaric acid. An ester of the latter with caffeic acid was found in Rebula white grape [22], *Cichorium intybus* L., *C. endivia* L. and *Lactuca sativa* L (Fig. 2). Spinach leaves biosynthesizes meso-tartaric acid as an ester of p-coumaric acid. *Pelargonium zonale* L. produced all three isomers from glycolate-1- ^{14}C [19].

An isolation procedure has been invented for the separation of the cinnamate derivatives from Müller-Thurgau white wine. The products, isolated in crystalline state, were *cis*- and *trans-p*-coumaroyl-(+)-tartaric (coutaric) acid and *trans*-caffeoyl-(+)-tartaric (caftaric) acid, as demonstrated by spectral data, hydrolysis, chromatography, etc. Surprisingly, neither ferulic acid derivatives nor the free cinnamic acids were detected in this white wine. These compounds could constitute a biochemical pattern for this food product [23].

In phytoplasma susceptible grapevine variety 'Chardonnay' (*Vitis vinifera* L.), concentration of coutaric and caftaric acid changed as a function of the stage of infection [24]. Chardonnay grape pomace contained a diversity of esterified and glycosylated polyphenols which included trans-caftaric acid and cis- and trans-coutaric acids, that were characterized by ^{1}H and ^{13}C NMR spectra [25]. In case of caftaric acid (the ester of tartaric acid with caffeic acid) desymmetrization is increased by S-glutathionylation [23]. The attachment of cinnamate derivatives to tartaric acids may occur by transacylation from acyl-CoA activated forms [26].

Of the three possible isomers of 1,4-diphenyl-2,3-butanediol, a *C2 symm*. isomer (dextrorotatory) has been isolated from bull testis [27-29]. The absolute configuration of this compound has been determined to be (2S,3S), by synthesis of the natural diol from L-(+)-tartaric acid [30] (Fig. 3). Erythritol was among the first poyols discovered, before the elucidation of monosaccharides structure by E. Fischer. Erythritol was found in plants in free state or as an ester with orsellic acid. Some species of microorganisms of the genus *Bacterium* oxidize polyol to a 2-keto derivative, i. e., erythritol to erythrulose. The latter, when reduced, led to D-threitol (Fig. 4).

Alternatively, the enantiomeric threitols were prepared by D- and L-threose reduction, the latter being prepared by chain shortening from suitable pentoses [31].

D-Mannitol (Fig. 5), on which *C2 symm.* phenomenon was evidenced for the first time, was found in plants. Relatively recent results have indicated that more than 100 species of vascular plants contain mannitol, where it is responsible for different biochemical functions: a major carbon source, osmoprotectant, etc., [32]. Two mannitol biosynthetic pathways are known, one linear [32] and one cyclic [33]. The linear

mannitol biosynthetic pathway takes place in higher plants and starts with the isomerization of fructose-6-phosphate to mannose-6-phosphate, by mannose-6-phosphate isomerase (M6PI, EC 5.3.1.8), which is then converted to mannitol-1-phosphate by mannose-6-phosphate reductase (M6PR, EC 1.1.1.224). In the final step, mannitol-1-phosphate is cleaved by mannose-1-phosphate phosphatase (M1PP, EC 3.1.3.22) to mannitol and inorganic phosphate (Fig. 6). In the cyclic biosynthesis of mannitol, biochemical transformations are the same, only mannitol is oxidized to fructose, and the latter phosphorylated, and thus the metabolic loop is resumed.

The isomers of mannitol, iditol, mannaric and idaric acids were prepared by Fischer et al., [34-37]. Of the two enantiomers of iditol, L-iditol (Fig. 7) was found in natural materials, in the fruits of *Sorbus aucuparia* [38]. Both isomers are prepared especially by chemical synthesis [39,40]. Dimerization of one of the two enantiomeric halves of galactitol gives D-iditol, while the other half gives L-iditol. The same reasoning applied to allitol leads to D- and L-mannitol. Galactaric acid was obtained by oxidation of lactose with nitric acid. Then the following sequence was accomplished by Fischer: galactaric acid (meso) → (±)-galacturonic acid (constit.) → (±)-galactonic acid (constit.) → (+)-galactonic acid (constit.) + (–)-galactonic acid (constit.). Every separated galactonic acid was reduced to galactose (*constit*.) and then to galactitol (*meso*) [41]. Ribitol has been found in nature at least in two plants, *Adonis vernalis* and *Bupleurum falcatum* root (the Chinese drug, Chei-Hou). In a combined form it is a constituent of riboflavin (vitamin B2).

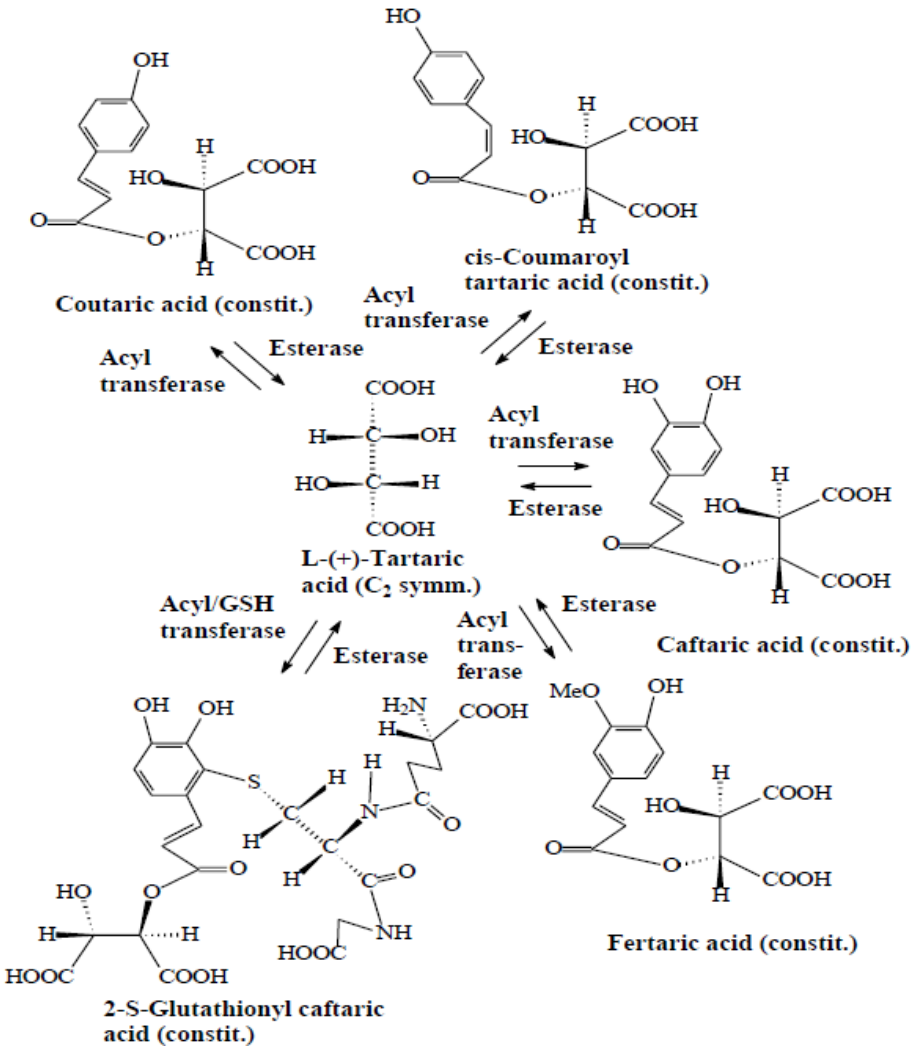


Fig. 2. Acylation and glutathionylation of L-(+)-tartaric acid

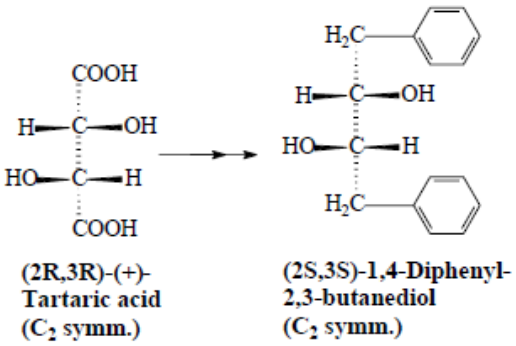


Fig. 3. Configuration of a natural compound,1,4-diphenyl-2,3-butanediol, has been proved by its synthesis from (+)-tartaric acid

