MESO COMPOUNDS SYSTEMATIZATION – A CHEMICAL PARADOX AMONG INOSITOLS AND A GROUP OF SUPER-SYMMETRIC COMBINATIONS

ABSTRACT. *meso* Compounds have been defined by themselves, as well as by their relationship with another group of diastereomeric combinations, *C_2 symmetrical* ones, isomer to *meso*. Every *meso* compound should present a homodimer equivalent able to display at least one *C_2 symmetrical* isomer. Cahn-Ingold-Prelog test, however limited, is also valuable. A systematization of *meso* combinations includes the following types: (A) *meso* Homodimers possessing one super-symmetric isomer or two real or envisaged *C_2 symmetrical* enantiomers; (B) *meso* Heterodimers with a binding support having geometric or optical symmetry (e.g. >CR_2, etc.). (C) *meso* Heterodimers with a binding support devoid of symmetry (of the form >CRR', etc.), seeable as *meso*, and provable in this way not by themselves but by their equivalent *meso* homodimers. A paradoxical behavior has been shown at one of inositol isomers, in comparison with the others. Moreover, a new group of compounds has been disclosed, which are concomitantly *meso* and *C_2 symmetrical*, and of this reason they have been called super-symmetrical.

Keywords: chemical paradox; meso; C2 symmetrical; mirror plane of symmetry; linking support (matrix); homodimers; heterodimers; inositols; super-symmetrical.

1. Introduction

Chemical symmetry includes three types: *meso* [1], *C_2 symmetrical* (*C_2 symm.*) [2] and *centrosymmetrical* [3], and all operates with chiral carbons, contrary to geometrical symmetry that works with achiral carbons, and this property is decided by geometrical and not by chemical concepts. The molecule of a *meso* compound is formed either of two chiral enantiomeric halves uniformly linked with each other (homodimers) or linked on a mono- or polyatomic support (heterodimers). (The term uniform indicates that the linkage is made between the atoms of the same rank. A vast group of dimers, isomers to *meso* and *C_2 symm.* is known, whose identical chiral halves are linked in a non-uniform manner [4]. The linking support can be symmetric (of the >CR_2 form, etc.) or non-symmetric (of the >CRR' form, etc.). *meso* Compounds are characterized by their mirror plane of symmetry and they are distinguished by the fact that in homodimers it intersects only bonds, while in heterodimers it intersects one or more atoms. When the two enantiomeric halves of *meso* combinations are alternatively dimerized, one or two *C_2 symm.* isomers are produced, most frequently optically active and enantiomeric. Among the isomers of inositol, only one was found to produce two chiral, *C_2 symm.* enantiomers. Alternative dimerization of the two halves of *meso* heterodimers includes the binding support when it is symmetric. However, duplication is preceded by removing of linking support when it is devoid of symmetry. The molecule of *C_2 symm.* compounds is formed of either two identical chiral halves uniformly linked with each other or linked on a binding support, invariably of the >CR_2 form. Rotation of a *C_2 symm.* compound by 180° around a defining axis arrives at the same structural context as initially. In this paper, the analysis of *meso* homo- and heterodimers when confronted with the above concepts has been made.

2. On the Planes of Symmetry

The plane of symmetry of 1,2-cis-dimethylcyclobutane cuts two bonds. Since at least one isomer, 1,2-trans-dimethylcyclobutane (*C_2 symm.*), has been prepared [5,6] (Fig. 1), one can assert that the plane of symmetry of 1,2-cis-dimethylcyclobutane is a mirror plane of symmetry, and 1,2-cis-dimethylcyclobutane is a *meso* compound. The analysis of symmetry of cis- and trans-1,3-cyclobutane dicarboxylic acids [7] indicates the following. cis-1,3-Cyclobutane dicarboxylic acid has two planes of symmetry, one intersecting C-2 and C-4, and the other C-1 and C-3, but only the first one separates two enantiomeric halves. Rather as final results than a

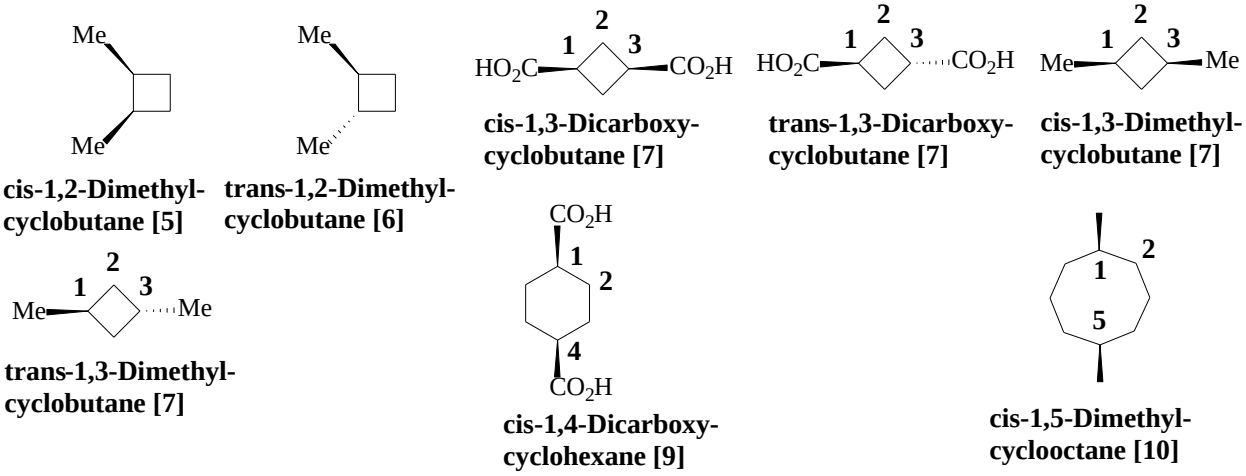

Figure 1. A comparison of planes of symmetry of some disubstituted cycloalkanes.

general procedure, the two planes of symmetry have different ranks: the first one is a veritable chemical plane of symmetry and the other is a non-chemical, i.e. a geometrical plane of symmetry. trans-1,3-Cyclobutane dicarboxylic acid has no mirror plane of symmetry, consequently it is not *meso*; the trans isomer is in fact *C_2 symm*. However, cis,trans,trans-1,2,3,4-tetracarboxy-cyclobutane [(1β,2β,3α,4β)-1,2,3,4-tetracarboxy-cyclobutane] [8] (see Fig. 6) is a *meso* heterodimer: its mirror plane of symmetry intersects C-1 and C-3 and some of the atoms linked to them. The same results are obtained with cis- and trans-1,3-dimethyl-cyclobutane [7] as well as with cis-1,4-dicarboxy-cyclohexane [9] and cis-1,5-dimethyl-cyclooctane [10]. C-1 and C-6 in 1,6-dimethyl-cyclodecane binds and shares a proton and the whole molecule becomes a carbocation [11].

