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TARTARIC ACID AND ITS *O*-ACYL DERIVATIVES. PART 1. SYNTHESIS OF TARTARIC ACID AND *O*-ACYL TARTARIC ACIDS AND ANHYDRIDES

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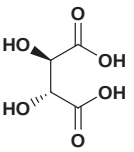
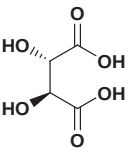
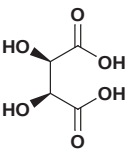
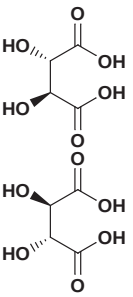
INTRODUCTION

Tartaric acid (**1**) and its derivatives and especially acyl derivatives, are very widely used in organic synthesis. In their monograph,[1] Gawroński and Gawrońska distinguish four types of applications a) resolution of racemic mixtures,[1-5] b) ligands (in chiral catalysts),[1,6,7] c) chiral auxiliaries,[1,7,8] and d) chiral tetracarbon building blocks.[1,5] In spite of the considerable practical importance of acyl derivatives of **1**, reports on the methods of their preparation are scattered and rather scarce. Many of them are very old, in difficult to access journals, and some are even erroneous. These are often patent information, short reports in Chemical Abstracts, or only notes in experimental sections. The present review collects and critically evaluates all available information on the preparation and production of acyltartaric anhydrides and acids, especially of dibenzoyltartaric acid up the year 2004.

Tartaric acid **1** occurs in four forms: a pair of optically active enantiomers (+) (**L-1**), (–) (**D-1**) and racemic mixture (***rac*-1**) as well as the symmetric form *meso* (***meso*-1**). Some physicochemical properties of tartaric acids are summarized in *Table 1*.[9]

L-Tartaric acid is a natural product occurring both in the free form as well as a salt in many fruits, especially grapes. It is produced as its calcium salt[10] from potassium hydrogen tartrate (cream of tartar) – a by-product of the wine industry. Hence Italian, French, Hungarian, Chinese and Japanese companies belong to the largest tartaric acid producers. Due to the considerable, continuously replenished sources and simplicity of preparation, it is one of the cheapest enantiomerically pure organic compounds available. It is also less expensive than the other enantiomers obtained synthetically. If the catalog price for 100g of acid **L-1** is set as 1, the price of racemic acid is 3, of **D-1** 20, and of ***meso*-1** 270.[11] Although examples on biotechnological

Table 1. mps, Specific Rotation and Solubility of Tartaric Acids[9a]

Common Name	Systematic Name [CAS No.]	Structure	mp. (°C)	$[\alpha]_D^{20}$	Solubility in H_2O[a] 20°C	100°C
L-Tartaric Acid[b] (**L-1**)	(*2R*,*3R*)-2,3-dihydroxy-butane-1,4-dioic acid [87-69-4]		168-170	+12.0[c]	139	343
D-Tartaric Acid[b] (**D-1**)	(*2S*,*3S*)-2,3-dihydroxy-butane-1,4-dioic acid [147-71-7]		168-170	–12.0[c]	139	343
meso-Tartaric Acid (***meso*-1**)	(*2R*,*3S*)-2,3-dihydroxy-butane-1,4-dioic acid [147-73-9]		140[d]	0	125	----
D,L-Tartaric Acid[e] (***rac*-1**)	Dihydroxy-butane-1,4-dioic acid [133-37-9]		206	0	20.6	185

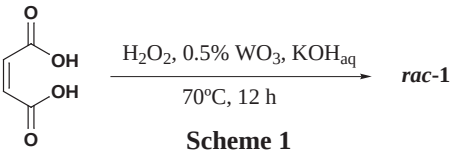
a) Grams in 100 mL of water; b) Solubility in other solvents: good in *iso*butanol (4.6%[9b]), dioxane,[40] ethanol (41.1%,[9c] 32.5%,[9d] 21.6%[9e]), furfural (10.9%[9f]), glycerol,[9a] methanol,[9g] propanol;[9a] poor in HOAc (1.4%[9b]), diethyl ether (0.31%[9h]); insoluble in chloroform,[9a] dichloroethane,[9i] trichloroethane[9i]; c) 20% in water; d) As monohydrate; e) Solubility in other solvents: HOAc (0.11%[9b]), *iso*butanol (0.37%[9b]), diethyl ether (1.08%[9c]), ethanol (2.08%,[9c] 3.15%[9j]).

methods to obtain **L-1** are given in a monograph,[12] they do not appear to be of any practical importance. **L-1** has been obtained from the fermentation of panthothenic acid or its salt with *Gluconobacter suboxydans*,[13] from *cis*-epoxysuccinic acid (obtained chemically from maleic acid) or its salts as a result of asymmetric hydrolysis in the presence of *Acinetobacter, Agrobacterium, Rhizobium, Pseudomonas*,[14] *Nocardia tartaricans* (or *cis-epoxysuccinate hydroxylase* obtained from *N. Tartaricans*)[15] or biocatalyst, e.g. *Achromobacter tartarogenes* immobilized on a polymer, *e. g.* polyacrylamide.[16]

Although the acid **D-1** is mainly obtained synthetically by separation from the racemic

acid (***rac*-1**) with diastereomeric salts with amines, it also occurs in small quantities in the fruit and leaves of the African plant *Bauchinia reticulata* D. C.[17] Among other amines used, cinchonidine (12%),[18] (*2S*)-2-[2-(*1'S*)-(1'-methyl-1'-phenyl-*p*-chlorobenzyloxy)ethyl]-1-methylpyrrolidine (48%),[19] metamphetamine (76-79%)[20,21] or 2-[L-gluco-L-gulo-heptohexahydroxyhexyl]benzimidazole (96,5%)[22] were used for the resolution.