Since ribitol is a *meso* combination, the two ends are not equivalent. An answer should be given: ribitol is linked at heterocycle with its former aldehyde group in D-ribose. The enzyme D-xylulose reductase (xylitol:NAD^+ oxidoreducstase, EC 1.1.1.9) catalyses the oxidation of xylitol and 3-deoxyxylitol. The substrate specificity of L-iditol dehydrogenase (L-iditol:NAD^+ oxidoreducstase, EC 1.1.1.14) (Fig. 7) is nearly to that of D-xylulose reductase, the first was used for oxidation of xylitol, ribitol and 3-deoxyxylitol [42]. By reduction of L-(+)-tartaric acid only one isomer, D-malic, was obtained [43]. It's a unique trait of *C2 symm*. compounds.

A variety of biochemical functions are played by inositol and its derivatives (Figs. 8 and 9). A group of phosphatides contain inositol. Phosphatidylinositol, as well as smaller amounts of phosphatides containing phosphate esters of inositol are present in membranes of all eukaryotes and have a specific role in regulating responses of cells to hormones and other external agents. One action of PAF on platelets is to induce a rapid cleavage of phosphatidylinositol 4,5-bisphosphate by phospholipase C to give diacylglycerol and inositol 1,4,5-trisphosphate. Phosphatidylinositol forms part of "anchors" used to hold certain proteins onto membrane surfaces. In birds and turtles erythrocytes, an important constituent is inositol pentaphosphate.

Methylation of myo-inositol produces bornesitol (1-O-methyl myo-inositol) or ononitol (4-O-methyl myo-inositol). [However, sequoyitol (5-O-methyl myo-inositol is *meso*). In anchor molecule, myo-inositol is phosphorylated on C-1 and/or glycosylated on C-6.

Linkage of two D-Glc (*constit*.) molecules gives trehalose (Glcpα1-1αGlcp, unreducing, *C2 symm*.) (Fig. 10), and phosphorylation produces trehalose-6-phosphate. Trehalose is also found as 6,6'-dimycolate (*C2 symm*.) [44-46] (Fig. 11). Hydrolysis of trehalose by trehalase destroys the symmetric system. There are only three abundant naturally occurring disaccharides important to the metabolism of plants and animals: lactose (*constit*.), sucrose (*constit*.), and trehalose (*C2 symm*.) [47].

Trehalose, or "mushroom sugar," is found not only in fungi but also in many other organisms, especially insects. It serves as the primary transport sugar in the hemolymph of insects and also acts as an "antifreeze" in many species. It forms up to 20% of the dry weight of anhydrobiotic organisms, which can survive complete dehydration. These include spores of some fungi, yeast cells, macrocysts of *Dictyostelium*, brine shrimp cysts (dried gastrulas of *Artemia salina*), some nematodes, and the resurrection plant. These organisms can survive for years in a dehydrated state. Hydrogen bonding between the trehalose and phosphatidylcholine may stabilize the dry cell membranes. One of the first detectable changes when the spores germinate is a rapid increase in the activity of the enzyme trehalase which hydrolyzes trehalose to glucose. Yeast cells guard against too intense glycolysis by synthesizing trehalose 6-phosphate, which acts as a feedback inhibitor of hexokinase.

