BIOCHEMICAL SYMMETRIZATION/DESYMMETRIZATION OF ORGANIC COMPOUNDS. DENDRIMERIC RELATIONSHIP WITH MOLECULAR FORMULAS

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 C_2 *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 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 C_2 *symmetrical* (C_2 *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.

Key words: isomers, meso, C_2 symmetrical (C_2 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 (Polya, 1937), physics (Heisenberg, 1958), biology (Linnaeus, 1753, 1758; Porter, 1994). 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) component chiral carbons. The phenomenon can be named isoskeletomeric relationship ([Fujita, 2016)]. (**B2**) The forth type of isomers possibly possessing a different skeleton from the aforementioned three have been defined as for the aimed task. It has been constantly searched the capacity of organic compounds to exist in a symmetric form (Iga, 2021, 2022; Iga et al., 2022).

Organic compounds can be classified as follows: (**A**) Symmetric (symmetry in chemistry includes chirality). Symmetric compounds constitute a minority in organic chemistry. The most studied symmetric compounds are in two groups: (**A1**) *meso* and (**A2**) C_2 *symmetrical* (C_2 *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 C_2 *symm.*, and *meso* but they differ only by configuration of constitutional (*constit.*) and they are either chiral or achiral.

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

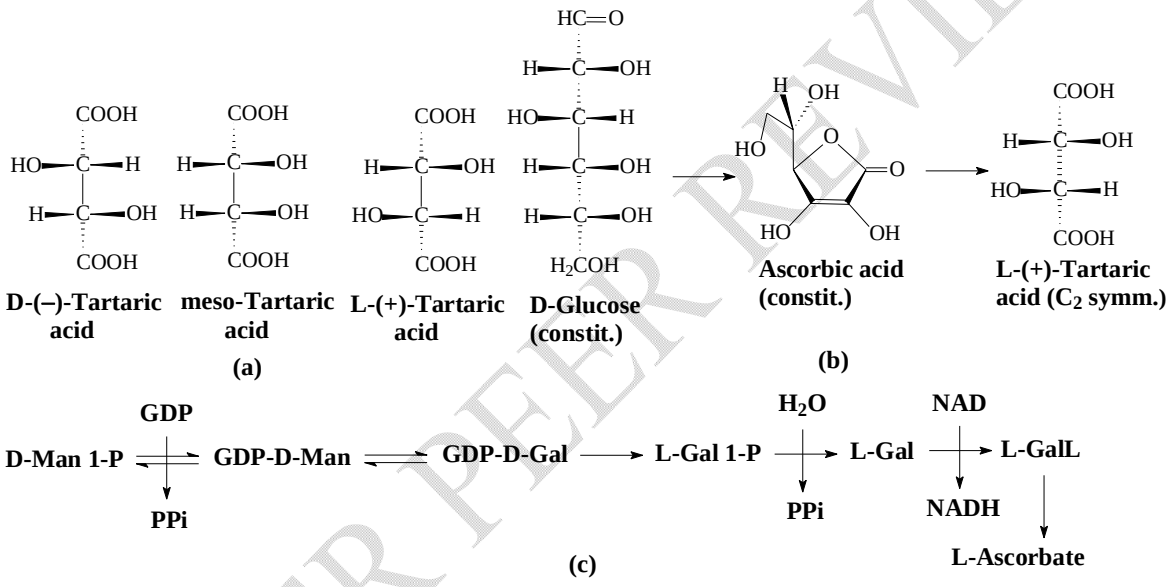
The demanded conditions for every type have been described in previous papers ([Iga, 2018, 2020, 2021)].

2. BIOCHEMICAL SYMMETRIZATION/DESYMMETRIZATION OF ORGANIC COMPOUNDS

Transformation of a *constit.*, compound in either *meso* or C_2 *symm.*, means symmetrisation; 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 (Wagner et., 1975) (Figure. 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 C_2 *symm.* compounds (homodimers) are, in theoretical terms, derivatives of *meso* ones (Azarnia et al., 1972).



(Moh5D)

Figure 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).

The direct precursor of tartaric acid is L-ascorbic acid (Conklin et al., 2006) (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).

Vitaceae and Geraniaceae give (+)-tartaric acid, and *Bauhinia reticulata* (–)-tartaric acid. An ester of the latter with caffeic acid was found in *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.