(A) *meso* Homodimers and their *C_2 symmetrical* Isomers

Numerous results suggest that every *meso* homodimer (Fig. 2) presents at least one *C_2* symm. isomer. Fischer and Hertz [12] reduced galactaric acid (a *meso* homodimer) with Na-amalgam and obtained a racemic mixture of D- and L-galactonic acid. They separated the two enantiomers of the mixture as salts of strychnine. Of every enantiomer they prepared the matching aldohexose, i.e. D- and L-galactose. As expected, both aldohexoses gave the same galactitol or galactaric acid, by reduction with Na-amalgam or oxidation with nitric acid, respectively. By this experiment, Fischer proved that the molecule of *meso* homodimers is formed of two enantiomeric halves. On the other hand, reduction of dextrotartaric acid with HI produced a single species of malic acid, that is D isomer [13]. Fischer had previously made similar experiments on D-mannitol: by oxidizing it kinetically, only one type of aldohexose, D-mannose, was obtained [14]. By these experiments, Fischer discovered a group of compounds whose molecule is formed of two identical chiral halves. Their distinct features were also noticed by Vickery [15]. Subsequently, these compounds have been gathered under the group called *C_2 symm.* [2,16-18]. NMR technique confirmed the perfect identity of the component halves of *C_2 symm.* homodimers: only half of the expected signals appeared [19].

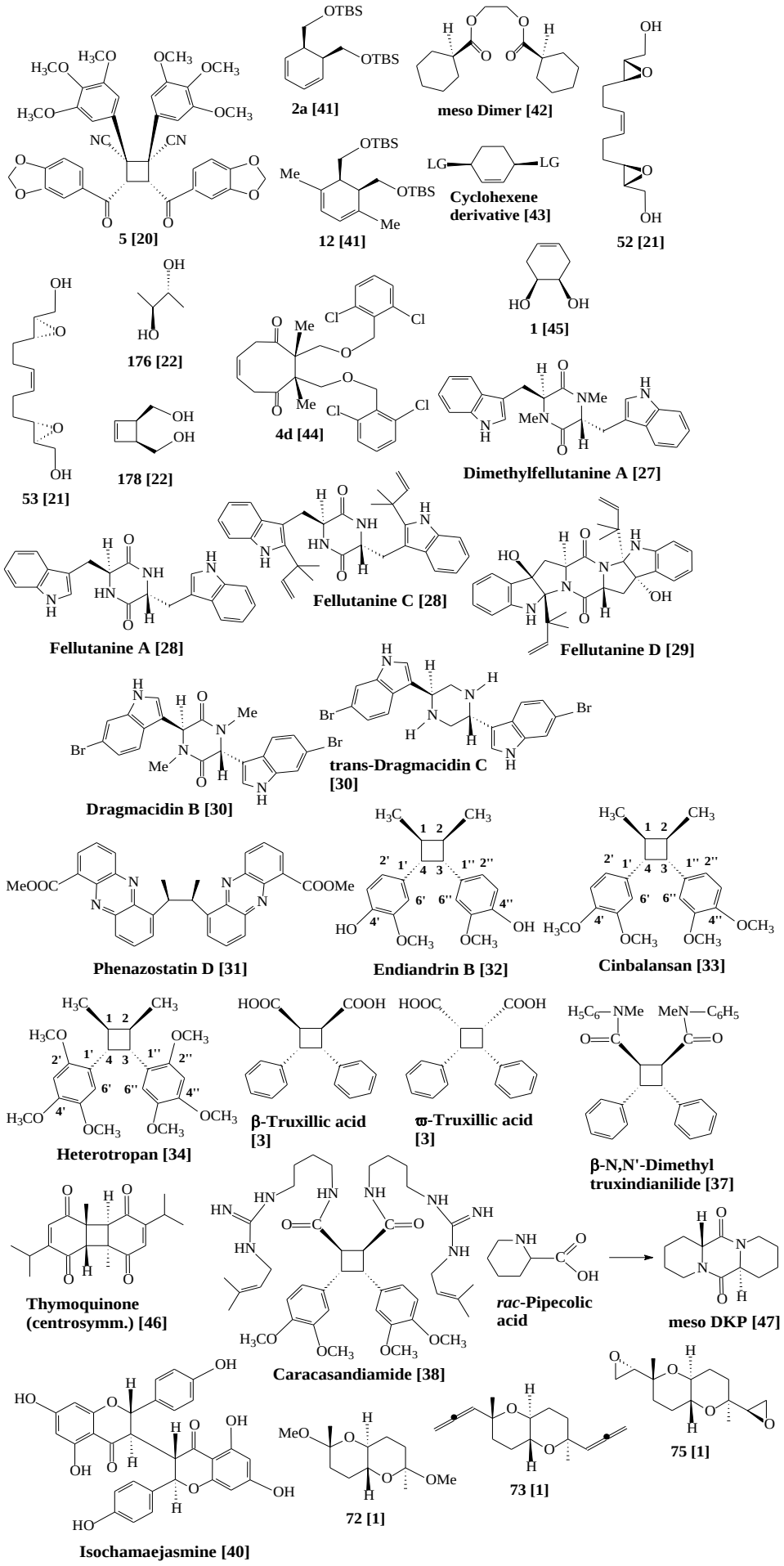

Figure 2. *meso* Homodimers liable to present chiral enantiomeric C_2 *symm*. isomers.