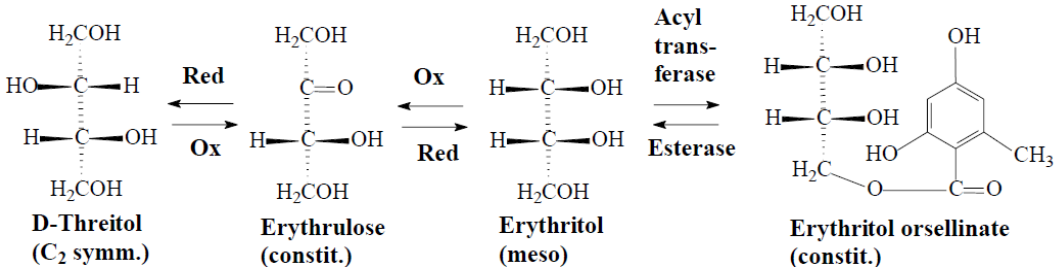


Fig. 4. Production of natural and artificial derivatives of erythritol

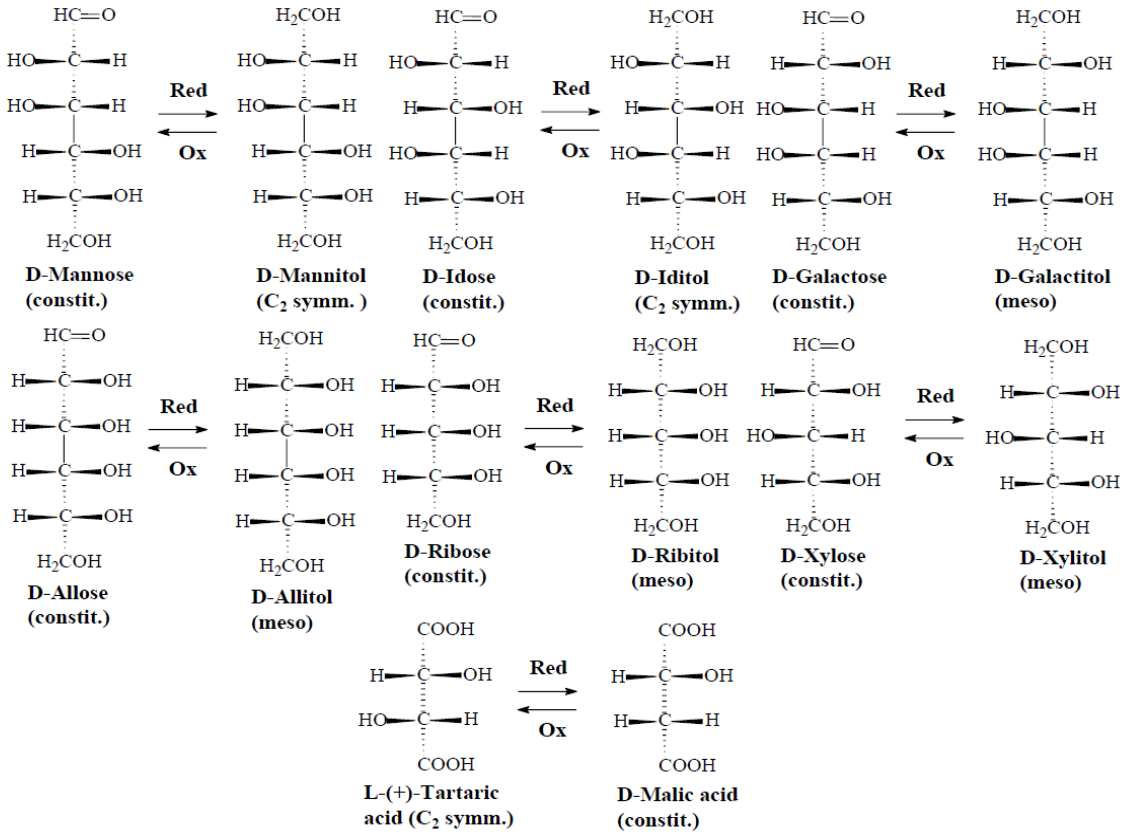


Fig. 5. Natural and artificial redox reaction of some monosaccharides

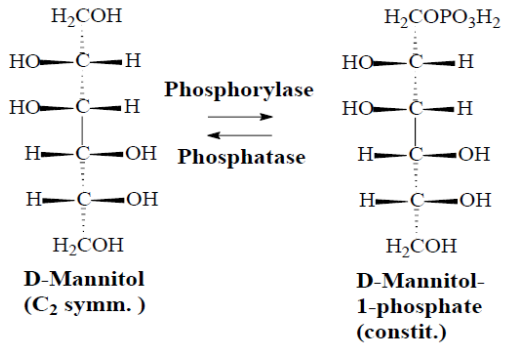


Fig. 6. Phosphorylation-dephosphorylation of D-mannitol

3. DIMERIC DIESTERS

A distinct subgroup of dimeric diesters is formed of chiral hydroxyl acids with relatively high molecular weight. Swinholides A and misakinolide A (bistheonellide A) (Fig. 12. and Table 1) are similar compounds [48-50]. Swinholide A was isolated from the sponge *Theonella swinhoei* [48,51]. Swinholide A and misakinolide A are *C2 symm*. However, isoswinholide A is *irrechi* (ester bond on C-21 is alpha, while on C-21' is beta). Other dimeric diesters are formed of similar chiral hydroxy acids (Fig. 13).

The macrolide marinomycin A has been found in the actinomycete *Marinispora* [52,53]. A new metamorphosis-enhancing macrodiolide, luminaolide, was isolated from the crustose coralline algae *Hydrolithon reinboldii*. Its structure was elucidated by spectroscopic analysis [54,55]. SCH 351448 is an activator of low-density lipoprotein receptor promoter, which was discovered from the organic extract of the fermentation broth of a *Micromonospora* microorganism. It was also prepared by chemical synthesis [49]. Verbalactone, vermiculin, malyngolide dimer and tanikolide dimer are *C2 symm*. macrocyclic dimer lactones isolated from the roots of *Verbascum undulatum* Lam. a biennial plant of the genus *Verbascum* that belongs to the family Scrophulariaceae. These compounds were also prepared by chemical synthesis [56-58].

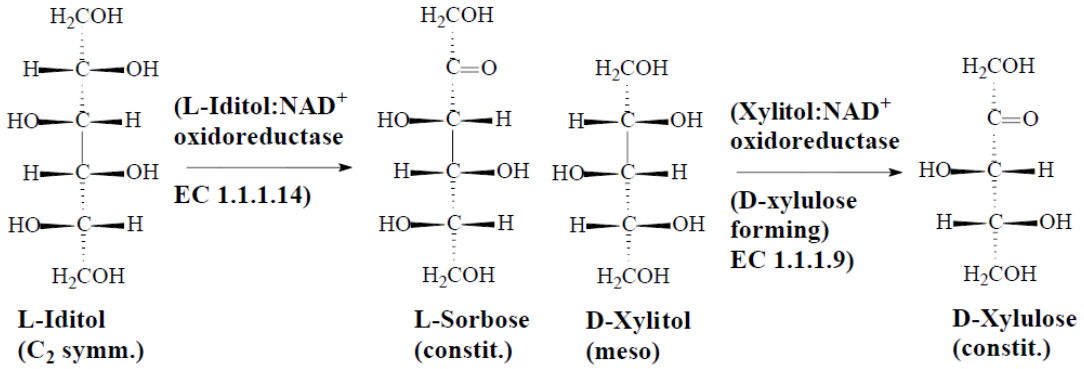


Fig. 7. Enzymatic oxidation of L-iditol and D-xylitol

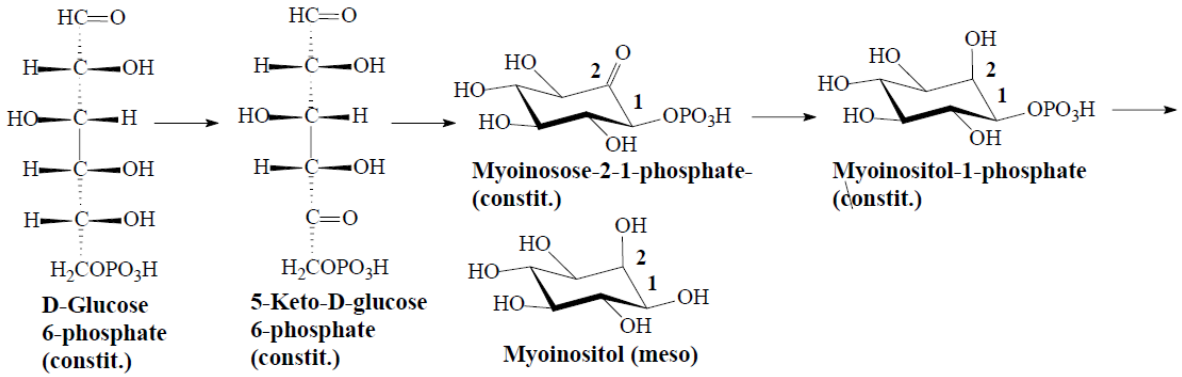


Fig. 8. Biosynthesis of myoinositol

4. GLYCOLIPIDS

C2 symm. complex glycolipids are constructed by the same principle as dimeric diesters (Fig. 14). Cycloviracin B1 is produced by the actinomycete strain *Kibdelosporangium albatum* so. nov. (R761-7). The compound was also prepared by chemical synthesis [49]. In fact, cycloviracin B1 is simply chiral. However, its biochemical precursor, before the linkage of terminal glucosyl residue, is *C2 symm*. Glucolipsin A was found in *Streptomyces purpurogeniscleroticus* and *Nocardia vaccinii* strains. Spectroscopic investigations disclosed the symmetric structure of glucolipsin A and showed the presence of two β-glucose entities within its macrocyclic core. However, the absolute stereochemistry of the four chiral centers at the periphery remained elusive. The compound was also prepared by chemical synthesis [49]. Cyanolide A is characterized by its content of permethylated monosaccharides [57,59].

5. AMINO ACIDS AND THEIR DERIVATIVES

The major part of amino acids are *constit*. However, all of them, including the 20 fundamental ones, possess a symmetric correspondent [7,11].

5.1 Meso and C2 Symmetric Amino Acids

Meso term for amino acids and their derivatives has been attributed by a visual mirror plane of symmetry (Fig. 15.a). *meso*-Cystine [60,61], *meso*-diaminopimelic acid [47,62-64] and *meso*-lanthionine [64-66] were studied within metabolism of amino acids as well as in investigations concerning resolution power of separation methods of these important compounds. Linear synthetic dicarboxylic acids present also *meso* isomers (L/D). Only amino acids with an even number of atoms in their skeleton (L,D-cystine) or an odd number (L,D-diaminopimelic acid, L,D-lanthionine, L,D-homolanthionine) [61,65,67,68] diamino have a mirror plane of symmetry.