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,

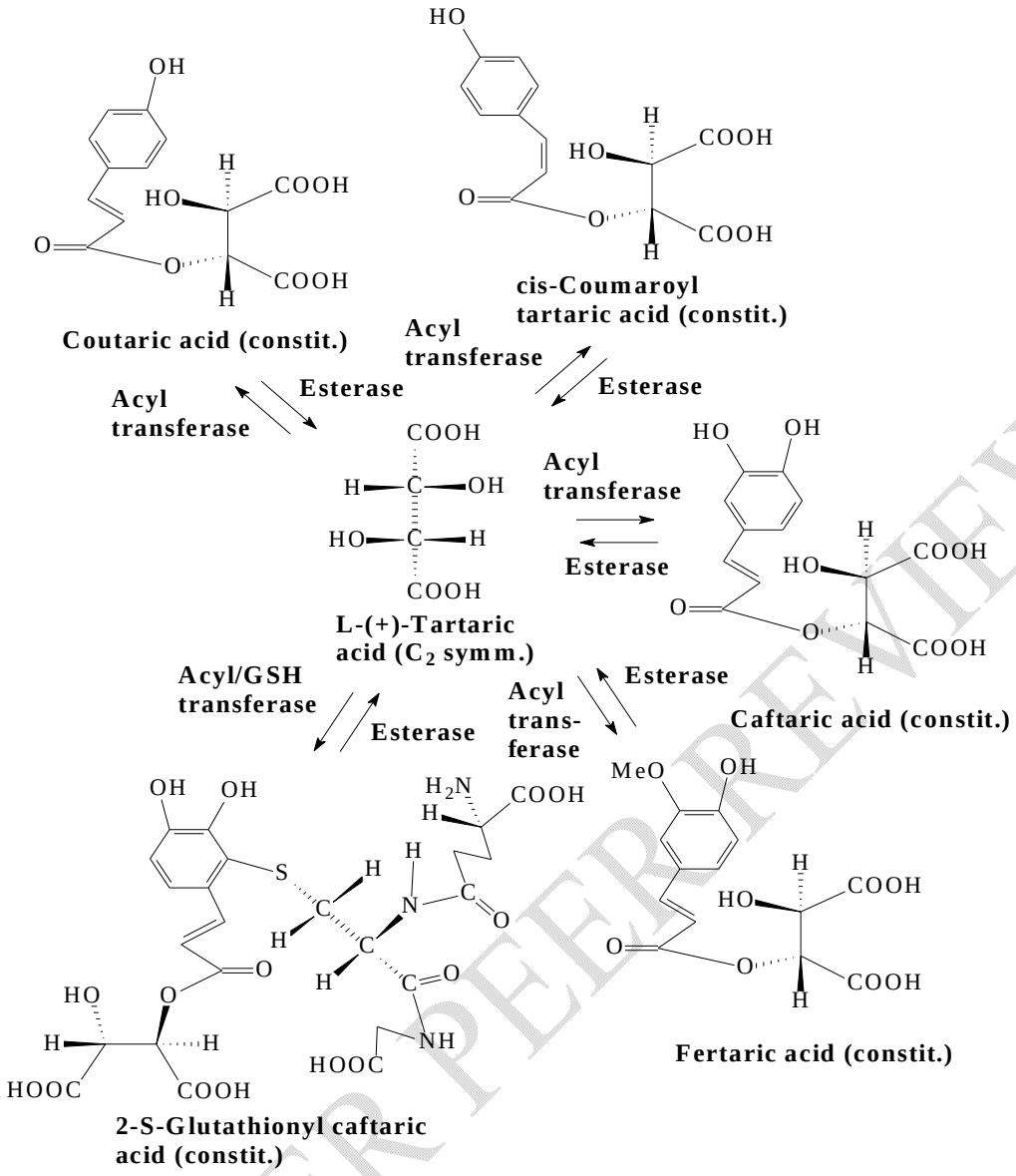


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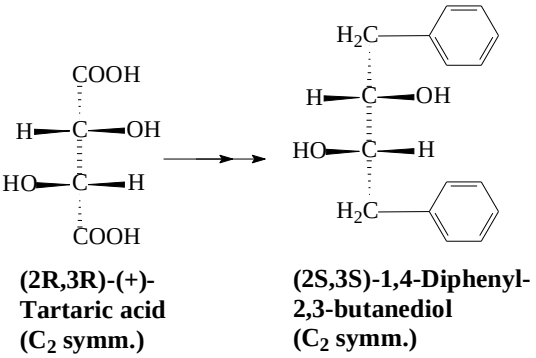
Figure 2. Acylation and glutathionylation of L-(+)-tartaric acid.

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 (Singleton et al., 1978). In phytoplasma susceptible grapevine variety 'Chardonnay' (*Vitis vinifera* L.), concentration of coutaric and caftaric acid changed as a function of the stage of infection (Rusjan et al., 2012). 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 (Lu and Foo, 1999). In case of caftaric acid (the ester of tartaric acid with caffeic acid) desymmetrization is increased by S-glutathionylation. The attachment of cinnamate derivatives to tartaric acids may occur by transacylation from acyl-CoA activated forms (Fry et al., 2000).

Of the three possible isomers of 1,4-diphenyl-2,3-butanediol, a *C_2 symm.* isomer (dextrorotatory) has been isolated from bull testis (Neher, 1963; Eik-Nes, 1967; Iturriza, 1977). The absolute configuration of this compound has been determined to be (2S,3S), by synthesis of the natural diol from L-(+)-tartaric acid (Hill and Bradberry, 1982) (Fig. 3).

Erythritol was among the first poyols discovered, before the elucidation of

monosaccharides structure by E. Fischer (year). 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).



(2R,3R)-(+)-Tartaric acid (C_2 symm.) **(2S,3S)-1,4-Diphenyl-2,3-butanediol (C_2 symm.)**

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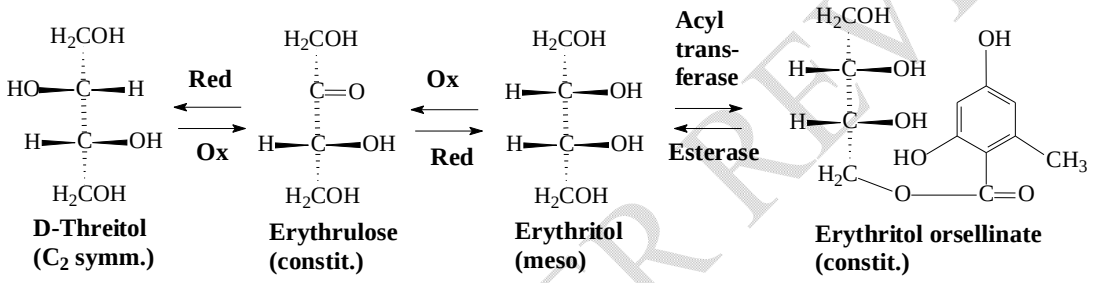
Figure 3. Configuration of a natural compound, 1,4-diphenyl-2,3-butanediol, has been proved by its synthesis from (+)-tartaric acid.



D-Threitol (C_2 symm.) **Erythrulose (constit.)** **Erythritol (meso)** **Erythritol orsellinate (constit.)**

(des5D)

Figure 4. Production of a natural and artificial derivatives of erythritol.

Alternatively, the enantiomeric threitols were prepared by D- and L-threose reduction, the latter being prepared by chain shortening from suitable pentoses (Meldola, 1904).

D-Mannitol (Fig. 5), on which *C_2 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., (Saxena et al., 2013). Two mannitol biosynthetic pathways are known, one linear (Saxena et al., 2013) and one cyclic (Velez et al., 2008). 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., (Fischer and Hirschberger, 1888; Fischer, 1891; Fischer and Fay, 1895). Of the two enantiomers of iditol, L-iditol (Fig. 7) was found in natural materials, in the fruits of *Sorbus aucuparia* (Bertrand and Lanzenberg, 1906). Both isomers are prepared especially by chemical synthesis (Cramer and Pacsu, 1937; Wright and Hartmann, 1961). 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