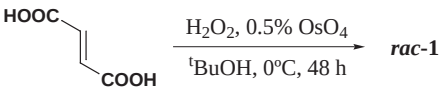
The ***rac*-1** acid can be obtained by several methods. The catalytic hydroxylation of maleic acid is of the greatest practical importance.[23] The best results were obtained when maleic acid was oxidized with an excess of hydrogen peroxide (1.5:1 mol/mol) in the presence of 0.5% of the tungsten catalysts, in an aqueous medium (70∞C, 12 h). After cooling, very pure ***rac*-1** acid crystallized directly from the post-reaction mixture in 80% yield. The filtrate containing mainly unreacted maleic acid, catalyst, and also dissolved ***rac*-1** acid was recycled for subsequent syntheses (*Scheme 1*).



Scheme 1

The racemization of natural **L-1** acid in a strongly alkaline medium was the previously used method to obtain the ***rac*-1** acid.[18,24-37] Many variants of this process have been described, such as changing the excess of the base (3-13 equivalents per equivalent of ***rac*-1**),[33,35] concentration of acid **1** (12-88%),[24,27] temperature (100-176∞C),[24,35] reaction time (4 hrs-one week),[33,35] types of salt used for the resolution of tartrates (Na, Ba, Ca),[18,32,35] and finally by crystallization of the racemic sodium hydrogen tartrate (after partial neutralization) and thus purifying it from the less soluble *meso* derivative.[18] Despite the simple chemistry, the process is technologically complicated and does not proceed in high yields. The concurrent formation of the ***meso*-1** acid during racemization and the prolonged and arduous crystallization of both sodium and calcium salts of **1** and the tendency of the latter ones often used for the resolution of the ***rac*-1** acid, to form super-saturated solutions, may be the two basic reasons for the low yields.[33]

The oxidation of fumaric acid is another method to obtain the ***rac*-1** acid. Potassium perman-ganate was initially used as the oxidant;[25,26] sodium chlorate (55% *rac*-sodium tartrate)[29] or hydrogen peroxide in the presence of a catalytic amount of osmium tetraoxide (99.5% *rac*-potassium tartrate),[30] (48% *rac*-calcium tartrate) have also been used (*Scheme 2*).[34]

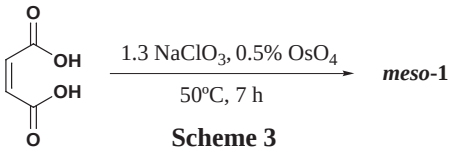


Scheme 2

The ***meso*-1** acid is formed as a by-product during the racemization of **L-1** (17%),[35] whereas it is obtained mainly by the oxidation of maleic acid. Potassium permanganate was

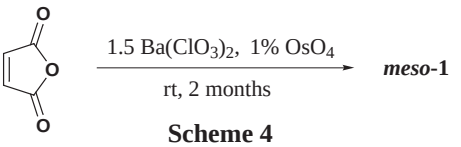
initially used as the oxidant,[25,26] and later sodium chlorate in the presence of a catalytic amount of osmium tetraoxide (72% *meso*-calcium tartrate) has been utilized.[29] *meso*-Potassium tartrate was obtained directly after the reaction, and then *meso*-calcium tartrate was precipitated with calcium chloride.

Milas and Terry reported the highest yield of the ***meso*-1** salt (98% of *meso*-sodium tartrate) as a result of maleic acid oxidation with sodium chlorate in the presence of OsO_4 carrying out the process for 7 h at 50∞C (*Scheme 3*).[30]



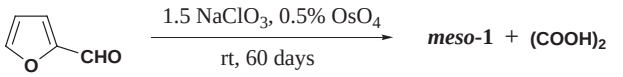
Scheme 3

However, somewhat later Milas and Sussman obtained the ***meso*-1** acid in only 30% yield when hydrogen peroxide was used instead of sodium chlorate.[34] Braun obtained the ***meso*-1** acid exclusively when maleic anhydride was oxidized with barium chlorate at room temperature over a period of two months (91% of *meso* barium tartrate) (*Scheme 4*).[32]



Scheme 4

The preparation of ***meso*-1** from maleic acid by bromination and hydrolysis[38] or from furfural by oxidation with sodium chlorate in dilute hydrochloric acid in the presence of a catalytic amount of osmium tetraoxide, are of lesser importance. After the addition of calcium chloride, the product was isolated in the form of *meso* calcium tartrate (49%), and the oxalic acid formed as by-product remained in solution (*Scheme 5*).[31]



Scheme 5

The anhydride of **1** could not be isolated and characterized, probably due to the facile polymerization resulting from the presence of free hydroxyl groups; its formation is postulated, however, as a reactive intermediate.[39,40] The report in Chemical Abstracts[41] of the existence of acid **1** anhydride is an error, since this compound is not mentioned in the referenced paper. Similarly, Peynaud,[42] cited in a monograph,[1] postulates the formation of an intermolecular ester (lactide), and not of the anhydride of **1**, despite the fact that she calls it an anhydride.

O-Acylation is a simple and economical method to protect the hydroxy groups of acid **1**. The acyl group can be readily removed by hydrolysis or basic methanolysis; *O*-acetyl groups are particularly easy to deprotect. *O*-Acylation increases the acidity of the neighboring carboxy

group.[1,5] *O,O'*-Diacyl acids and their anhydrides, in particular diacetyl or dibenzoyl derivatives, are the most often used. Recently, monoacyltartaric acids have gained increasing importance.

I. *O,O'*-Diacyltartaric Acid Anhydrides

Diacyltartaric acid anhydrides (**2**) are stable compounds (*Fig. 1*, *Table 2*), which are most often used for the resolution of racemic alcohols "*via* esters" (also including the kinetic method),[43-47] or of amines "*via* amides".[44,46,48-51] They are important intermediates for the preparation of the corresponding acids. They can be obtained by esterification of the hydroxy groups with acid anhydrides or acid chlorides.[2,40,45,52-89] The methods described differ in the type of the acylating agent used, solvent (toluene, xylene, dioxane, acetone, hexane), reaction conditions, types of crystallization system, mode of precipitation and maceration as well as removal of side-products. Economic aspects and the properties of the carboxylic acid formed as a by-product (if it is volatile, as in the case of acetic acid, then an acid anhydride as the acylating agent would be used, and a solvent is not necessary) are major factors in the choice of the method used. Due to the corrosive nature of the medium, resulting from the presence of mineral and carboxylic acids, and the possibility of metal complexation by tartaric acid, the apparatus used must be made of glass, enamel or special steel.