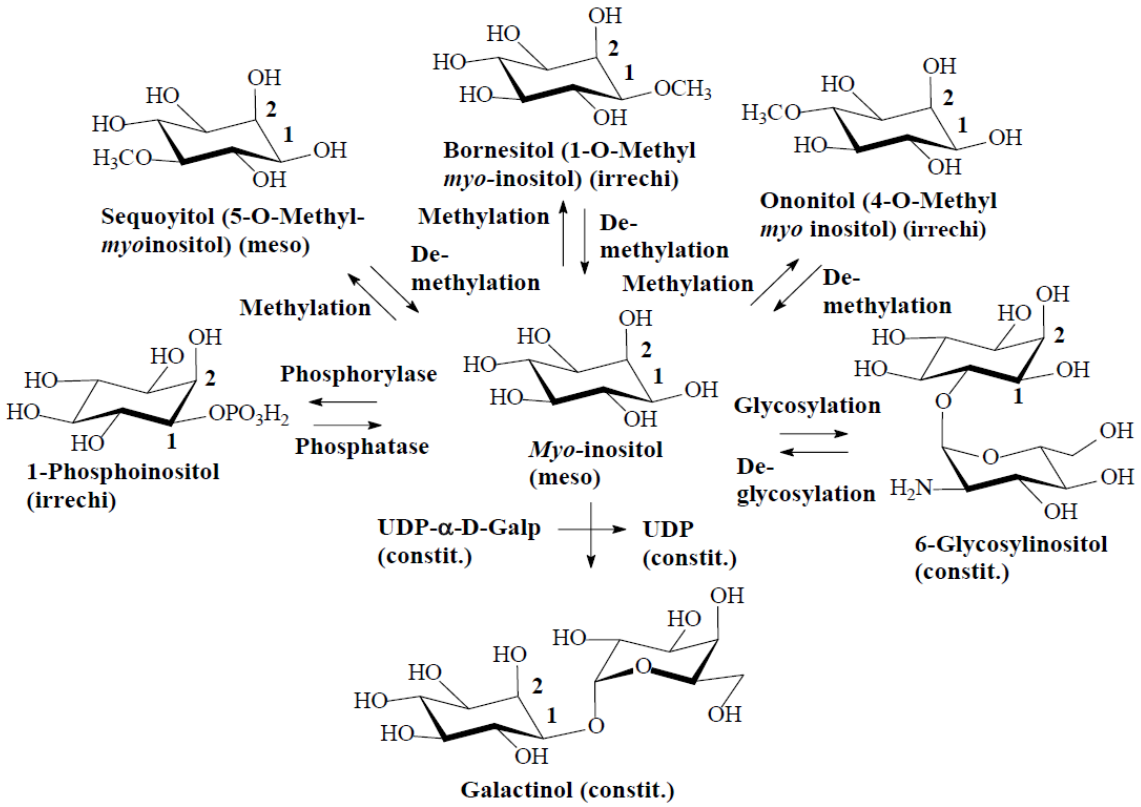


Fig. 9. Alternative phosphorylation, glycosylation, methylation, of myoinositol

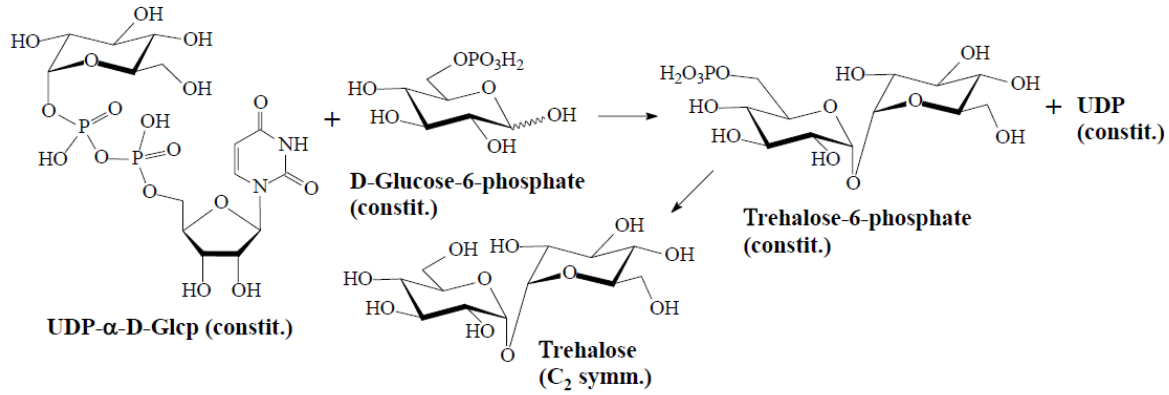


Fig. 10. Biosynthesis of trehalose

C2 Symmetric Amino Acids. *C2 symm.* forms of amino acids and their derivatives are much more numerous and of a higher structural variety than their *meso* isomers e.g. diamino-dicarboxylic acids (Fig. 15.b, etc.). Natural cystine (L,L-cystine; Cys-Cys) is a veritable *C2 symm.* representative; both *C2 symm.* isomers of this amino acid are known: (L,L)-cystine and (D,D)-cystine [61]. Both of them may suffer a reducing reaction, the reduced form being D- and L -cysteine (Cys) (*constit*.). Cys is relatively widespread in proteins' constitution and this redox equilibrium reaction is characteristic to all oligo- and polypeptides containing Cys. It has been hypothesized that a cystine residue could bind two chains of cell wall polysaccharides [69,70]. When the two polysaccharide chains are identical, *C2 symm.* dimers are produced. Lanthionine presents a similar isomerism: (L,L)- and (D,D)-lanthionine are both *C2 symm.*. α,ε- Diaminopimelic acid presents also two *C2 symm.* isomers: (L,L)- and

(D,D)-diaminopimelic acid (Fig. 15.b). Linear synthetic diamino dicarboxylic acids (L/L or D/D) are *C2 symm.* molecules. A series of representatives of these compounds were synthesized and their biochemical activity investigated [71,72]: α,α'-diaminoglutaric, α,α'-diaminoadipic, α,α'-diaminosuberic, α,α'-diaminoazelaic, α,α'-diaminosebacic, α,α'-bis(dimethylamino)sebacic, 1,10-diaminodecane-1,10-dicarboxylic.