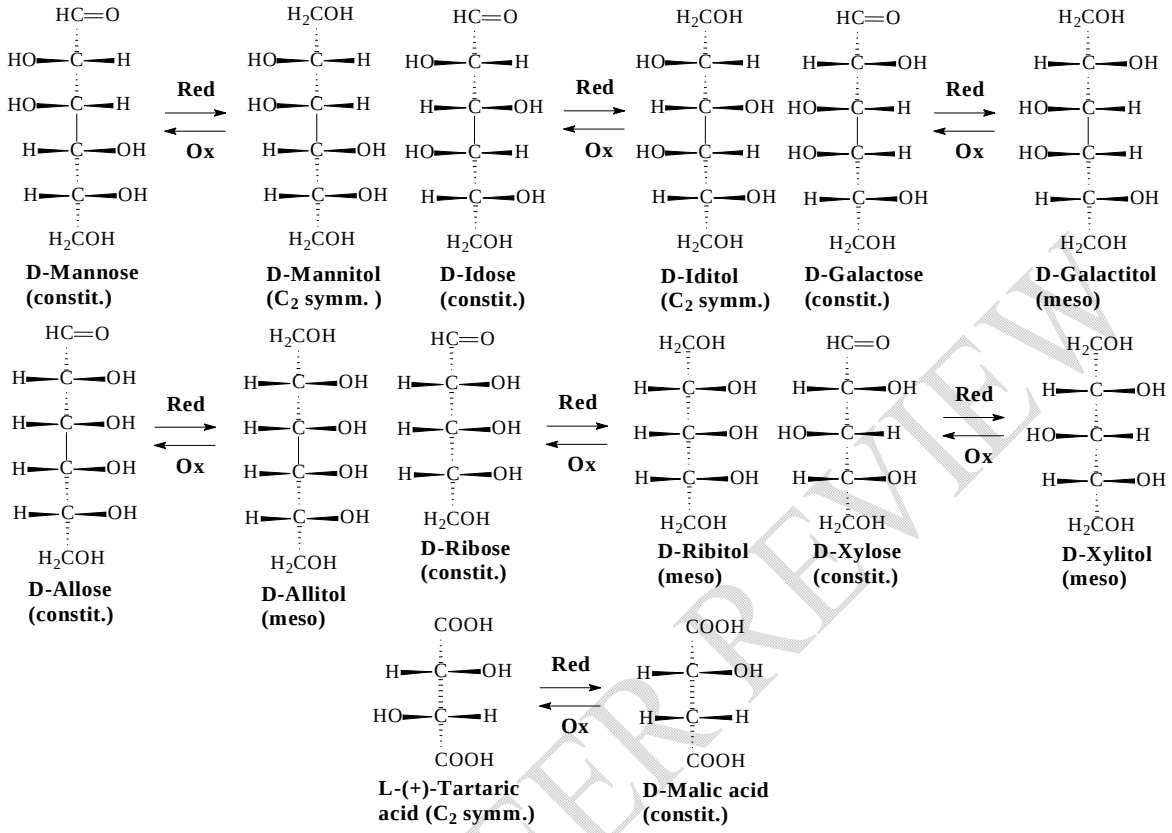


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Figure 5. Natural and artificial redox reaction of some monosaccharides.

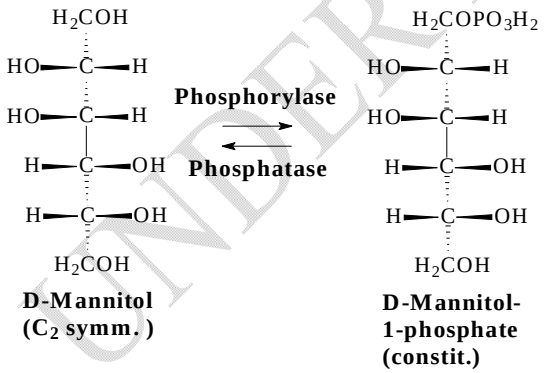

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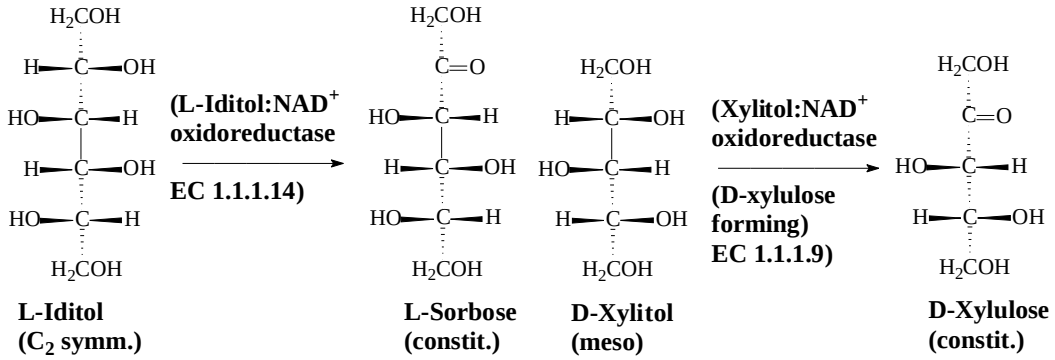
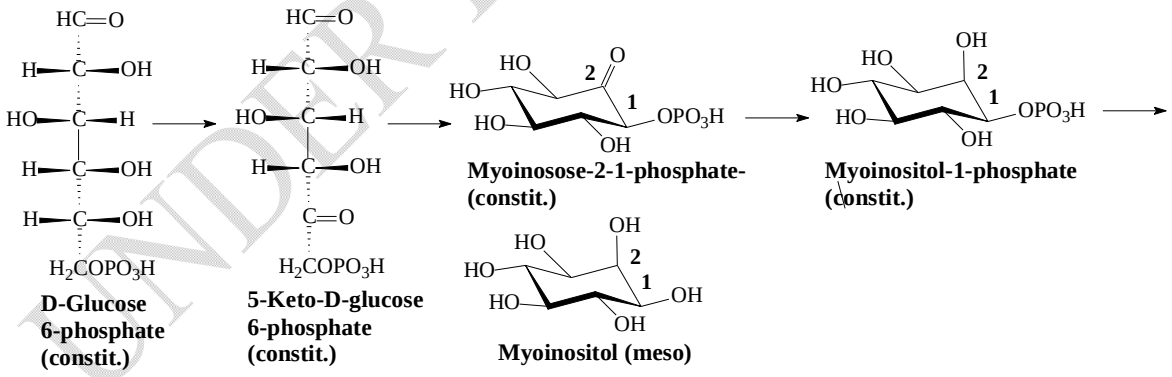
Figure 6. Phosphorylation-dephosphorylation of D-mannitol.



(Moh5A)
Figure 7. Enzymatic oxidation of L-iditol and D-xylitol.

reduced to galactose (constit.) and then to galactitol (meso) (Fischer and Hertz, 1892). 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). 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^+ oxidoreductase, EC 1.1.1.9) catalyses the oxidation of xylitol and 3-deoxyxylitol. The substrate specificity of L-iditol dehydrogenase (L-iditol:NAD^+ oxidoreductase, 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 (Anderson, 1965). By reduction of L-(+)-tartaric acid only one isomer, D-malic, was obtained (Fischer, 1896). It's a unique trait of C_2 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



(des5I)
Figure 8. Biosynthesis of myoinositol.

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, C_2 *symm.*) (Fig. 10), and phosphorylation produces trehalose-6-phosphate. Trehalose is also found as 6,6'-dimycolate (C_2 *symm.*) (Fig. 11). Hydrolysis of trehalose by trehalase destroys the symmetric system. There are only three abundant naturally occurring disaccharides important to