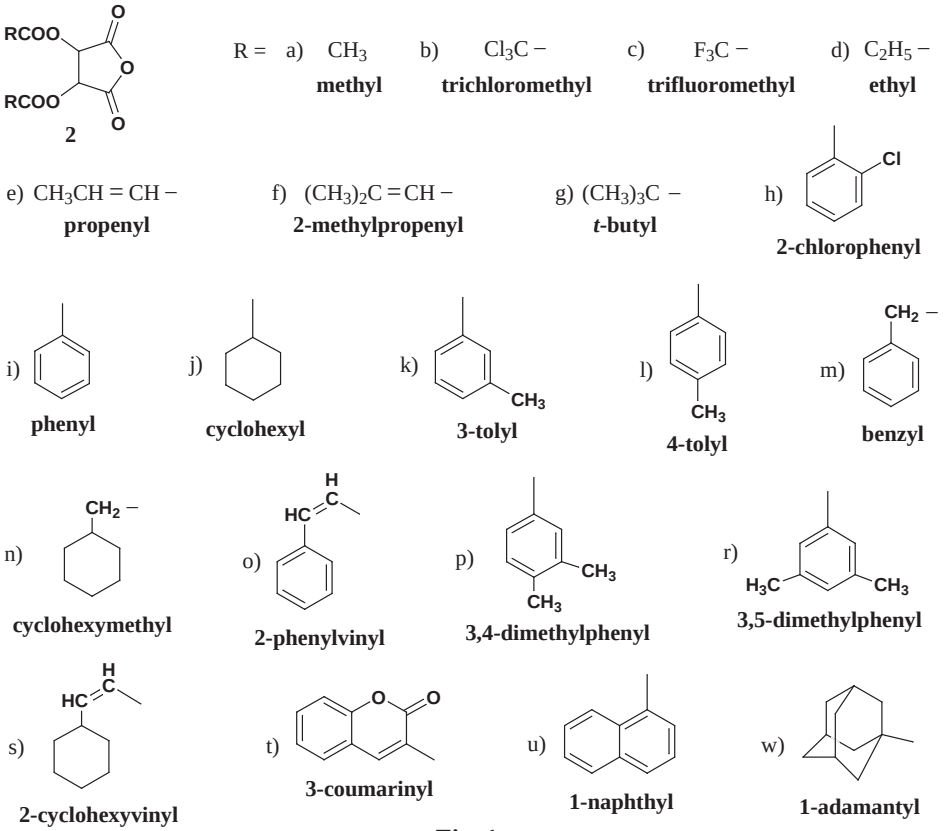
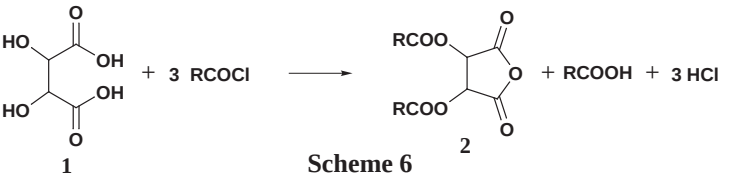


Fig. 1

*a) By Acylation-Dehydration with Acid Chlorides (Method **A**)*

This method has been known since 1880, when Anschütz and Pictet obtained diacetyl-**L**-tartaric (**L-2a**) diacetyl-**D,L**-tartaric (***rac*-2a**) and dibenzoyl-**L**-taratric (**L-2i**) anhydrides by treatiment of **L-1** or ***rac*-1** with acid chlorides.[52] Since that time, this original method was used routinely and, only during the last decade of the 20th century, have considerable modifications been made to it (*Scheme 6, Fig. 1, Table 2*).[1,2,40,45,52,54,56-61,63,65-69,71,74,75,79-83,87,88]



1 **2**

Scheme 6

The necessity of using 3 equivalents of the acid chloride as the acylating agent for **1** stems from the fact that 2 moles are used for the *O*-acylation of two hydroxy groups, and 1 mole for formation of the anhydride. One equivalent of the corresponding carboxylic acid is formed as a by-product and 3 equivalents of hydrogen chloride evolve.

The acylation is usually carried out at 120-170∞C, without solvent, using 3-3.5 equivalents of the chloride per 1 equivalent of **1**. The carboxylic acid formed as a by-product and unreacted acyl chloride were extracted into aromatic solvents. In this fashion, a number anhydrides have been obtained (*Fig. 1, Table 2*). The basic disadvantage of this procedure is that the reaction mixture becomes thick, solidifies quickly and is difficult to remove from the reaction vessel; then the side-product must be extracted from the mixture and the anhydride purified.

The procedure to prepare the **L-2l** anhydride was modified by Kidd[2] by the introduction of xylene to the reaction system. The use of a solvent allowed the reaction to be performed at a lower temperature and prevented solidification of the mixture. Purification of the product also became much easier, since the monocarboxylic acids formed as by-products are more soluble in aromatic solvents than the corresponding anhydrides **2**.

Since 1983, reactions to obtain anhydrides **2** have been prepared in the presence of catalysts such as iron oxide,[81] mineral acids (sulfuric, hydrochloric, nitric, phosphoric), organic acids (*p*-toluenesulfonic, acetic),[82] and Lewis acids ($AlCl_3$,[83] $FeCl_3$,[75,83] $ZnCl_2$,[83] $BF_3 \bullet Et_2O$[83]). The syntheses were carried out in various solvents (acetone, hexane and chloroform,[82] toluene and xylene,[83] and dioxane[81]), the best yields being achieved in toluene. The application of catalysts improved the safety of the process (the reaction starts at a lower temperature, and thus is less violent) and favorably affected the yields obtained. Contamination of the product is a side-effect of using catalysts which are insoluble in the reaction system; this is especially obvious in the formation of color when $FeCl_3$ was used. The use of mineral acids, provided the highest yields (>90%) and $BF_3 \bullet Et_2O$ does not cause coloration of the product. The contamination with the catalyst is especially important in the case when anhydride **2** is the desired final product, and not an intermediate for the preparation of the corresponding acid.