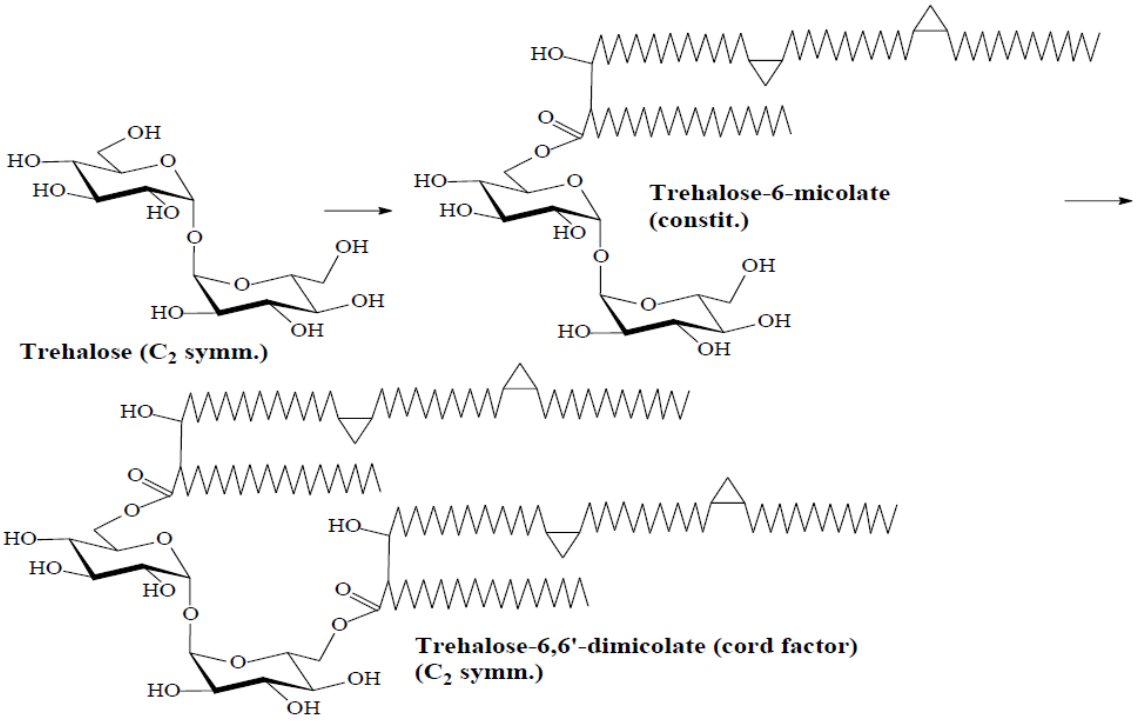


Fig. 11. Biosynthesis of trehalose-6,6'-dimicolate (cord factor)

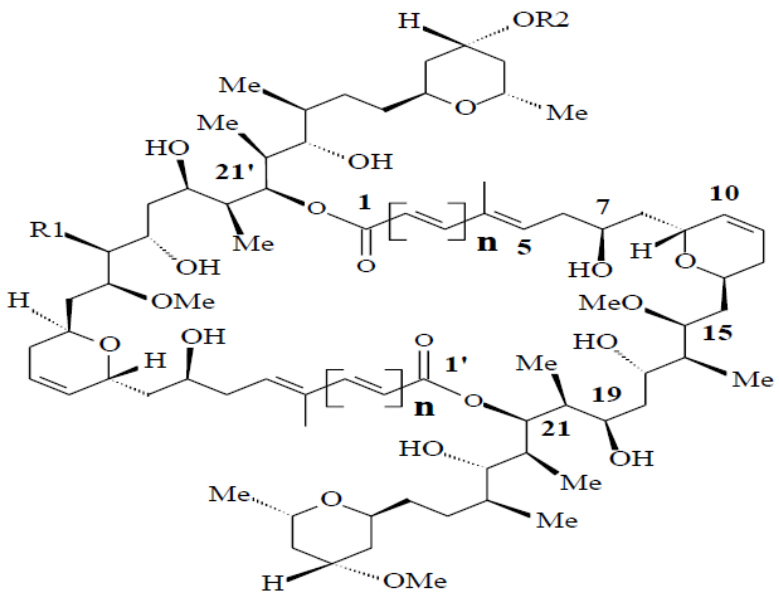


Fig. 12. Natural *C2 symm*. and *irrechi* polyketides

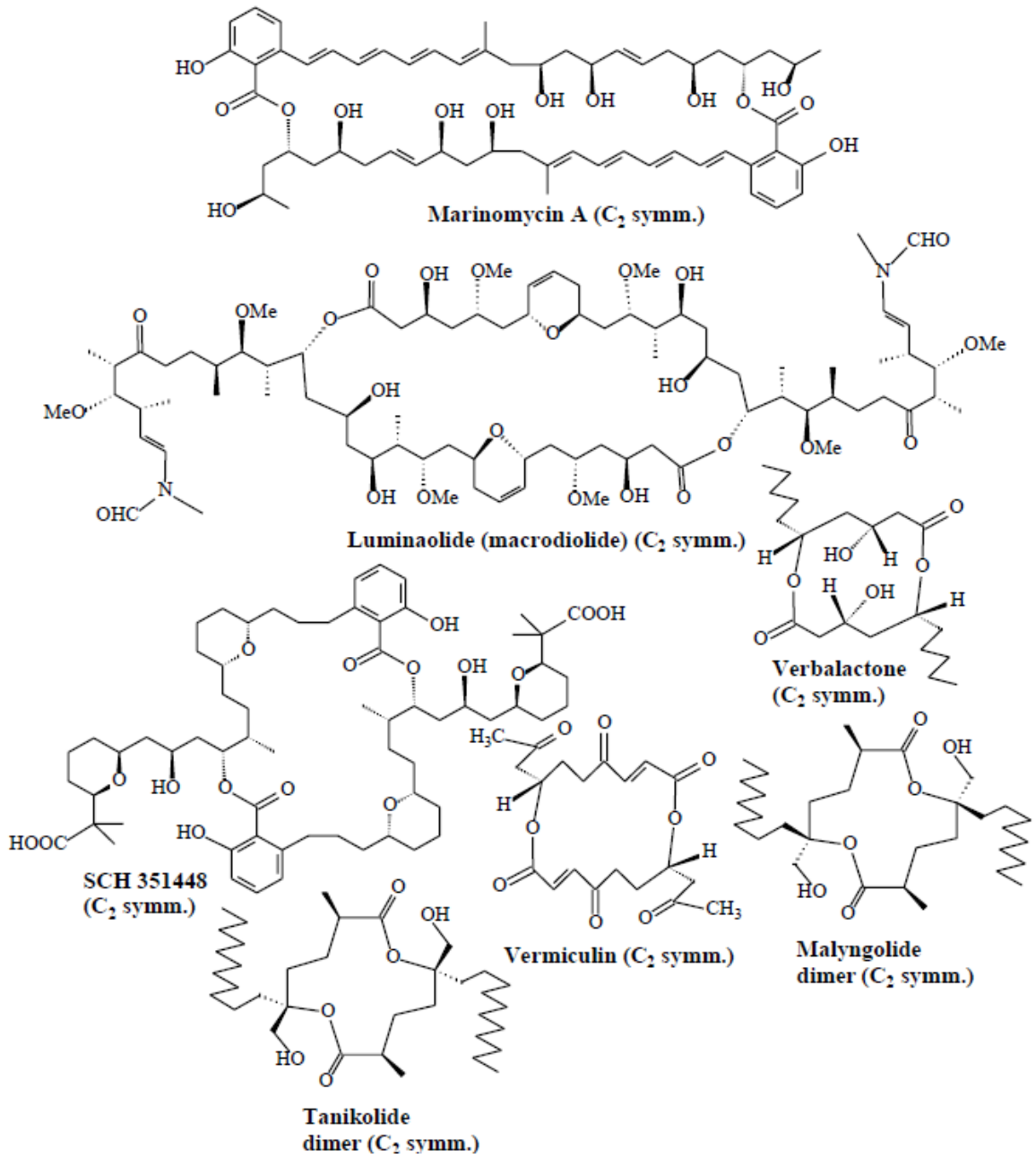


Fig. 13. *C2 symm*. dimeric esters formed by internal esterification

It is easy to understand how Vickery (1957) [73] got involved in the compounds called *C2 symm*. In our opinion, there are three major arguments which disclosed these molecules to Vickery: (i) publications of the group directed by Work and Greenstein concerning chemistry and biochemistry of diaminopimelic acid; (ii) the results of the groups involved in investigations about chemistry and biochemistry of lanthionine; (iii) a dispute appeared in the sixth decade of the past century concerning the chemical representations of tartaric acid, carbohydrates and amino acids [73,74-76]. It is almost certain that amino acids, especially lanthionine and diaminopimelic acid, and not carbohydrates disclosed these molecules to Vickery. He evidenced an essential and characteristic feature of these compounds, and moreover he admitted that the problem is extremely important and complex. He got involved systematically in these compounds, including their chemical nomenclature [77]. Vickery (1957) [73] included α,ε-L,L- diamminopimelic acid in the same category with threitol, tartaric acid

and cystine. Lanthionine was discovered as a product of action of alkali on wool [78,79]. Subsequently, this *C2 symm.* amino acid was discovered in living matter and its isomers synthesized and characterized [65,66]. When *meso* isomer is naturally methylated, methyl group is found on D-moiety since this fragment come from L-Thr *via* a didehydro intermediate [80-82]. As expected, homolanthionine [68] presents also three linear isomers, two *C2 symm.* and one *meso*. α,ε-Diaminopimelic acid was discovered in bacterial products [83]. 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 isomerides (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 [61,67]. At least L,L- and *meso* forms are natural compounds [47], and an epimerase converts L,L-diaminopimelic acid to the *meso*-isomer [84]. An interesting biochemical equivalence of lanthionine and diaminopimelic acid has been noticed [85].