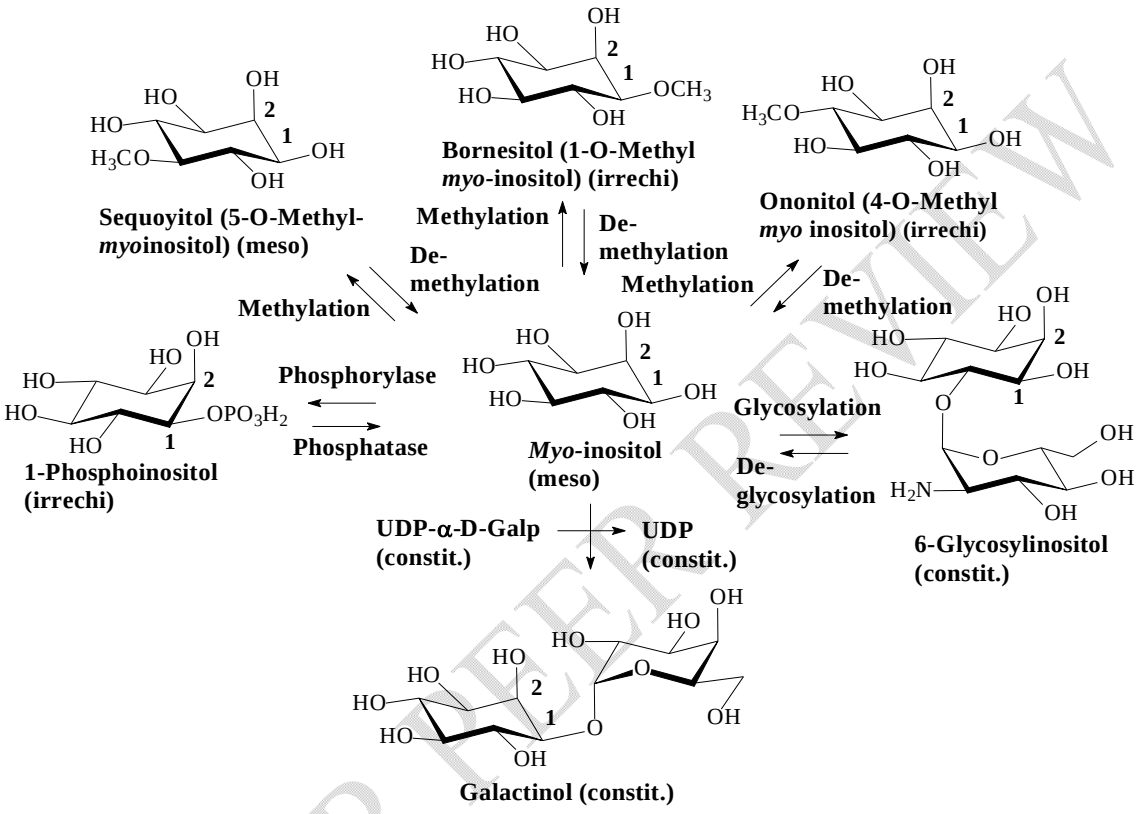


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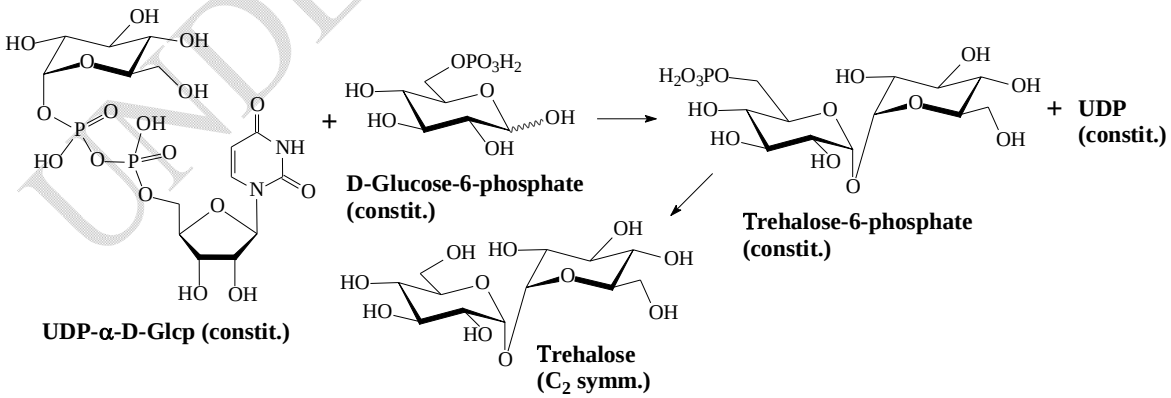
Figure 9. Alternative phosphorylation, glycosylation, methylation, of myoinositol.

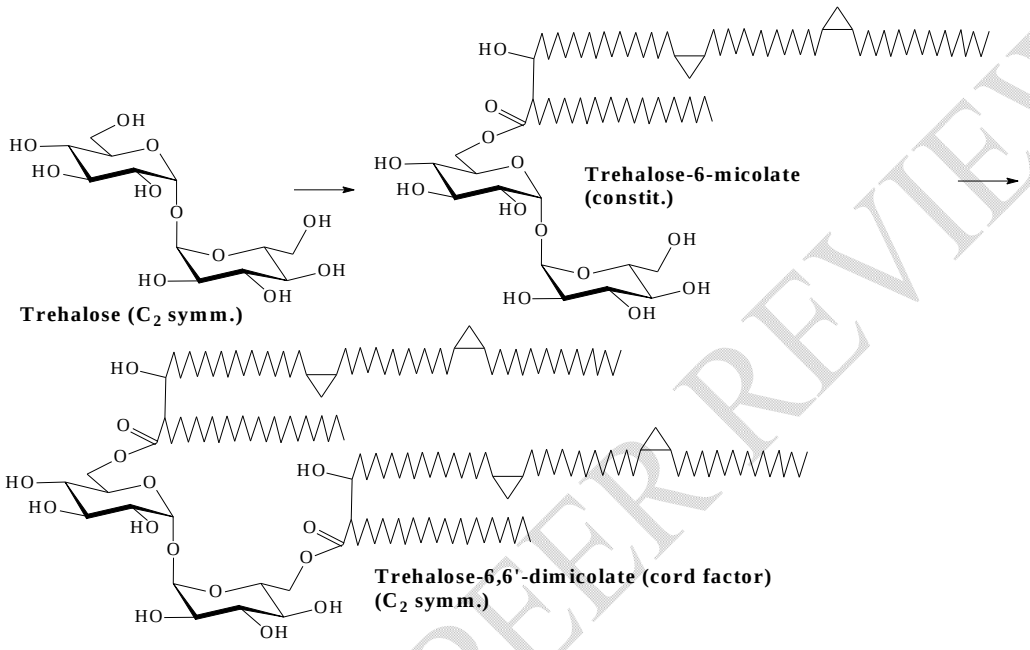


(disacch5F)

Figure 10. Biosynthesis of trehalose.

the metabolism of plants and animals: lactose (*constit.*), sucrose (*constit.*), and trehalose (C_2 *symm.*) (Metzler and Metzler, 2004). 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.