Imaginary dimerization of the (R)-half of tartaric acid would produce (R,R)-tartaric acid, while (S)-half would give (S,S)-tartaric acid. A similar procedure applied to galactitol would produce D- and L-iditol. Other triads in carbohydrate chemistry are erythritol, (R,R)-threitol, (S,S)-threitol; allitol, D-mannitol, L-mannitol, as well as their aldaric acids. L-Cys-D-Cys forms a triad with L-Cys-L-Cys and D-Cys-D-Cys, and numerous triads of 2,5-diketopiperazines are known. At least seven triads of carotenoids of the the type *meso*-zeaxanthin, (R,R)-zeaxanthin, (S,S)-zeaxanthin, have been found. Two triads of lignans are based on nordihydroguaiaretic and dihydroguaiaretic acids, and one of alkaloids includes *meso*-, (+)- and (–)-chimonanthine isomers. Diolmycin B2 is the C_2 *symm*. isomer of (2S,3R)-diolmycin B1 (phenols), and daibudilactone B of daibudilactone C (terpenoids) [4]. As can be noticed, all C_2 *symm*. isomers are optically active.

Exposure of the (Z)-isomer of 2-(3,4,5-trimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxo-2-butenonitrile (β-cyanochalcone) in the solid state to sunlight led by dimerization to a symmetrical Z-Z dimer. Exposure of the (E)-isomer (4E) to the same conditions determined an unusual dimerization and produced an unsymmetrical E-Z dimer [20]. The structure of both dimers was established by X-ray crystallographic analysis. This diversity indicate the possibility to produce also a C_2 *symm*. isomer. Synthesis of 52 and 53 *meso* diepoxy derivatives produced also two C_2 *symm.* isomers, 51 and 54 [21]. The two C_2 *symm.* isomers of *meso* isomer 176 [22] are known [23]. The configuration of chiral centers of 2,3-butanediols was correlated with the enantiomers of mannitol [24]. L,L-, L,D- And D,D-2,5-diketopiperazines of tryptophanes are known [25,26], and this opens the possibility for the synthesis of C_2 *symm*. isomers of dimethylfellutanine A [27], fellutanine A, fellutanine C [28], fellutanine D [29], dragmacidin B, trans-dragmacidin C [30]. An isomer of phenazostatin D, phenazostatin B, whose molecule is formed by dimerization of a half of phenazostatin D, is also known [31]. Structure comparison of *meso* cyclobutane derivatives endiandrin B, cinbalansan and heterotropan [32-34] indicate a metabolic relationship between them. On the other hand, endiandrin A corresponds to endiandrin B, di-O-methyl-endiandrin A to cinbalansan, and magnosalin to heterotropan, all as C_2 *symm.* isomers. Some of the isomeric truxillic and truxinic acids have to be treated as homodimers and others as heterodimers [3]. β-Truxinic and ω-truxillic have a plane of symmetry intersecting two bonds and their pairs C_2 *symm*. are δ- and μ-truxinic, respectively [35,36]. β-Truxinic acid is related also with β-N,N'-dimethyl truxindianilide [37] and caracasandiamide [38]. α-Truxillic acid is centrosymmetric [39]. γ-, epi-, ε- And peri-truxillic acids [3] have planes of symmetry intersecting atoms, hence their equivalent *meso* homodimer are (R,S)-tartaric acid or (R,S)-2,3-diphenylbutane. Both isochaejasmine (*meso*) and its isomer chaejasmine (C_2 *symm.*) have been discovered [40]. All the above mentioned C_2 *symm*. isomers are optically active.

There isn't any doubt to question the possibility to construct chiral C_2 *symm*. isomers of 2a and 12 [41], *meso* dimer [42], *meso* cyclohexene derivative [43], 4d [44], 1 [45], thymoquinone [46], *meso* DKP [47], and 72, 73, 75 [1] (Fig. 2).

(B) *meso* Heterodimers with a binding support of the >CR_2 form, accompanied by at least one C_2 *symmetrical* isomer

meso Compounds based on a binding support of the >CR_2 form allow the existence of chiral C_2 *symm*. isomers (Figs. 3 and 4), alhough they are not rigorously homodimers. E.g. all three asarolignans, as well as some of their isomers are known [48]. About 15 triads have been found especially among natural compounds: 2 carbohydrates, 2 amino acids, 5 lignans, 4 phenols, 2 polyols [4]. The things are also prepared for trehalose: since ent-glucose (L-glucose) has been synthesized [49,50], the following triad might be envisaged: trehalose (α-D-Glcp-1,1-α-D-Glcp), meso-trehalose (α-D-Glcp-1,1-α-L-Glcp), ent-trehalose (α-L-Glcp-1,1-α-L-Glcp). 3-Deoxyxylitol [51] or 3-deoxyribitol [52] with the two enantiomeric 3-deoxyarabinitols [53] should be added to carbohydrate list. L,D-Diaminopimelic acid and *meso* lanthionine are components of two triads of amino acids. 3,3'-Didemethoxynectandrin B, isonectandrin B, zuonin B and nectandrin B are *meso* isomers of lignans triads. Neolignans are represented by three asarolignans. Two *meso* hybocarpone, (3S,5R)-octahydrocurcumin and (3R,5S)-hannokinol are *meso* constituents of

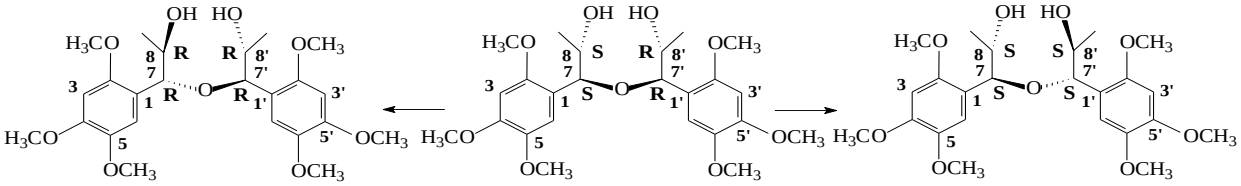

Figure 3. *meso* And *C₂ symm*. isomers of asarolignans neolignans [48].

phenols triads [4]. Where known, all *C₂ symm*. isomers are chiral.