*b) By Acylation-Dehydration with Acid Anhydrides (Method **B**)*

Acylation with acid anhydrides is performed mainly to prepare diacetyl-[45,52,53,55,60,62,64,70-73,76-78,84-86,89] dipropionyl-[62] and trihaloacetyltartaric anhydrides (*Table 2*).[40] It is necessary to use 3 equivalents of the anhydride per 1 equivalent of acid **1**, 2 equivalents being used for the *O*-acylation of the two hydroxy groups of acid **1**, and one for cyclization to the anhydride **2** (*Scheme 7*).

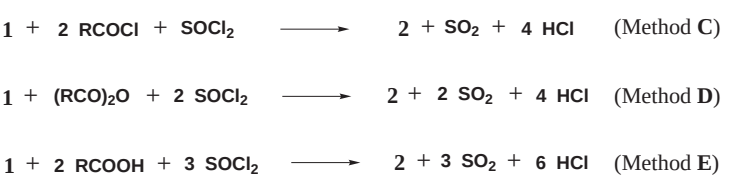
Scheme 7

The syntheses were most often carried out without a solvent, taking advantage of the fact that both the anhydrides used for acylation as well as the acids formed as by-products are liquids; there is only one report of the reaction being performed in a solvent (dioxane)[40] in which tartaric acid is very soluble and the tartaric anhydrides are not and thus easily precipitate readily. Sulfuric acid,[53,55,62,64,70,71,78,84-86] phosphoric acid[62] or hydrogen chloride[60] were used as catalysts. Benzene, toluene, ethanol, diethyl ether were used for the crystallization of anhydrides.

The ease of purification of the product in the case of acids of low boiling point is a great advantage of this method which was applied for the first time by Wohl and Oesterlin to obtain anhydride (**L-2a**).[53] The highest yield (95%) in this procedure was achieved when 3.5 equivalents of acetic anhydride containing 3% of hydrogen chloride was used and the reaction was performed at 60∞C for 20 h[60] or when 3.5 equivalents of the anhydride and sulfuric acid as catalysts were used at 120∞C with concurrent gentle distillation of the acetic acid generated.[55,85]

*c) By Reaction with Thionyl Chloride (Methods **C-E**)*

The principal observation of the newest methods to synthesize these anhydrides is the fact that the inclusion of agents such as thionyl chloride, phosphorus pentachloride or trichloride, may cause chlorination of monocarboxylic acids (by-products) only, but not of both the carboxy groups and the secondary hydroxy groups of acid **1**; therefore, it is not the source of by-products.[83] Thus carboxylic acid formed as a by-product during acylation of **1** with an acid anhydride or chloride, is converted *in situ* to an acid chloride. Moreover, the carboxylic acid **1** alone can be applied for the acylation of **1**, as a precursor of the acylating agent, which is the acid chloride (*Scheme 8*).



Scheme 8

The application of a chlorinating agent allowed the amount of the acid chloride (from over 3 to 2.0-2.4) or anhydride (from over 3.0 to 1-1.2) equivalents per equivalent of acid **1** to be decreased. The reactions were carried out in aromatic hydrocarbons, with toluene being the best, at 40-200ºC, without catalysts or in the presence of a catalytic amount of $AlCl_3$, $FeCl_3$, $ZnCl_2$ or BF_3•Et_2O. It was stressed that the conversion of the carboxylic acid formed as a by-product to acid chloride, proceeds already below 110ºC.

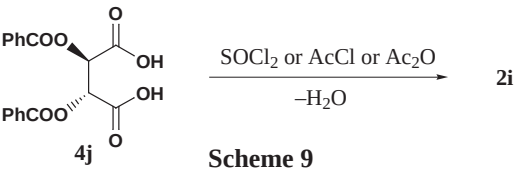
For the reaction with carboxylic acids, the use of 2.2 equivalents of a corresponding acid and 3.5 equivalents of $SOCl_2$ per equivalent of **1** is favored. The reaction with aromatic carboxylic acids has been carried out in the presence of $AlCl_3$, $FeCl_3$, $ZnCl_2$ or BF_3 as catalysts, for 1-3 h at temperatures as high as 170°C.

The more efficient use of acylating agents is one great advantage of the method described, and is especially important in the case of expensive acid chlorides or anhydrides because it allows the use of carboxylic acid instead of the corresponding chloride or anhydride for the acylation of acid **1**, as the cheapest and more commonly available source of acyl groups.

Thionyl chloride has been used most often, since it produces sulfur dioxide and hydrogen chloride as gaseous by-products, which are easily removable from the reaction medium, thus making product purification easier;however, on a technical scale it is necessary to have available the means for the separation and absorption of these gases and their utilization. The use of thionyl chloride requires great caution, since it is an extremely toxic compound which reacts very vigorously with water.

*d) By Dehydration of O,O'-Diacyltartaric Acids (Method **F**)*

Anhydrides **2** may be obtained from corresponding O,O'-diacylacids **4** through dehydration by means of such agents as thionyl chloride,[60,63] acetyl chloride (in benzene)[46] or acetic anhydride[90] (*Scheme 9, Fig.1, Table 2*). This method found application only for anhydride **2i** since acid **4j** is easily accessible and inexpensive.