Table 1. Polyketides

R1	R2	n	Compound	Isomer
Me	Me	1	Swinholide A	*C2 symm*.
Me	Me	0	Misakinolide A (bistheonellide A)	*C2 symm*.

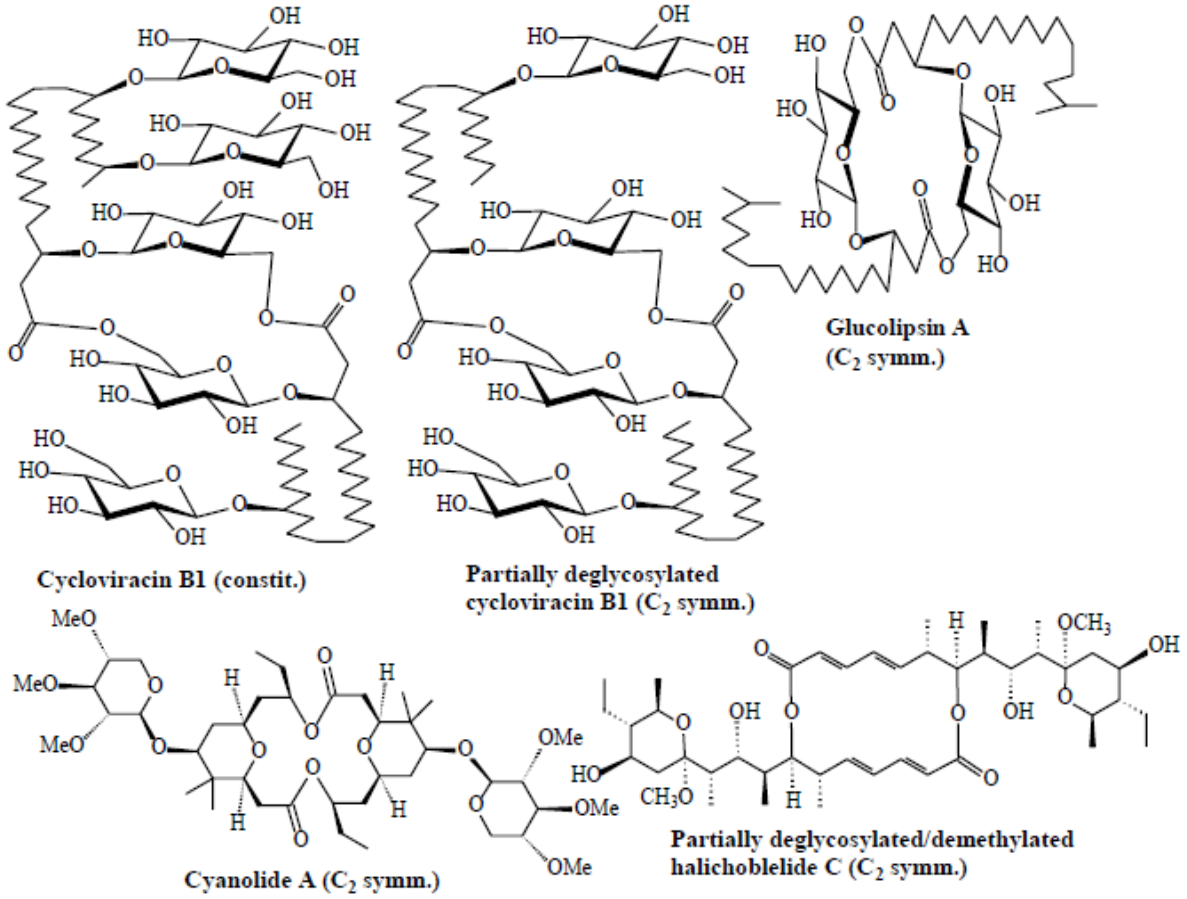


Fig. 14. Symmetric glycolipids

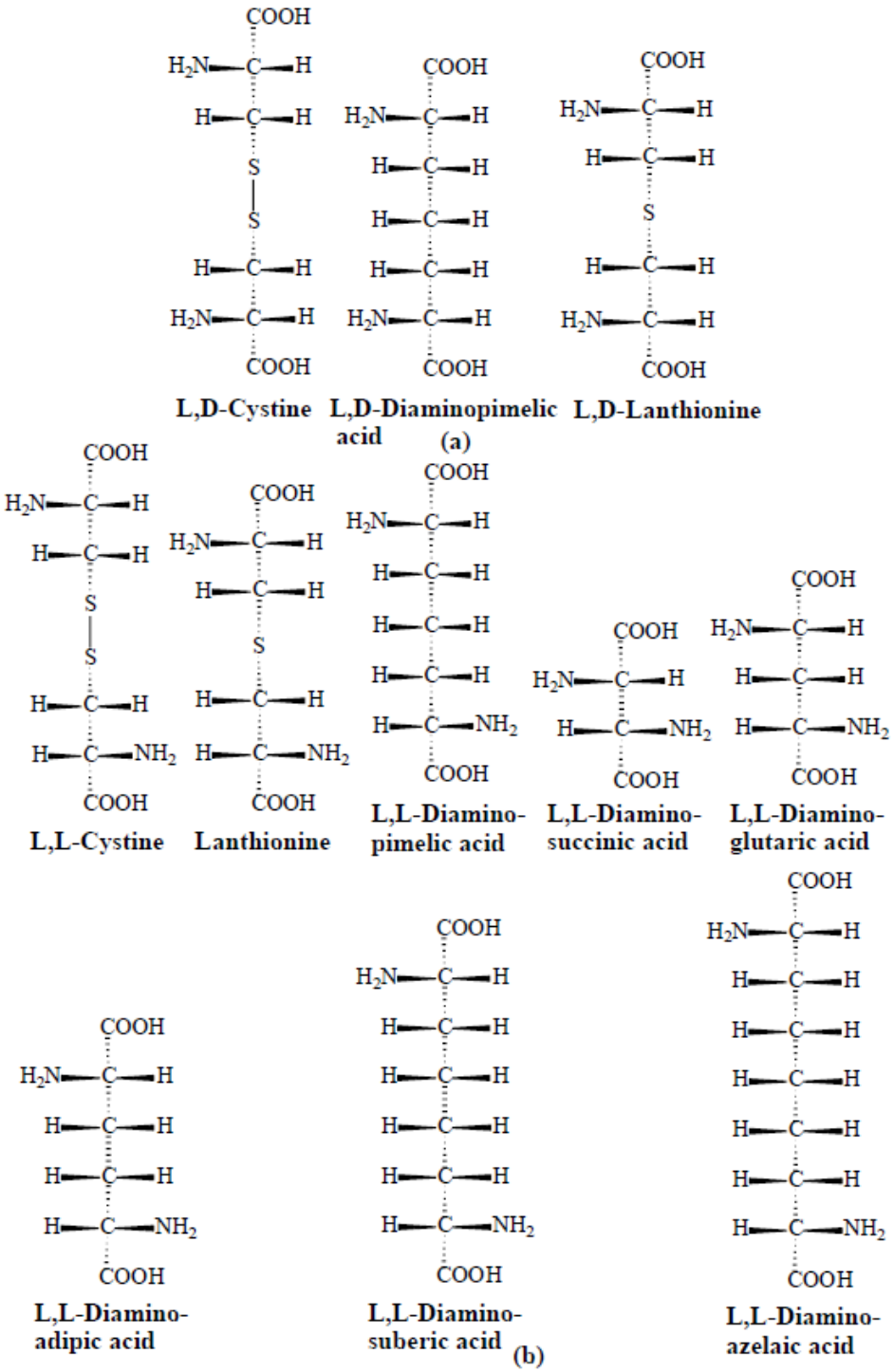


Fig. 15. *Meso* (a) and *C2 symm*. (b) amino acids

5.2 Bioactive Natural Products – Diketopiperazines (DKPs) and Their Derivatives

An impressive number of natural products containing 2,5-diketopiperazine ring in their molecule have been isolated and studied [86-89]. When the two aminoacids are identical, *C2 symm*. diketopiperazines are produced. These compounds disclose a large variety of biological activities and accordingly they are investigated concerning

their biosynthesis, genetics, synthesis and medicinal properties.

5.2.1 DKPs of amino acids coded in DNA (the common amino acids)

2,5-Diketopiperazines were discovered by E. Fischer [90]. Of the 20 common amino acids, 19 produce homogenous *meso* or *C2 symm*. 2,5-diketopiperazines (DKPs) and derivatives. Their symmetrical properties are investigated especially by Cahn-Ingold-Prelog analysis of all chiral centers. When the result consists of two enantiomeric halves (evident or imaginary), DKPs are *meso*. Hence all DKPs formed of two enantiomers of amino acids are *meso*. A spectacular green-like reaction consisted in dimerization of rac-pipecolic acid. In the absence of every catalyst, an unusual case of chiral self-recognition took place, the only DKP being the *meso*-product [91] (Fig. 16).

When the result of Cahn-Ingold-Prelog analysis of a 2,5-diketopiperazine consists of two identical chiral halves uniformly linked (evident or imaginary), it is *C2 symm*. (Table 2). All possible forms of homogenous (LL, DD) and mixed (D and L) DKPs, as well as of different amino acids, were synthesized and/or discovered in natural materials [87,88,92-95]. 2,5-Diketopiperazines formed of different amino acids are important since their doubling as chiral molecules leads to *C2 symm*. ones. Cyclo(L-Val-L-Val) (*C2 symm*.) and cyclo(L-Val-D-Val) (*meso*) were synthesized in view of their comparative oxidation with dioxiranes [96]. Cyclodipeptide synthases were discovered as a novel enzyme family that employs aminoacyl-tRNAs as substrates for 2,5-diketopiperazine synthesis [97]. A number of 51 cyclodipeptide synthases were analyzed concerning their substrate specificity, and the conclusion was that they use 17 proteinogenic amino acids [98].

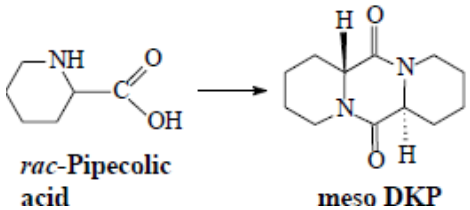


Fig. 16. By dimerization of *rac*-pipecolic acid, exclusively *meso* DKP is obtained

5.2.2 DKPs with varying structure