Numerous heterodimers are known (Fig. 4) and their classification has been made:

(a) Of 3-deoxyxylitol or 3-deoxyribitol type: cis-1,2-dimethyl cyclopropane [54], 1 [55], 15-18 [21], L,D-Diaminopimelic acid [56], 20, 22-24 [1], 40a, 42a, 83a [22], 2e, 2f [57], 23 [45], 9 [58], 2 [59], cyclopentene derivative [43], eurorubrin [60], daibudilactone D [61].

(b) Similar to 3-deoxy-3-keto xylitol: 11 [62], 209a, 215b, 215c [22], cuscohygrine [63].

(c) Of *meso* 2,5-dimethyl tetrahydrofuran type [64]: 14, 16 [65], 2 [66], 83 [67], glabrescol, teurilene [68], 50, 54 [22].

(d) Similar to cis-2,3-dimethyl aziridine [69]: 36 [22].

(C) *meso* Heterodimers with a Binding Support Devoid of Symmetry (>CRR', etc.), Seeable as *meso*, and Provable in This Way not by Themselves but by their Equivalent *meso* Homodimers

Let's make the following theoretical experiment: the midle bond of erythritol [70] is broken and the two halves are linked on the >CHOH residue. It is obvious that xylitol or ribitol are produced, hence erythritol is the *meso* homodimer equivalent for both (Fig. 5). In this manner, by uniformly linking two enantiomeric halves to an arbitrary binding support, an unlimited number of compounds could be produced. The following derivatives of xylitol have been prepared: 1,5-anhydro-xylitol, 2,3,4-tri-O-acetyl-1,5-anhydroxylitol [71], 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol and 2,4-methylene-xylitol [72]. Schmidt and Lieberknecht [73] synthesized meso-2,5-anhydro-3,4-isopropylidene-allaric acid. The latter compounds showed that the binding support can be either unitary or in a fragmented state (Fig. 5). Many *meso* heterodimers are produced by indirect paths, either chemicaly or biochemically, hence all of them have to be investigated *per se*, and not historically. Moreover, there is no connexion between the structure of the two enantiomeric halves, on one hand, and the binding support (Figs. 5-8).

1. Rules for finding *meso* homodimers equivalent to non-provable *meso* heterodimers. A number of rules have been elaborated for removing the binding support of *meso* heterodimers and finding their equivalent *meso* homodimers (equivalent, not isomer!). Contrary to *meso* heterodimers, the *meso* equivalents are able to present at least one *C₂ symm*. isomer. As all rules, the beyond rules will be better understood from their applications. In chemical terms, removing of linking support of *meso* heterodimers resembles to a surgical operation of medicine, probably. Here are some rules:

a. When cut by the mirror plane of symmetry, an oxygen atom is equivalent with two hydroxy groups, a nitrogen atom with two amino, etc.

b. A carbon apex is equivalent with two methyl groups or it is simply removed.

c. Chiral atoms of *meso* heterodimers are carefully preserved in the obtained equivalent homodimers, by the analysis of their substituents.

If oxygen atom in cis-2,3-dimethyl-oxirane (Fig. 6) [74] is replaced by two hydroxy groups, (2R,3S)-butanediol is obtained. In cis-trimethyl-cyclopropane and trans-trimethyl-cyclo-propane [75], the apex intersected by the mirror plane of symmetry cannot be replaced by two methyl groups since the chirality of the other two cyclopropane groups is anihilated. Consequently, that apex would be replaced by two imaginary R residues. In triethyl trans-cyclopropane-tricarboxylate [76] and triethyl trans-1,2,3-tricyano-cyclopropane-tricarboxylate [77],