4j

Scheme 9

II. *O*-Acyltartaric Acids

Monoacyltartaric acids (**3**) are not as commonly used as their disubstituted counterparts. However, they are acquiring increasing importance because of the important role, *e. g.* as a chiral ligand in borate complexes (CAB-Chiral Acylborane) used in asymmetric Diels-Alder reactions,[6,91-94] hetero Diels-Alder reactions,[95,96] aldol condensations[97-101] and the allylation of

Table 2. Preparation and Properties of O,O'-Diacyltartaric Acid Anhydrides

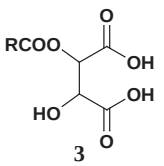
Cmpd	Conf.[a]	Yield (%)	Method[b]	mp. (ºC)	$[\alpha]^{20}_{D}$	References
2a	D	93	**A**	133-135	–89.3[c]	80[d,e]
2a	L	76[73]	**B**	128-129[73]	----	52, 73[e]
2a	L	95[85]	**B**[f]	133-134[70]	+97.2[c,70]	53, 55, 60, 62, 64, 70, 71, 72[d], 76[d], 77, 78[d,e], 84[d], 85, 86[e], 89
2a	D	----	**B**[f]	133-134	–97.0[c]	84[d]
2a	*rac*	----	**B**[f]	122-123	0	52
2a	L	63	**E**	132-134	-	83
2a	L	86	**D**	132-134	-	83
2b	L	85	**B**	176-177	+64.6[g]	40[d]
2c	L	89	**B**	54-55	+40,4[c]	40[d]
2d	L	----	**B**[f]	----	----	62
2e	L	54	**A**	76-77	----	68
2e	D	----	**A**	75-76	----	68
2f	L	91	**A**	106	----	68
2f	D	86	**A**	79-99	----	68
2g	L	79	**A**	167	+76[g]	74[d,e]
2h	L	54	**C**	----	----	83
2h	D	91	**C**[f]	----	----	83
2h	L	54	**E**	165-169	----	83[d,e]
2h	D	91	**E**[f]	----	----	83
2i	L	94[82]	**A**[f]	----	----	81, 82, 83
2i	L	80[79]	**A**	195-196[82]	+153[h,71]	52, 56, 58, 60, 71, 79[e], 83
2i	D	68	**A**	194-196	-161[h]	66
2i	*rac*	-	**A**	182[57]	0	57, 59
2i	*meso*	75	A	141-144	0	63
2i	L	91	**C**[f]	----	----	75, 83
2i	L	80[83]	C	----	----	83[d,e]
2i	L	81	**E**[f]	----	----	83[d,e]
2i	D	92	**E**[f]	----	----	83
2i	L	93	**D**[f]	----	----	83
2i	L	-	**F**	192-195[88]	196[c,88]	60, 90[d,e]
2i	*meso*	76[63]	**F**	139-142[63]	0	46[e], 63
2j	L	80	**A**	139.5-141	+35[i]	69
2k	L	76	**C**	----	----	83
2k	L	76	**E**	142-147	----	83[d,e]

Table 2. Continued...

Cmpd	Conf.[a]	Yield (%)	Method[b]	mp. (ºC)	$[\alpha]^{20}_D$	References
2l	L	76[61]	**A**	204-205[2]	+195[h,61]	2, 61
2l	D	84[87]	**A**	199.5-200.5[87]	–195[h,61]	61, 87
2l	*rac*	----	**A**	162-163	0	67
2l	L	91	**C**	----	----	83
2l	*rac*	80	**C**	----	----	83
2l	L	92	**C**[f]	----	----	83
2l	D	91	**C**[f]	----	----	83
2l	L	90	**E**	204-205	----	83[d,e]
2l	*rac*	80	**E**	----	----	83
2l	D	92	**E**[f]	----	----	83
2m	L	80	**A**	115.5-116	+53[i]	69
2n	L	93	**A**	111-112.5	+40[i]	69
2o	L	----	**A**	146-148	+291[h]	1
2o	D	----	**A**	158-159	–274[h]	54
2p	D	90	**C**[f]	----	----	83
2p	D	90	**E**	180-182	----	83
2p	D	90	**E**[f]	----	----	83
2r	L	60	**A**	----	----	88[d]
2s	L	58	**A**	106-107	+66[i]	69
2t	L	68	**A**	122-125	----	68
2t	D	----	**A**	----	----	68
2u	D	80	**A**	174	----	65
2w	L	70	**A**	220	+34.8[i]	74[d,e]

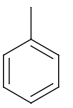
a) Configuration; b) In text; c) In chloroform; d) NMR data; e) IR data; f) With catalyst; g) In benzene; h) In acetone; i) In dioxane.

aldehydes.[102,103] The utilization of these complexes allowed to achieve high reaction stereoselectivity and yields. Acids **3** may be obtained by three methods (*Fig. 2*, *Table 3*).

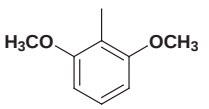


3

R = a) CH_3 – **methyl** b) $(CH_3)_3C$ – ***t*-butyl** c)

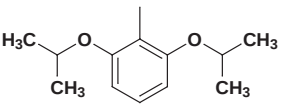


d)



2,6-dimethoxyphenyl

e)

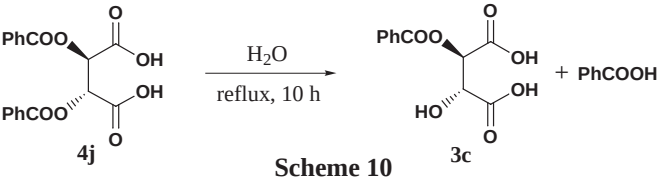


2,6-diisopropoxyphenyl

Fig. 2

*a) Partial Hydrolysis of O,O'-Diacyltartaric Acids (Method **A**)*

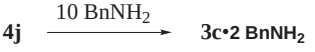
Langenbeck described the selective hydrolysis of dibenzoyltartaric acid (**4j**) in boiling water for 10 h (45%).[104] After filtration of the unreacted **4j** and of benzoic acid formed as a by-product, water was distilled off and the residue was crystallized from a benzene/ethanol (4:1) mixture. The authors of this review achieved a much lower yield (10%) when performing this reaction, since multiple crystallizations were required to obtain a pure product (*Scheme 10*).[ref]