A *C2 symm*. DKP derivative supposed to be biosynthesized from L-ornithine is dimerumic acid (Fig. 17). It has been isolated from the mold *Monascus anka*, [99]. β-Hydroxycaprinyl-serine is a *constit*. dihydroxy acid. According to the rule mentioned above, its anhydride, diether and dilactone, serratamolide, are *C2 symm*. Serratamolide is a metabolic product of *Serratia* sp. [100]. Both carboline homodimer and *ent*-carboline homodimer are *C2 symm*. (Fig. 13) and they both have been synthesized either from L- or from D-Trp [101]. Pipecolic acid derived DKP (*C2 symm*.) was synthesized by using scandium triflate-catalyzed [4 + 2] aza-annulation and temporary anchoring to a resin [102]. Bipolaramide was isolated from cultures of *Bipolaris sorokiniana*; it was also prepared by chemical synthesis, and many of intermediates are also *C2 symm*. [103]. Two artificial *C2 symm*. DKPs has been synthesized, one destined to the preparation of pure aminoacids methylated on the asymmetric carbon [88], and the other, CWO-324, destined to mimick safranin C [104].

5.2.3 Chlorinated leu monocyclic derivatives

Dysamides A-E (Fig. 18) are all *C2 symm*. structures, DKPs of chlorinated Leu; they are all N-methylated in DKP ring. They have been isolated from marine organisms i.e. from marine sponges of the genus *Dysidea* [105].

5.2.4 L-Phe and L-Tyr monocyclic derivatives

Some monocyclic derivatives of L-Phe and Tyr are *C2 symm*. dimers (Table 3). Cyclo(L-Phe- L-Phe) was isolated from *P. nigricans* [106] and from a marine mangrove endophytic fungus and presented a remarkable anthelmintic activity against *H. nana* and *Schistosoma mansoni* in mice [107]. All three DKP of Phe – LL, DD and DL have been synthesized and compared [108]. The tyrosine analogue cyclo(L-Tyr-L-Tyr) was isolated from the culture liquid of *Cordyceps sinensis* (Berk.) Sacc [109]. Biochemical and physiological activities of the tyrosine dimer consisted in reversible blockage of voltage-dependent L-type calcium channels, increased the heart rate and cardiac function in the rat and was converted into the DOPA analogue by PC12 cell lysate, a good producer of tyrosine hydroxylase [110]. In fact, both cyclo(LTyr-L-Tyr) and the DOPA analogue were intermediates in the biosynthesis of the anticancer natural products, the ecteinascidins [111]. The dimethyl analogue of cyclo(L-Tyr-L-Tyr) was isolated from *Streptomyces griseus* (SC488) [112].

6. A DENDRIMERIC RELATIONSHIP WITH MOLECULAR FORMULAE

Compounds resembling to a tree have been called dendrimers [113, 114]. We have found a dendrimeric relationship within molecular formulae (Fig. 19): the trunk is molecular formula, branches of order I (that depart directly from the trunk) are isomers structure ... the terminal branches represent physical, chemical and biological properties of every isomer.