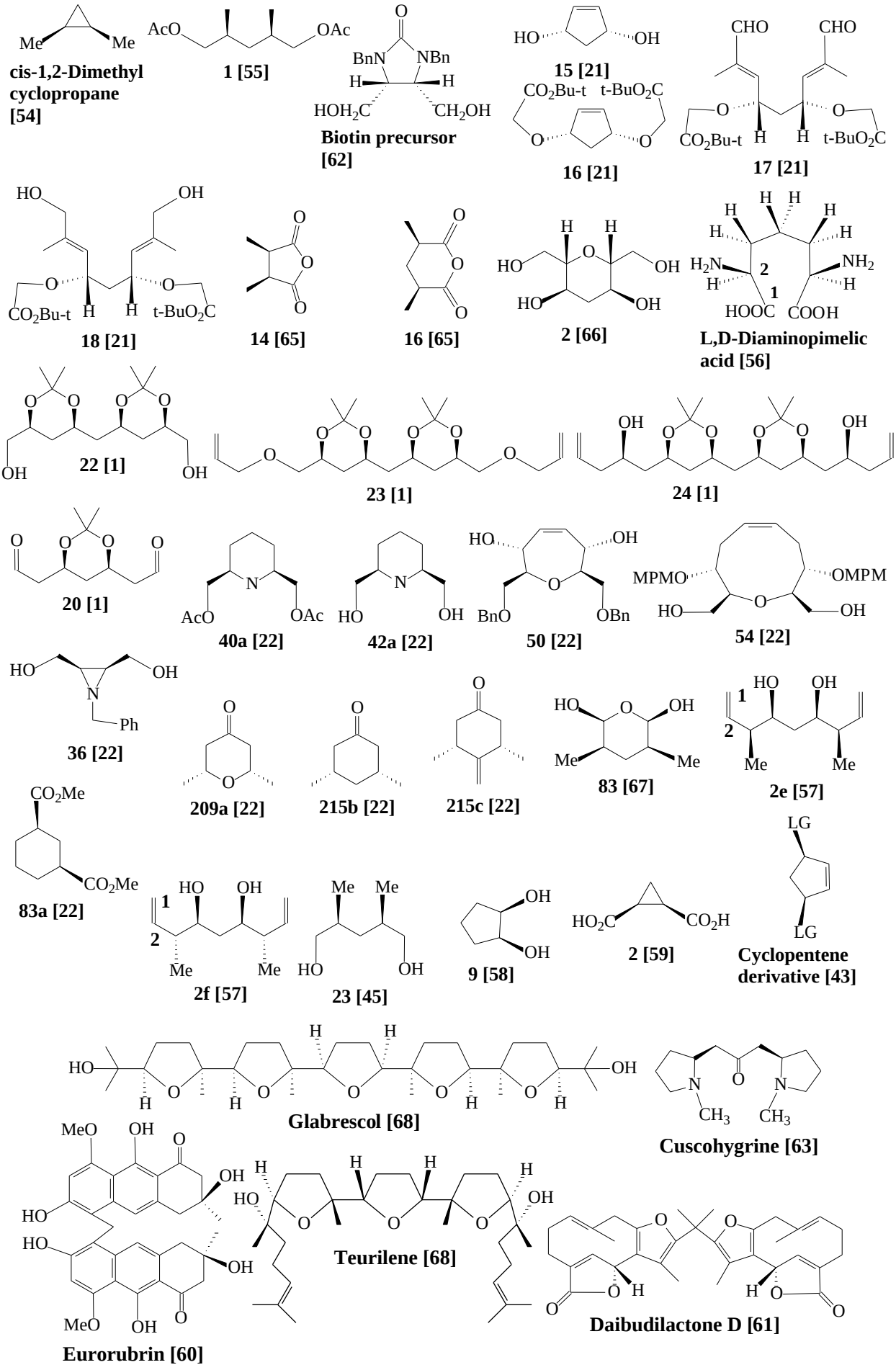

Figure 4. Heterodimers with symmetric binding support, able to form *C₂ symm*. isomers.

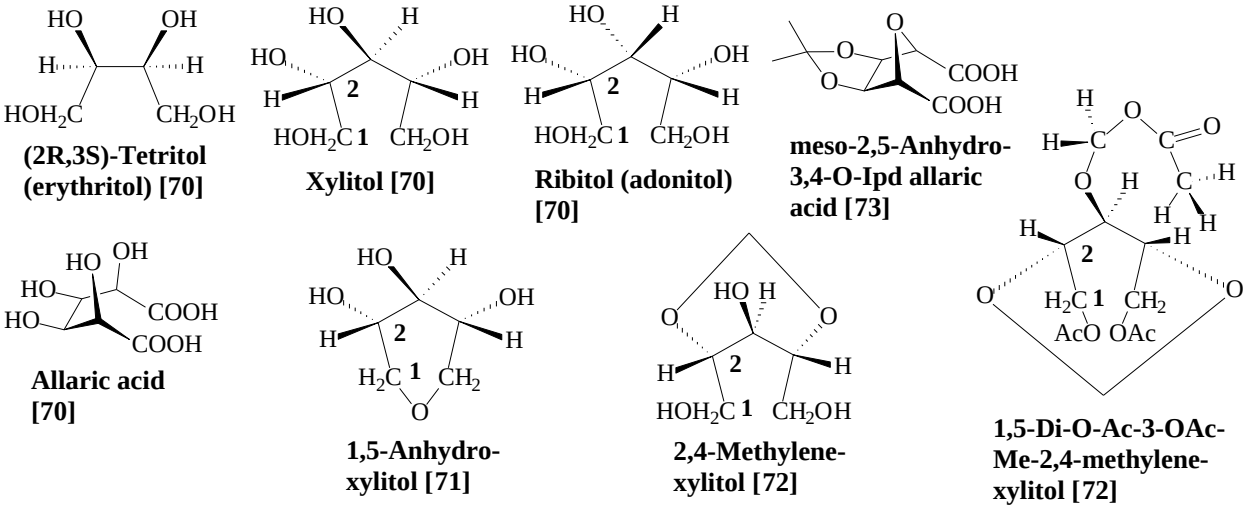

Figure 5. Binding support of *meso* heterodimers can be also in a fragmented state.

replacement of the suitable apex by two methyl groups would produce *meso* dimethyl- and *meso* dimethyl-dicyano-succinic acid, hence the chiral character of the two carbons is preserved.

Four isomers are possible for tetrasubstituted cyclobutane with the same substituent, and all four are known [8,78-79]. Two of them – cis,cis,cis-1,2,3,4-tetracarboxycyclobutane and cis,trans,cis-1,2,3,4-tetracarboxy-cyclobutane – have mirror plane of symmetry intersecting bonds only, hence they have to be considered *meso* homodimers. The other two, cis,trans,trans-1,2,3,4-tetracarboxy-cyclobutane and trans,trans,trans-1,2,3,4-tetracarboxy-cyclobutane have to be treated as *meso* heterodimers. The *meso* homodimer of the latter two is *meso* tartaric acid. cis,trans,cis-1,2,3,4-Tetracarboxy-cyclobutane is *meso* and concomitantly it is the C_2 *symm*. isomer of cis,cis,cis-1,2,3,4-tetracarboxycyclobutane. Of this reason, we suggest the term *super-symmetric* for cis,trans,cis-1,2,3,4-tetracarboxy-cyclobutane and for similar compounds.

Four isomers are known for pentahydroxy-cyclopentane, and all are *meso* heterodimers [80]. Two *meso* homodimer equivalents can be found to the four cyclopentanepentols, by removing the suitable apeces, and they are (1β,2β,3β,4β)-1,2,3,4-tetrahydroxy-cyclobutane (cis,cis,cis-1,2,3,4-tetracarboxycyclobutane) and (1β,2β,3α,4α)-1,2,3,4-tetrahydroxy-cyclobutane (cis,trans,cis-1,2,3,4-tetracarboxy-cyclobutane). The first cyclobutane derivative has to be considered *meso*, although it gives only one C_2 *symm*. product, by alternative dimerization of its enantiomeric halves. The second equivalent, (1β,2β,3α,4α)-1,2,3,4-tetrahydroxy-cyclobutane, is *super-symmetric*.