Scheme 10

*b) Partial Aminolysis of O,O'-Diacyltartaric Acids (Method **B**)*

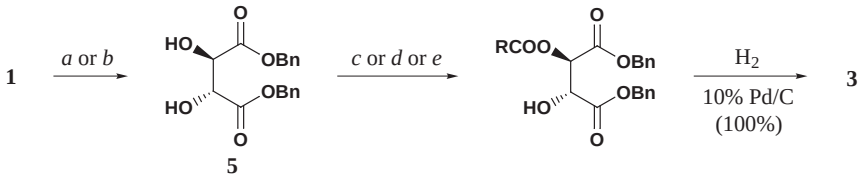
Bell obtained acid **3c** in the reaction of acid **4j** at low temperature, with a large excess of benzylamine.[105] The product was isolated in the form of the double benzylamine salt of **3c**. The advantage of this method is the fact that the double salt formed is insoluble in the reaction system and thus there is no possibility of aminolysis of the second benzoyl group. On the other hand, a disadvantage is the necessity of using a very large excess of the amine (yield 88%) (*Scheme 11*).



Scheme 11

*c) Hydrogenolysis of Dibenzyl O-Acyltartrates (Method **C**)*

Monoacetyl- (**3a**) and monopivaloyl- (**3b**),[6] monobenzoyl- (**3c**) and mono(2,6-dimethoxy-benzoyl)- (**3d**)[6,93,94,100] and mono(2,6-diisopropoxybenzoyl)tartaric (**3e**)[92,96,97,99,100,103] acids were obtained from dibenzyl tartrate (**5**), after it was converted into a monoacyl derivative. The dibenzyl monoacyltartrate thus obtained was hydrogenolysed on palladium to afford acid **3**. (*Scheme 12, Fig. 2, Table 3*)



a: BnBr, DBU, DMF, (94%).[100]
b: BnOH, TsOH, toluene 130ºC, 13 h.[93]
c: RCOOH, $(CF_3COO)_2O$, benzene or CH_2Cl_2, rt, 30-60 min, (65%).[92,94,96,99,103]
d: RCOOH, DCC, DMAP, CH_2Cl_2, rt, 48 h, (86%).[100]
e: RCOCl, Et_3N, DMAP, CH_2Cl_2, 0ºC-reflux, 12-18 h, (78-82%).[6,93,97]

Scheme 12

Table 3. Preparation and Properties O-Monoacyltartaric Acids

Cmpd	Conf.[a]	Yield[b] (%)	Method[c]	mp. (°C)	$[\alpha]_D^{20}$	References
3a	L	----	C	----	----	6
3b	L	-	**C**	----	----	6
3c	L	45	**A**	202-203	-4.4[d]	104
3c	L	88[e]	**B**	155-156[e]	----	105[f]
3c	*meso*	-	**B**	149-150[e]	----	105[f]
3c	L	70	**C**	211-212	-5.76[g]	100[f,h]
3c	-	----	**C**	----	----	6
3d	L	62	**C**	178-181	–75.1[d]	94[f,h]
3d	D	62	**C**	173-176	+72.2[d]	94[f,h]
3d	L	86	**C**	187-188	–69.2[g]	100[f,h]
3d	L	75[93]	**C**	184-186[93]	–73[d,93]	6, 93[f,h]
3e	L	65[92]	**C**	81[92]	–28.5[d,92]	92[f,h], 96[f,h], 99[f,h], 103[f,h]
3e	L	74	**C**	----	–23.6[d]	100[f,h]
3e	----	----	**C**	----	----	97

a) Configuration; b) for method **C** yield was count over for **1**; c) In text; d) In ethanol; e) As disalt with benzylamine; f) NMR data; g) In methanol; h) IR data.

III. *O,O'*-Diacyltartaric acids

The oldest use of diacyltartaric acids (**4**) for the resolution of racemic mixtures of compounds of basic character (amines,[2-5,106,107] aminoacids[5,108,109] by "diastereomeric salts" or racemic alcohols "by esters"[5,110]) is still their present application.

A two-stage synthesis is the main method of obtaining acids **4**. In the first step, the corresponding anhydride **2** is prepared and then it is hydrolyzed to the desired acid. The acylation of the second hydroxy group and cyclization proceed concurrently, and therefore the application in the reaction of only 2 equivalents of acid chloride does not lead to acid **4**, but to a mixture of mono- and diacylated acids as well as corresponding anhydrides **2**, from which the isolation of acid **4** is economically unjustified. Fortunately, the anhydride and ester bonds of diacyltartaric anhydrides **2** differ substantially in their tendency toward hydrolysis, the anhydride bond being much easier than the ester; thus under appropriate conditions it is possible to open the anhydride ring without or negligible cleavage of acyloxy groups. Diacetyltartaric acid (**4a**),[89,111] dibenzoyltartaric acid (**4j**),[56-59,63,66,75,83,104,112-114] ditoluoyltartaric acid (**4m**),[2,61,67,75,83,87] dipivaloyltartaric acid (**4g**),[74,113] chicoric acid (**4s**)[115,116] and several others mentioned in *Table 4* (*Fig. 3*) have been obtained in this way.[1,54,65,68,69,74,83,113,116-123]