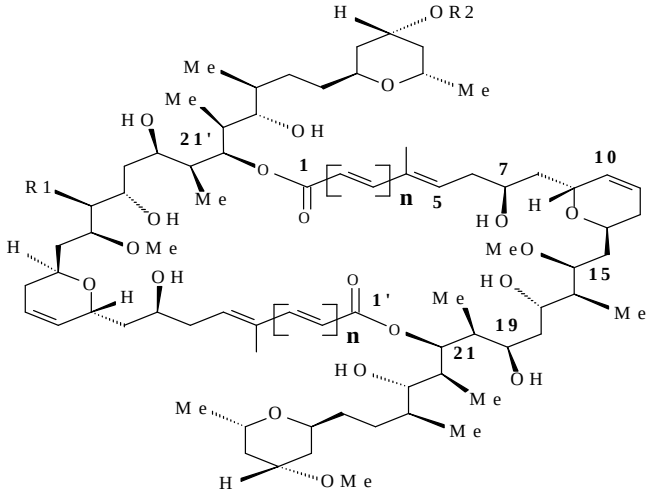


(alka51)

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

2. 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)

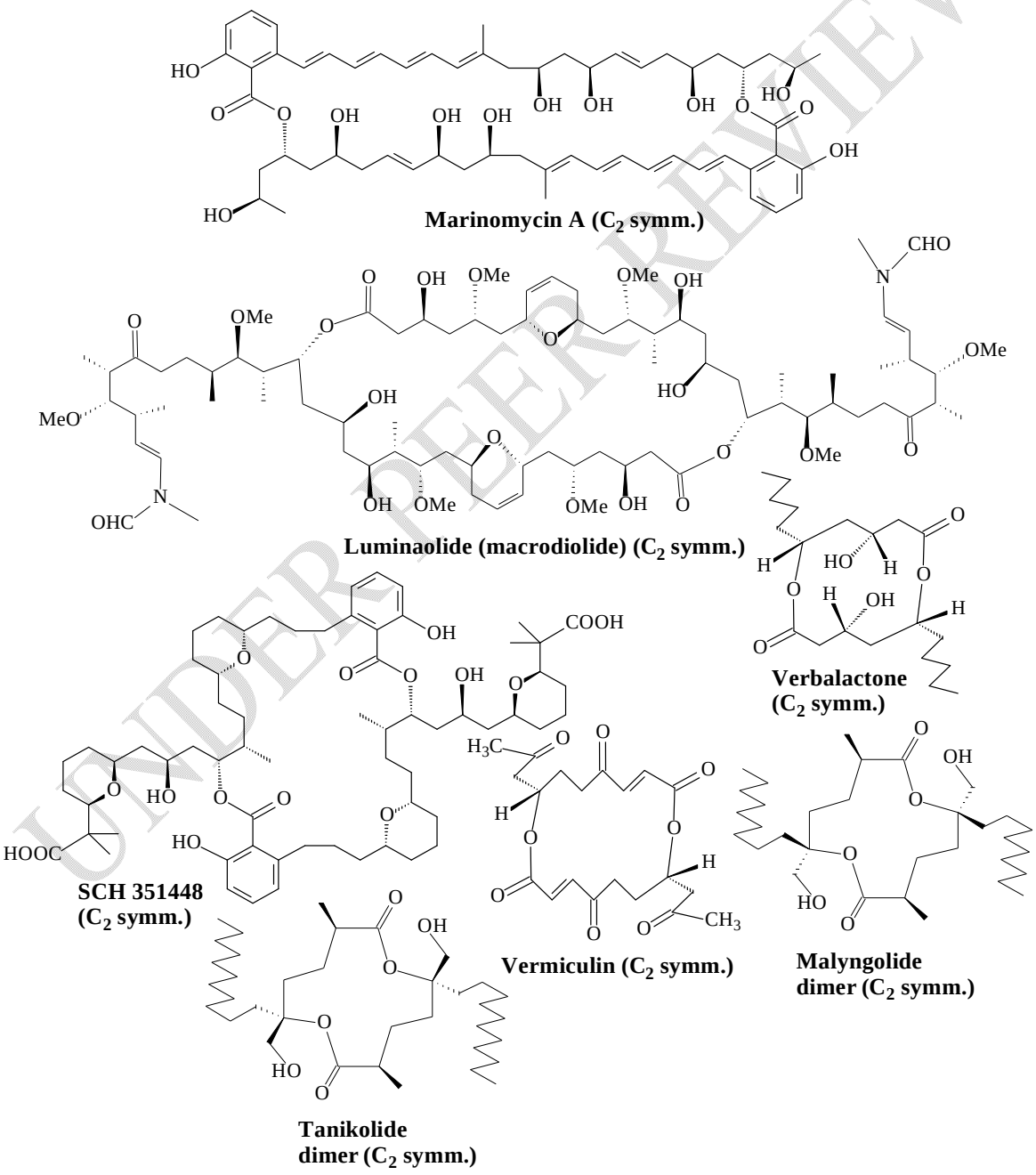


(swinh50):

Figure 12. Natural *C_2 symm.* and *irrechi* polyketides (see Table 1.1).
Table 1. Polyketides.

R1	R2	n	Compound	Isomer
Me	Me	1	Swinholide A	*C_2 symm.*
Me	Me	0	Misakinolide A (bistheonellide A)	*C_2 symm.*

are similar compounds (Kobayashi et al., 1990; Kang and Lee, 2005; Shin et al., 2016). Swinholide A was isolated from the sponge *Theonella swinhoei* (Carmely and Kashman, 1985; Kobayashi et al., 1990; Kitagawa et al., 1990; Doi et al., 1991). Swinholide A and misakinolide A are *chitwin*. However, isoswinholide A is *irrechi* (ester bond on C-21 is alpha, while on C-21' is beta) (Shin and Krische, 2015). Other dimeric diesters are formed of similar chiral hydroxy acids (Fig. 13).



(virtual52)
Figure 13. C_2 symm. dimeric esters formed by internal esterification.

The macrolide marinomycin A has been found in the actinomycete *Marinispora* (Kwon et al., 2006; Cragg et al., 2009; Cragg and Newman, 2013). A new metamorphosis-enhancing macrodiolide, luminaolide, was isolated from the crustose coralline algae *Hydrolithon reinboldii*. Its structure was elucidated by spectroscopic analysis (Kitamura et al., 2009; Humisto et al., 2018). 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 (Kang and Lee, 2005). Verbalactone, vermiculin, malyngolide dimer and tanikolide dimer are *chitwin* 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 (Das et al., 2009; Venkatesham et al., 2012; Vanjivaka et al., 2018).

3. GLYCOLIPIDS

C_2 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 (Kang and Lee, 2005). In fact, cycloviracin B1 is simply chiral. However, its biochemical precursor, before the linkage of terminal glucosyl residue, is *C_2 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 (Kang and Lee, 2005). Cyanolide A is characterized by its content of permethylated monosaccharides (Pereira et al., 2010; Venkatesham et al., 2012).