Nine inositols (hexahydroxycyclohexanes) are known [81,82], two are C_2 *symm*., chiral and enantiomeric, and seven devoid of optical activity. Of all the latter, only cis-inositol and muco-inositol can be treated as homodimeric *meso*. Alternative dimerization of the two enantiomeric halves of cis-inositol gives neo-inositol. The latter is a special molecule: it has a mirror plane of symmetry containing some atoms, hence it is a heterodimer. On the other hand, it has an axis of symmetry, and when rotated by 180° around this axis, the same structural context is found, that is a feature of C_2 *symm*. compounds. Of this reason neo-inositol (Fig. 6) has to be considered *super-symmetric*. When treated as *meso* heterodimer, and its linking support removed, neo-inositol gives another *super-symmetric* combination, i.e. (1β,2β,3α,4α)-1,2,3,4-tetrahydroxy-cyclobutane. epi-Inositol is a *meso* heterodimer and when its binding support removed, a *meso* homodimer, (1α,2α,3α,4α)-1,2,3,4-tetrahydroxy-cyclobutane, is obtained. The latter is *meso* since its isomer is *a super-symmetric* derivative, (1β,2β,3α,4α)-1,2,3,4-tetrahydroxy-cyclobutane. allo-Inositol is a homodimer with a mirror plane of symmetry. When its enantiomeric halves are alternatively dimerized, the symmetry is perturbed and two chiral, C_2 *symm*. enantiomers are produced, D-(+)-chiro- and L-(−)-chiro-inositol. allo Inositol is the only inositol isomer with a typical behavior of *meso* compound giving a triad. mio-Inositol is a *meso* heterodimer leading directly to (1β,2β,3α,4α)-1,2,3,4-tetrahydroxy-cyclobutane, while the latter is obtained from muco-inositol (*meso*) via scillitol, scillitol being also *super-symmetric*.

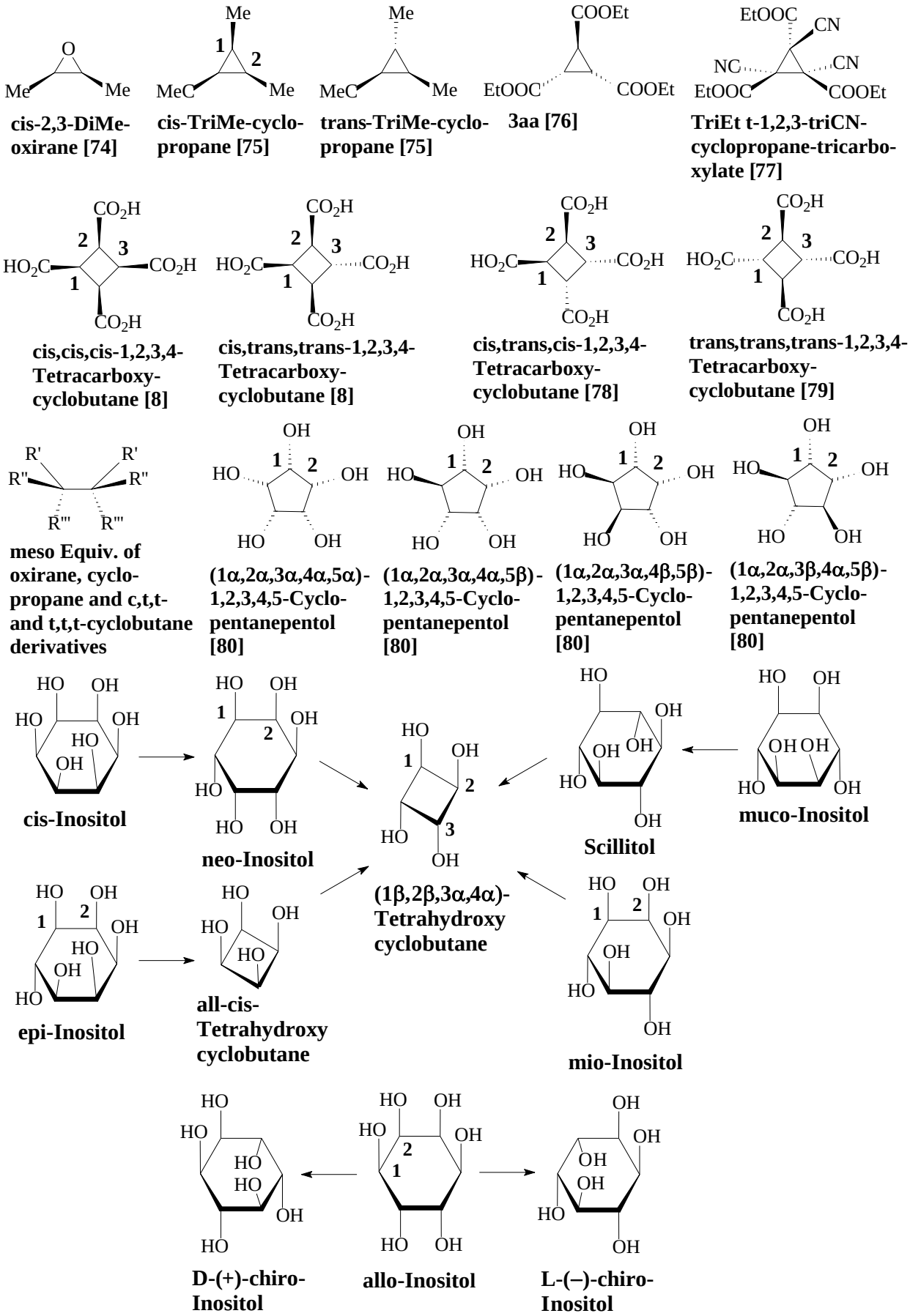

Figure 6. Illustration of finding of meso homodimer equivalents of meso heterodimers and of behavior of some homodimers.