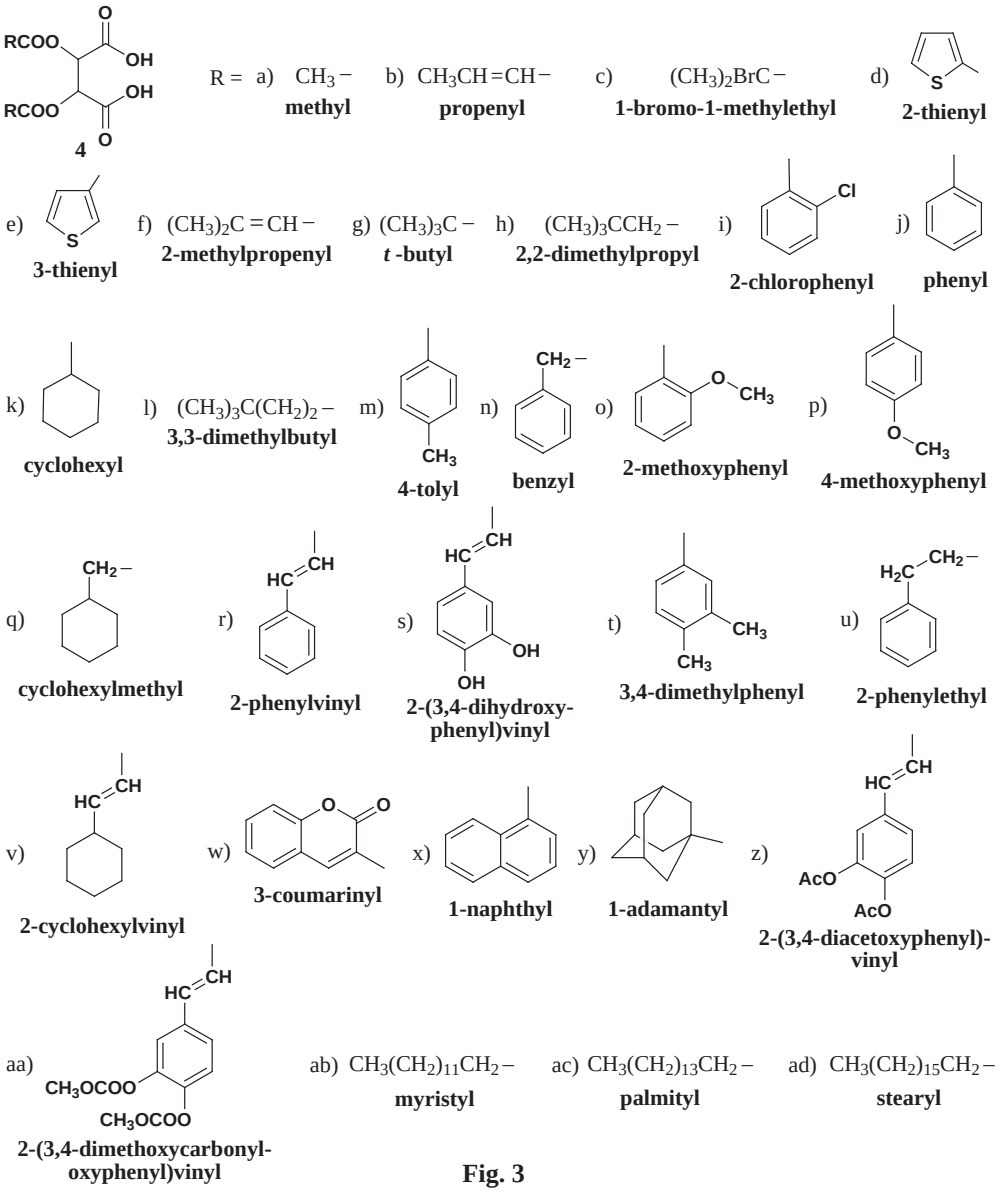
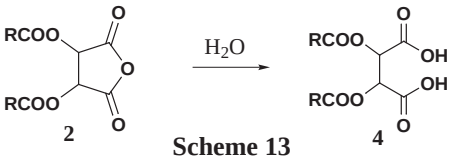


Fig. 3

*a) Hydrolysis of O,O'-Diacyltartaric Acid Anhydrides (Method **A**)*

The hydrolysis of anhydrides **2** has been carried out in an acetone and water mixture,[74,87] or in water, most often at the boiling point of the reaction mixture in 0.5-1 h,[83] without or with the addition of a solvent immiscible with water,[83,112] which prevented agglomeration of acid **4** during crystallization (*Scheme 13*). Benzene, toluene, xylene and chlorobenzene have been used as solvents.[83] Mezei *et al.*[112] carried out the hydrolysis of anhydride **D-2i** to the

corresponding acid in a mixture of dichloromethane and a small amount of water, under the pressure of 0.15-0.5 MPa (87%).



Scheme 13

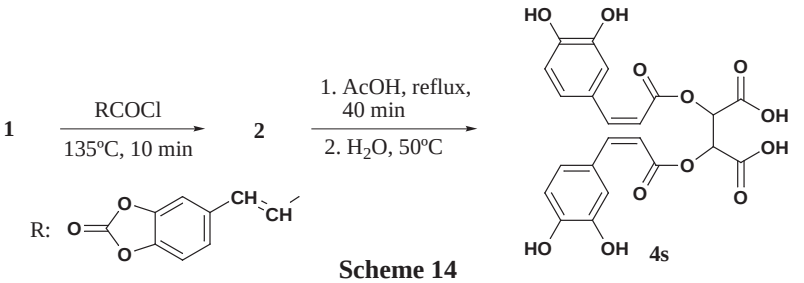
In a majority of cases, the acids obtained or their monohydrates formed an oily phase, immiscible with water and easily overcooled, which makes crystallization difficult; the yield after crystallization are >90%. On the basis of our own experience,[ref.] it can be stated that heating the anhydride in water at boiling point without solvent, is the best way of carrying out the hydrolysis. An organic solvent causes a decrease in the yield and may additionally cause problems with waste water treatment.

b) Hydrolysis without Anhydride Isolation after Acylation

The preparation of acids **4** by direct reaction of acid chlorides with acid **1** in a 2:1 ratio has rarely been applied. Rabe[119] carried out the reaction of anisoyl chloride with **L-1** (2:1, 120ºC, 2 h), followed by the hydrolysis with water at boiling point without isolation of anhydride **2**. Drying over sulfuric acid, isolation of anisic acid by crystallization from acetone, and boiling five-time with benzene was necessary to isolate pure dianisoyltartaric acid **4p** from the mixture of products. The yield was not given, but it was probably not high. According to a Hungarian patent,[75] acid **4j** can be obtained using 2 equivalents of benzoyl chloride per equivalent of acid **1** in the presence of $AlCl_3$ as catalyst; however, this patent raises doubts.