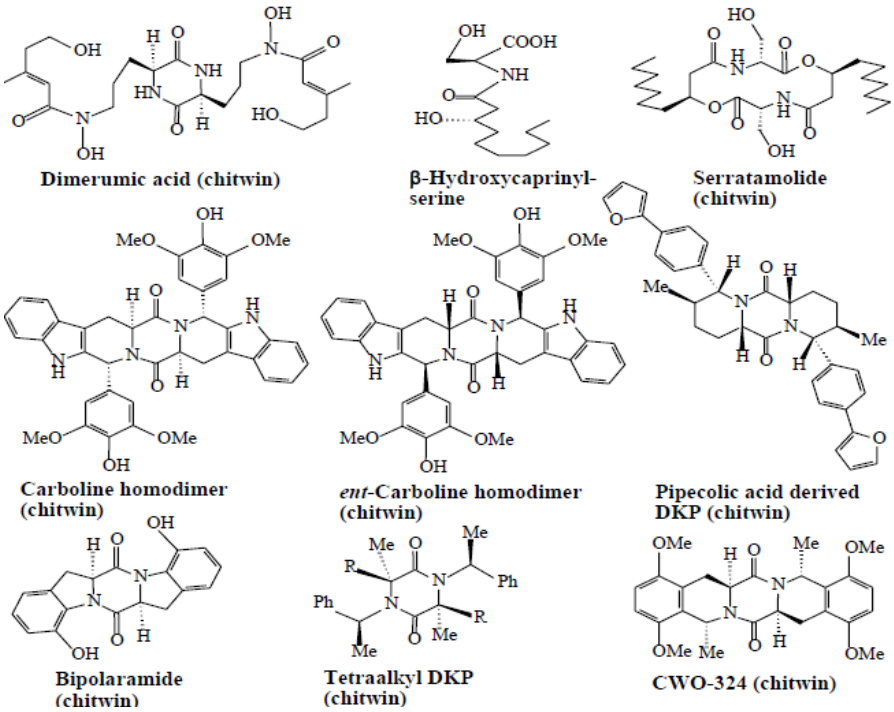
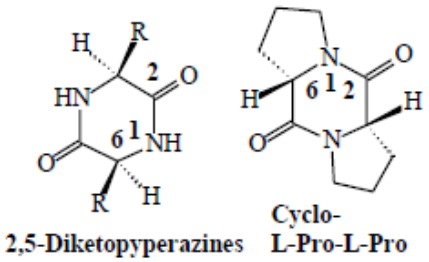


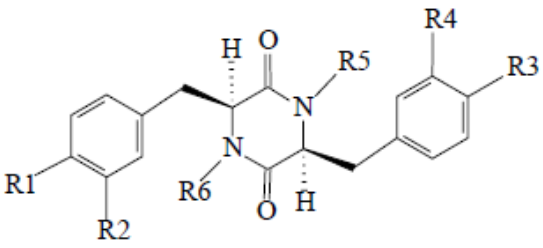
Fig. 17. *C2 symm*. natural DKPs derivatives

Table 2. 2,5-Diketopiperazines of natural aminoacids, as *C2 symm*. molecules



R	2,5-Diketopiperazine	R	2,5-Diketopiperazine
-CH_3	Ala	-CH_2-CH_2- $CONH_2$	Gln
-$CH(CH_3)_2$	Val	-CH_2-COOH	Asp
-CH_2-$CH(CH_3)_2$	Leu	-CH_2-$CONH_2$	Asn
-$CH(CH_3)$-CH_2-CH_3 (3S)	Ile	-CH_2-(4-OH)Phenyl	Tyr
-CH(OH)-CH_3 (3S)	Thr	-CH_2-Phenyl	Phe
-CH_2-OH	Ser	-CH_2-Imidazolyl	His
-CH_2-SH	Cys	-CH_2-Indolyl	Trp
-CH_2-CH_2-S-CH_3	Met	-$(CH_2)_2$-guanidyl	Arg
-CH_2-CH_2-COOH	Glu	-$(CH_2)_3$-NH_2	Lys

Table 3. Diketopiperazines of L-Phe and L-Tyr



R1	R2	R3	R4	R5	R6	Compound	Isomer
H	H	H	H	H	H	cyclo(L-Phe-L-Phe)	*C2 symm*.
OH	H	OH	H	H	H	cyclo(L-Tyr-L-Tyr)	*C2 symm*.
OH	OH	OH	OH	H	H	cyclo(L-DOPA-L-DOPA)	*C2 symm*.
OH	H	OH	H	Me	Me	N,N-Dimethyl-cyclo(L-Tyr-L-Tyr)	*C2 symm*.

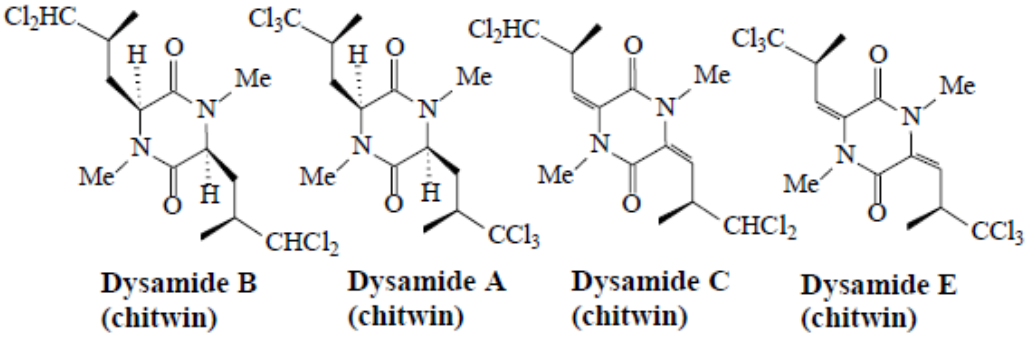


Fig. 18. *C2 symm*. DKPs based on chlorinated leu

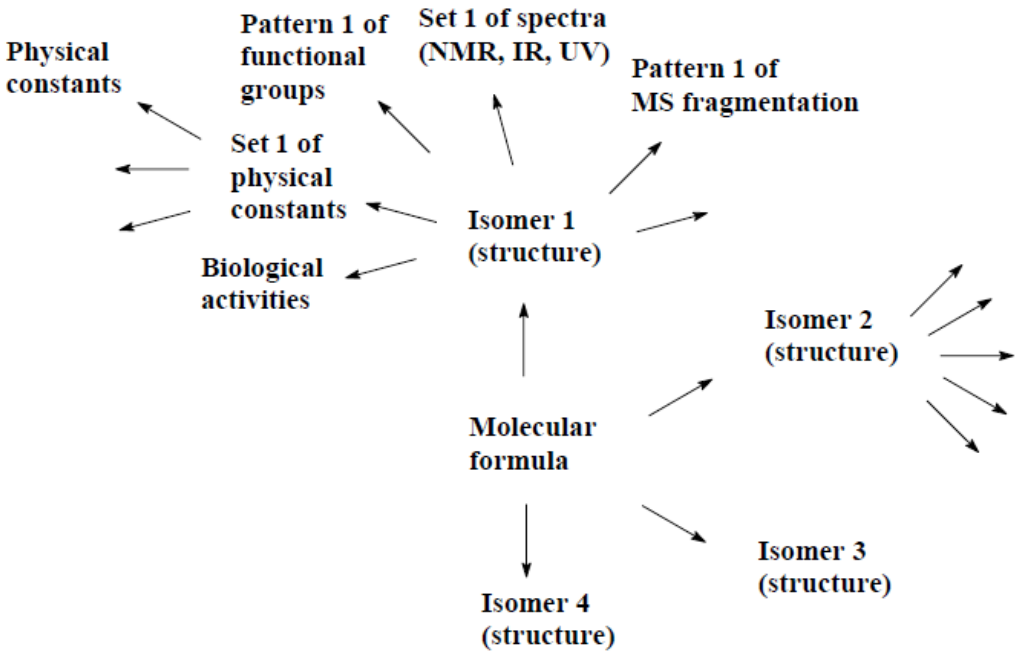


Fig. 19. Dendrimeric relationships within molecular formula

7. CONCLUSIONS

1. All organic compounds, natural or synthetic, are of three types: (A) symmetric (*meso* and *C2 symmetric*), (B) possible symmetry generators: *irrechi* and *constitutional*), and (C) *archaic* (or *primitive*).
2. The three groups are interchangeable by (bio)chemical techniques. Often, symetrization- desymetrization processes can be noticed.
3. Molecular formulas, above a complexity level, can be represented by dendrimeric schemes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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