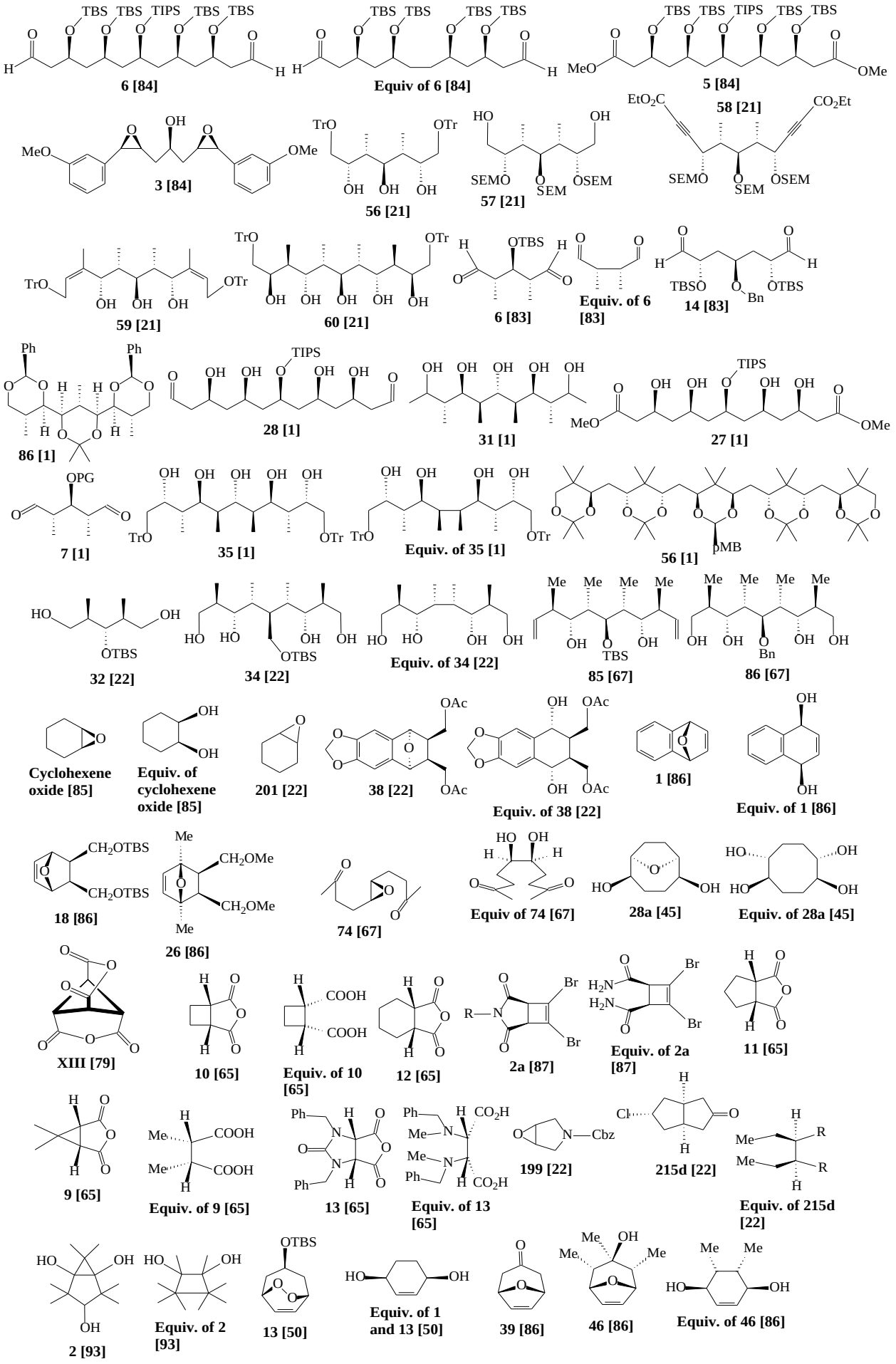

Figure 7. *meso* Homodimer equivalents of polyols, epoxy compounds and anhydrides.