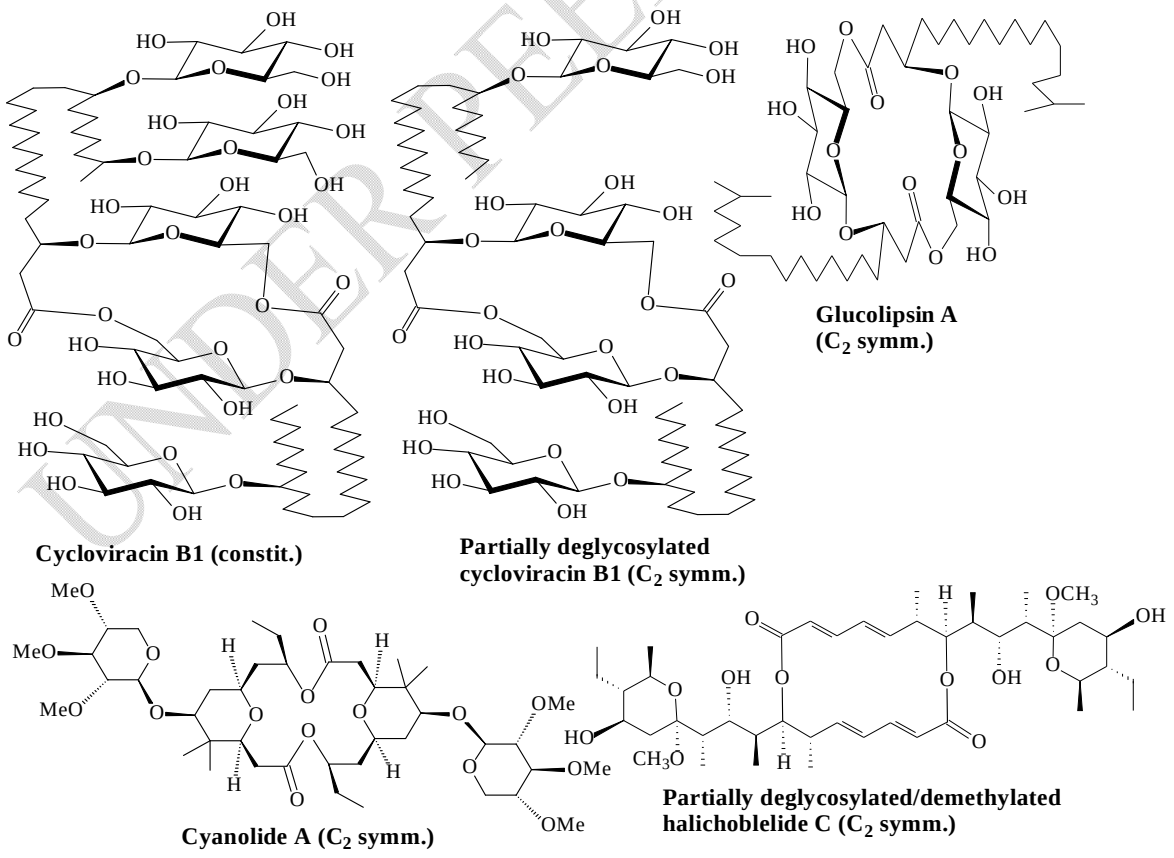


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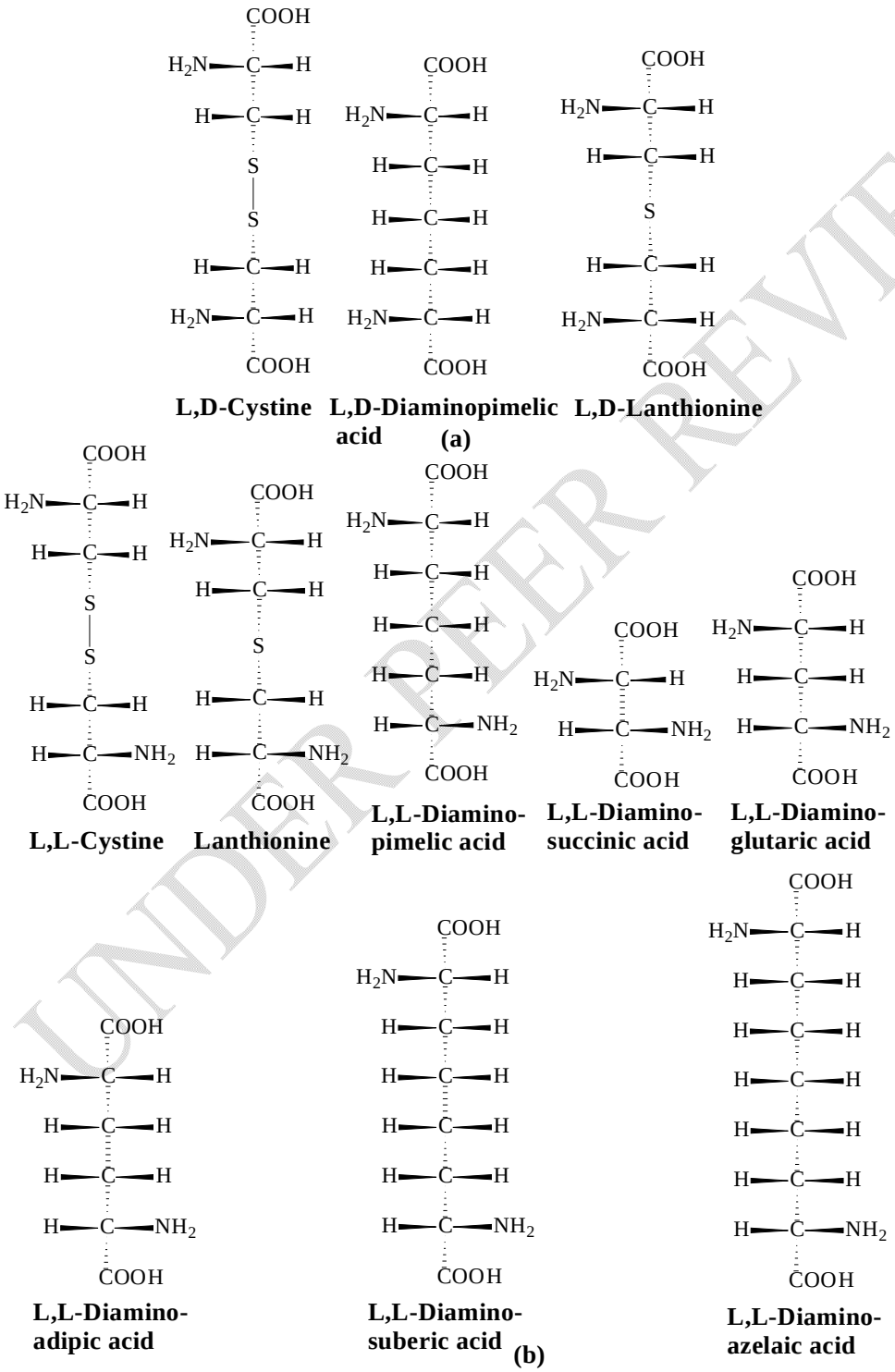
Figure 14. Symmetric glycolipids.

4. AMINO ACIDS AND THEIR DERIVATIVES

4.1. MESO AND C_2 SYMMETRIC AMINO ACIDS

Meso term for amino acids and their derivatives has been attributed by a visual mirror plane of symmetry (Fig. 15a). *meso*-Cystine (Hirs et al., 1954; Work et al., 1955), *meso*-diaminopimelic acid (Meadow and Work, 1959; Richaud et al., 1987; Metzler and Metzler, 2003; Uehara et al., 2006) and *meso*-lanthionine (Brown and du Vigneaud, 1941; Kellner et al., 1988; Uehara et al.,



(meso55)

Figure 15. *Meso* (a) and *C_2 symm.* (b) amino acids.