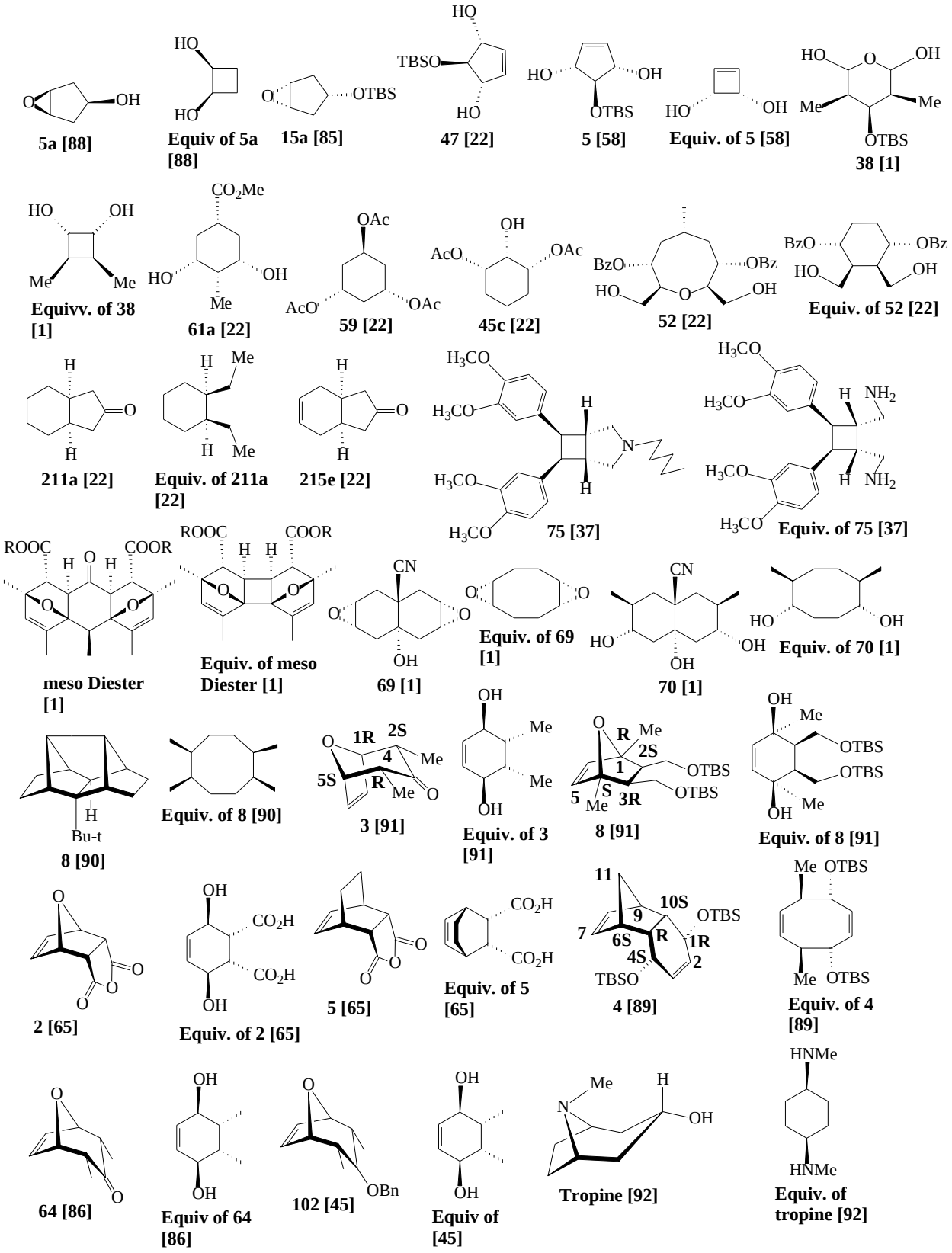

Figure 8. Finding of *meso* homodimer equivalents of cyclic *meso* heterodimers.

2. (C) *meso* Heterodimers with a Binding Support Devoid of Symmetry (>CRR', etc.). Compounds of different clases – linear (polyols), cyclic, bicyclic, etc., – have been approached (Figs. 7 and 8). Skipped polyols *per se* or intermingled with methyl or dimethyl groups have been synthesized since they are structural motifs of some natural compounds. Erythritol is not only a *meso* homodimer polyol for xylitol and ribitol as *meso* heterodimer polyols but also for 6

and 14 [83], 7 [1], 32 [22] etc. meso-Hexitol is homodimer for 3, 5, 6 [84], 56-59 [21], 27, 28 [1], etc. meso-Octitol is homodimer for 31, 86 [1], 34 [22], 85 and 86 [67], and meso-decitol for 60 [21], 35 and 56 [1], etc.

Epoxy group – in cyclohexene oxide [85], 201, 38 [22], 1, 18, 26 [86], 74 [67], 28a [45], XIII [79], 10, 12 [65], 2a [87] – is equivalent to two hydroxyls in homodimers. In all previous epoxy or anhydride compounds, the number of C atoms is the same in the equivalent *meso* homodimers. The *meso* homodimers of the next *meso* heterodimers would be found by elimination of the suitable apeces and linking of the adjacent atoms. For a series of *meso* heterodimers, their *meso* homodimer equivalents are indicated (Fig. 7). Others could be found according to the rules explicitly presented or tacitly included. Dianhydride XIII [79] has trans,trans,trans-1,2,3,4-tetracarboxy-cyclobutane as equivalent *meso* homodimer (Fig. 6). 11 [65] and 199 [22] has cis-1,2-dicarboxy-cyclobutane and cis-1,2-dihydroxy-cyclobutane, respectively. Both 13 [50] and 39 [86] have cis-3,6-cyclohexene-1 as *meso* homodimer equivalent, and 46, a similar equivalent.

Di- or tetrasubstituted cyclobutane or disubstituted cyclobutene are the *meso* homodimer for: 5a [88], 15a [85], *meso* diester [1], 47 [22], 5 [59], 38 [1], 61a, 59, 45c [22]. For a substituted ring of eight atoms, 52 [22]; and for bicycle structures 211a and 215e [22], *meso* homodimer is based on a cyclohexane or cyclohexene ring. N Atom of an bicyclic alkaloid 75 [37], has been transformed in two amino groups. *meso* Homodimer equivalents of trans decaline derivatives – 69 and 70 [1], 4 [89], and a highly pyramidalized alkane 8 [90], are based on cyclooctane or cyclooctadiene. *meso* Homodimer equivalents of numerous bicyclic compounds – 3 and 8 [91], 2 and 5 [65], 64 [86], 102 [45], tropine [92] – are based on cis-1,4-disubstituted cyclohexane or cyclohexene (Fig. 8).

Also to this group belongs some compounds with a symmetric binding support, that are characterized by a relatively low structural plasticity, due to a rigid linking between the *meso* homodimeric unit and their binding unit. These seeable *meso* heterodimers appear especially when two rings, both containing fewer atoms than six, forms bicyclic molecules. Although in relatively small number these molecules justify the existence of a distinct group. The quality of *meso* of the constituents of this group, although seeable, can be proved only by removing their linking support and then acting on their *meso* equivalent homodimer. Such molecules are: XIII [79], 2 [93], 9, 10, 11, 13 [65]; 2a [87], 199, 215d [22] (Fig. 7), 5a [88], 15a [85] (Fig. 8).

CONCLUSIONS

1. The two enantiomeric halves of *meso* compounds constitute the most important chemical duality. Of this reason these compounds constitute a(n) (unexploited) treasure for chemical duality, and it significantly reduces the huge advance of physics in comparison with chemistry as the choice and the most successful object of philosophy.
2. The relationship between two groups of diastereomeric isomers – *meso* and C_2 *symmetrical* – has been studied in detail and it disclosed a chemical paradox among inositols and a new distinct group of chemical combinations, the *super-symmetrical* ones.
3. The chemical paradox of inositols found in this paper, harmoniously complete the definition of *meso* compounds as an ensemble of two enantiomeric halves.
4. For the first time in chemical literature, probably, a systematization of *meso* compounds has been made.
5. The fundamental characteristic of a *meso* compound consists in its capacity to produce at least one C_2 *symmetrical* isomer, by alternative dimerization of its enantiomeric halves.

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