2006) were studied within metabolism of amino acids as well as in investigations concerning resolution power of separation methods of these important compounds. Linear synthetic diamino dicarboxylic acids present also *meso* isomers (L/D). Only amino acids with an even number of atoms in their skeletom (L,D-cystine) or an odd number (L,D-diaminopimelic acid, L,D-lanthionine, L,D-homolanthionine) (Work et al., 1955; Hoare and Work, 1957; Brown and du Vigneaud, 1941; Chiku et al., 2009) have a mirror plane of symmetry.

C_2 Symmetric Amino Acids. *C_2 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 *C_2 symm.* representative; both *C_2 symm.* isomers of this amino acid are known: (L,L)-cystine and (D,D)-cystine (Work et al., 1955). 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 (see **10. COENZYMES… and 11. HOMOMERIC PROTEINS**). It has been hypothesized that a cystine residue could bind two chains of cell wall polysaccharides (Fry, 1986; Hon and Shirashi, 2001). When the two polysaccharide chains are identical, *C_2 symm.* dimers are produced. Lanthionine presents a similar isomerism: (L,L)- and (D,D)-lanthionine are both *C_2 symm.*. α,ε-Diaminopimelic acid presents also two *C_2 symm.* isomers: (L,L)- and (D,D)-diaminopimelic acid (Fig. 4.1.b). Linear synthetic diamino dicarboxylic acids (L/L or D/D) are *C_2 symm.* molecules. A series of representatives of these compounds were synthesized and their biochemical activity investigated (Simmonds, 1954; Berger and Heppel, 1972): 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.

It is easy to understand how Vickery (1957) got involved in the compounds called *C_2 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 (Abernety, 1956, 1957; Vickery, 1957; Nenitzescu, 1957). 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 (Downey and Black, 1957). Vickery (1957) 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 (Horn et al., 1941; Horn and Jones, 1941). Subsequently, this *C_2 symm.* amino acid was discovered in living matter and its isomers synthesized and characterized (Brown and du Vigneaud, 1941; Kellner et al., 1988). When *meso* isomer is naturally methylated, methyl group is found on D-moiety since this fragment come from L-Thr *via* a didehydro intermediate (McAuliffe et al., 2001; Stein, 2005; Goto et al., 2010). As expected, homolanthionine (Chiku et al., 2009) presents also three linear isomers, two *C_2 symm.* and one *meso*. α,ε-Diaminopimelic acid was discovered in bacterial products (Work, 1951). 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 (Work et al., 1955;

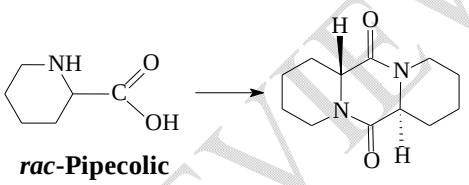
Hoare and Work, 1957). At least L,L- and *meso* forms are natural compounds (Metzler and Metzler, 2003), and an epimerase converts L,L-diaminopimelic acid to the *meso*-isomer (Hudson et al., 2006). An interesting biochemical equivalence of lanthionine and diaminopimelic acid has been noticed (Mengin-Lecreulx et al., 1994).

4.2. 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 (Witiak and Wei, 1990; Huang et al., 2010; Borthwick, 2012; Guo et al., 2013: cyclo(L-Phe-L-Phe). These compounds disclose a large variety of biological activities and accordingly they are investigated concerning their biosynthesis, genetics, synthesis and medicinal properties.

4.2.1. DKPs of amino acids coded in DNA (the common amino acids)

2,5-Diketopiperazines were discovered by E. Fischer (1906). Of the 20 common amino acids, 19 produce homogenous *meso* or C_2 *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 an L- and D-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 (Nonappa et al., 2011) (Fig. 16).



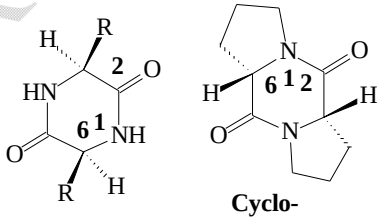
***rac*-Pipecolic acid** **meso DKP**

(alka51):

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

When the result of Cahn-Ingold-Prelog analysis consists of two identical chiral halves (evident or imaginary), are C_2 *symm*. (Table 2). All possible forms of homogenous (LL, DD) and mixed

Table 2. 2,5-Diketopiperazines of natural aminoacids, as C_2 *symm*. molecules. (evid56)



2,5-Diketopyperazines **Cyclo-L-Pro-L-Pro**

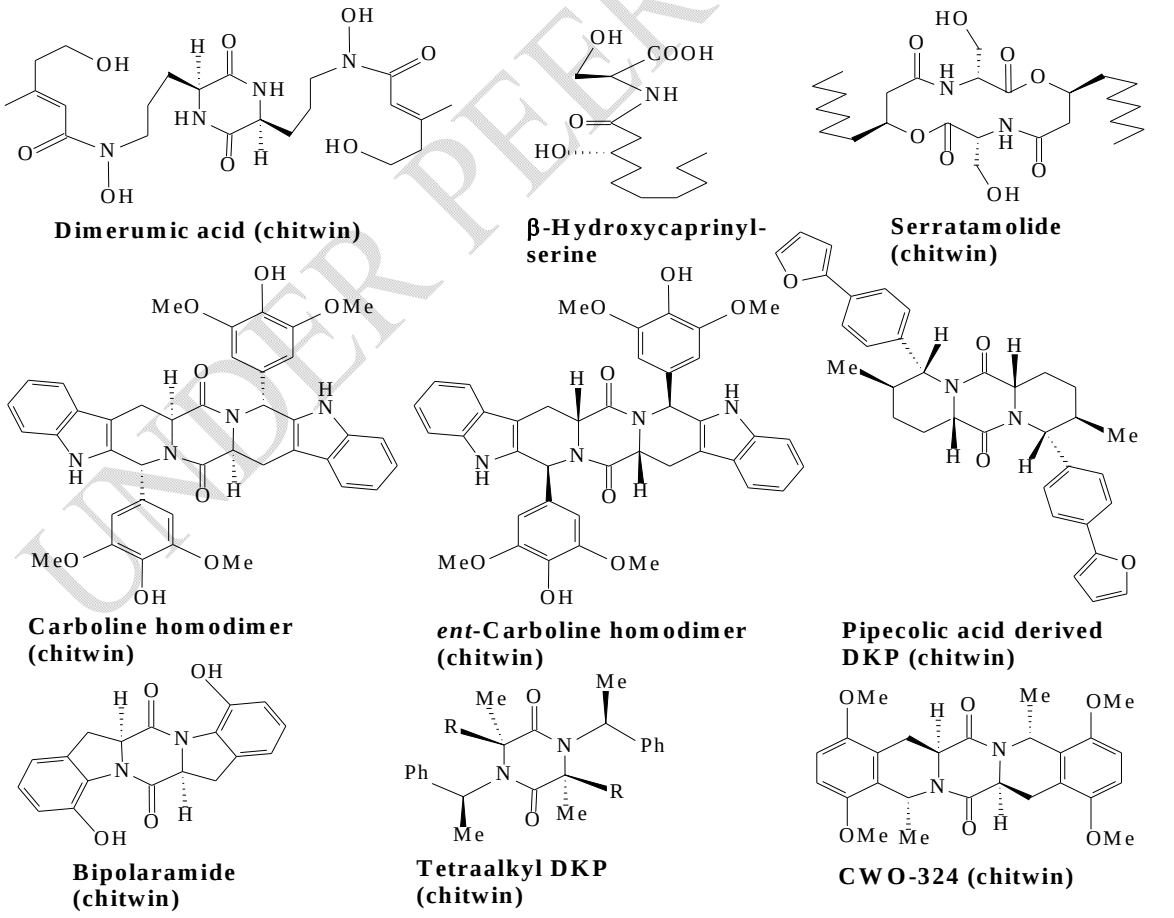
R	2,5-Diketopiperazine	R	2,5-Diketopiperazine
$-CH_3$	Ala	$-CH_2-CH_2-CONH_2$	Gln
$-CH(CH_3)_2$	Val	$-CH_2-COOH$	Asp
$-CH_2-CH(CH_3)_2$	Leu	$-CH_2-CONH_2$	Asn
$-CH(CH_3)-CH_2-CH_3$ (3S)	Ile	$-CH_2$-(4-OH)Phenyl	Tyr
$-CH(OH)-CH_3$ (3S)	Thr	$-CH_2$-Phenyl	Phe
$-CH_2-OH$	Ser	$-CH_2$-Imidazolyl	His
$-CH_2-SH$	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

(D and L) DKPs, as well as of different amino acids, were synthesized and/or discovered in natural materials (Nitecki et al., 1968; Kopple and Ghazarian, 1968; Jung and Rohloff, 1985; Cui et al., 1996; Huang et al., 2010;

Borthwick, 2012). 2,5-Diketopiperazines formed of different amino acids are important since their doubling as chiral molecules leads to C_2 *symm*. ones (see ??…). Cyclo(L-Val-L-Val) and cyclo(L-Val-D-Val) were synthesized in view of their comparative oxidation with dioxiranes (Annese et al., 2016). Cyclodipeptide synthases were discovered as a novel enzyme family that employs aminoacyl-tRNAs as substrates for 2,5-diketopiperazine synthesis (Gondry et al., 2009). A number of 51 cyclodipeptide synthases were analyzed concerning their substrate specificity, and the conclusion was that they use 17 proteinogenic amino acids (Jaques et al., 2015).

4.2.2. DKPs with heterogenic structure

A *chitwin* DKP derivative supposed to be biosynthesized from L-ornithine is dimerumic acid (Fig. 17). It has been isolated from the mold **Monascus anka**, (Taira et al., 2002). β-Hydroxycaprinyl-serine is a *constit.* dihydroxy acid. According to the rule mentioned above, its anhydride, diether and dilactone, serratamolide, are C_2 *symm*.. Serratamolide is a metabolic product of *Serratia* sp. (Wasserman et al., 1961). Both carboline homodimer and *ent*-carboline homodimer are *chitwin* (Fig. 17) and they both have been synthesized either from L- or from D-Trp (Deveau et al., 2008). Pipecolic acid derived DKP (*chitwin*) was synthesized by using scandium triflate-catalyzed [4 + 2] aza-annulation and temporary anchoring to a resin (Dandapani et al., 2006). Bipolaramide was isolated from cultures of *Bipolaris sorokiniana*; it was also prepared by chemical synthesis, and many of intermediates are also *chitwin* (Somei and Kawasaki, 1989). Two synthetic *chitwin* DKPs has been synthesized, one destined to the preparation of pure aminoacids methylated on the asymmetric carbon (Borthwick, 2012), and the other, CWO-324, destined to mimick safranin C (Ong et al., 2003).

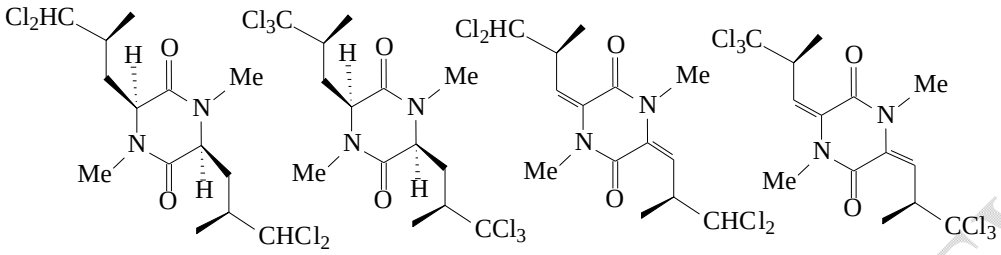


(ciclo14)

Figure 17. C_2 *symm*. natural DKPs derivatives.

4.2.3. Chlorinated Leu Monocyclic Derivatives

Dysamides A-E (Fig. 18) are all *C_2 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* (Su et al., 1993).



Dysamide B (chitwin) **Dysamide A (chitwin)** **Dysamide C (chitwin)** **Dysamide E (chitwin)**

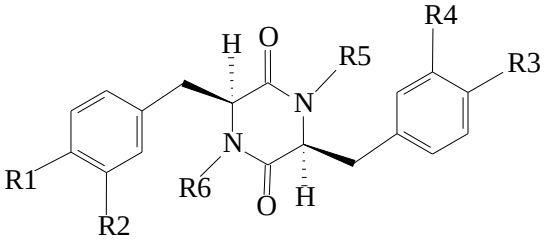
(ciclo14)

Figure 18. *C_2 symm.* DKPs based on chlorinated Leu.

4.2.4. L-Phe and L-Tyr Monocyclic Derivatives

Some monocyclic derivatives of L-Phe and Tyr are *C_2 symm.* dimers (Table 3). Cyclo(L-Phe-L-Phe) was isolated from *P. nigricans* (Birkenshaw and Mohammed, 1962) and from a marine mangrove endophytic fungus and presented a remarkable anthelmintic activity against *H. nana* and *Schistosoma mansoni* in mice (Walchshofer et al., 1997). The tyrosine analogue cyclo(L-Tyr-L-Tyr) was isolated from the culture liquid of *Cordyceps sinensis* (Berk.) Sacc (Jia et al., 2005). 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 (Saleh and Kerr, 2004). In fact, both cyclo(LTyr-L-Tyr) and the DOPA analogue were intermediates in the biosynthesis of the anticancer natural products the ecteinascidins (Jeedigunta et al., 2000). The dimethyl analogue of cyclo(L-Tyr-L-Tyr) was isolated from *Streptomyces griseus* (SC488) (Alvarez et al., 1994).

Table 3. Diketopiperazines of L-Phe and L-Tyr. (ciclo14) (ciclo58):



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)	*C_2 symm.*
OH	H	OH	H	H	H	cyclo(L-Tyr-L-Tyr)	*C_2 symm.*
OH	OH	OH	OH	H	H	cyclo(L-DOPA-L-DOPA)	*C_2 symm.*
OH	H	OH	H	Me	Me	N,N-Dimethyl-cyclo(L-Tyr-L-Tyr)	*C_2 symm.*

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