Scarpati and Oriente[115] obtained all the isomers of chicoric acid **4s** from the reaction of carbonylcaffeic acid chloride with **1** in a ratio of 1.8 of the chloride to **1** (such a small amount of the acid chloride was used probably due to its high cost). Acid **4s** and its analogs are utilized in studies of the HIV integrase inhibitors. It was found that the enantiomer of natural acid **4s** inhibits the HIV integrase in the extracellural enzyme synthesis and increases the immune defense of cells towards the possibility of HIV virus infection.

Carbonylcaffeic acid chloride was heated with tartaric acid under reduced pressure at 115-135ºC for 10 min (*Scheme 14*). After cooling, the resulting white solid was separated and

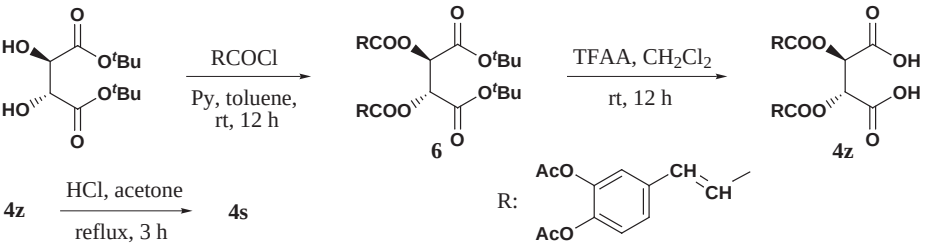


Scheme 14

heated with 80% acetic acid till complete dissolution. The solution was evaporated, and the residue (anhydride, acid **4s**, unreacted acid **1** and caffeic acid) was heated with water at 50ºC. The mixture was filtered, and the filtrate was extracted twice with ether. After evaporation of ether, the residue was dissolved in warm water and barium acetate was added, which caused precipitation of the acid **4s** as its barium salt. The salt was acidified with HCl and acid **4s** was extracted into ether. The acid obtained after evaporation of ether was crystallized from water. Such a way of obtaining acid **4s** is very laborious and moreover, the product is obtained in poor yield (35%). A further disadvantage is the use of diethyl ether and harmful (?) barium salt for the purification of the product.

*c) Synthesis via Tartaric Acid Esters (Method **B**)*

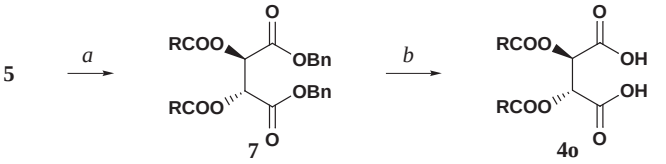
Zhao and Burke[116] obtained enantiomers of acid **4s** and indirectly tetraacetyl-**L**-chicoric acid (**4z**) in a three-stage process starting from 3,4-diacetylcaffeoyl chloride and di-*t*-butyl tartrate at 2.5:1 mol ratio (*Scheme 15*). Acylation of the tartrate has been carried out in the presence of pyridine in toluene (rt, 12 h). After removal of pyridine and of toluene, the residue was



Scheme 15

passed through silica gel (EtOAc-hexane 1:1) then crystallized from EtOAc-hexane to give ester **6** as a white solid (97%). In the second step, the *t*-butyl groups were removed with trifluoroacetic acid in dichloromethane (rt, 12 h) to afford acid **4z** (96%). The same acid was similarly obtained by Reinke *et al*.[120] starting from tartrate **5**; in the last stage, the acetyl groups were hydrolyzed with 3 M hydrochloric acid, in acetone (reflux, 3 h). After some work-up, evaporation of the solvent and crystallization from water, acid **4s** was obtained (90%), with respect to di-*t*-butyl tartrate (84%). High yields, elimination of the use of ether and of barium salts are advantages of this method. Despite the fact that it is a three-stage process, it is simpler than the method used by Scarpati and Oriente.

Tohma *et al*. [121] similarly obtained *bis*(2-methoxybenzoyl)tartaric acid (**4o**) from tartrate **5** and *o*-anisic acid. In the first step, upon the action of trifluoroacetic acid ester **7** is formed, which undergoes hydrogenolysis on palladium to **4o** (*Scheme 16*).

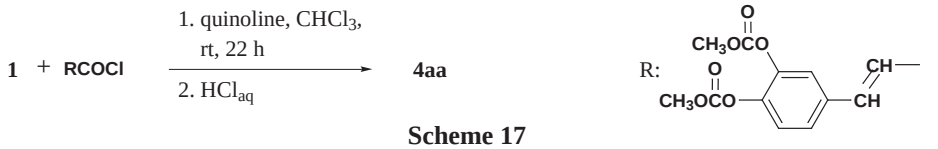


a) $MeOC_6H_4COOH$, $(CF_3CO)_2O$, benzene, rt, 1 h; *b)* H_2, Pd, AcOEt, 0.3 MPa, rt, 2 h

Scheme 16

*d) Synthesis via Tartaric Acid Salts (Method **C**)*

Kolodyńska and Wieniawski[122] performed the acylation of the quinoline salt of acid **1**. Dried acid **1** (100ºC, *vac*.), the acid chloride and quinoline were stirred in chloroform at room temperature for 22 h. The mixture was then acidified with 6% hydrochloric acid and the organic layer was washed with water, dried and evaporated to give the product **4aa** (25%) which was recrystallized from methanol (*Scheme 17*).



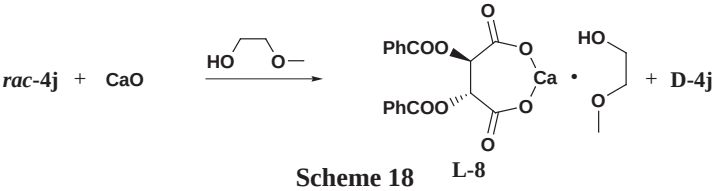
Scheme 17

Using the same method, but with pyridine instead of quinoline, Kunitake and Okahata,[123] obtained dimyristoyltartaric acid (**4ab**).

*e) Resolution of Racemic O,O'-Diacyltartaric Acids (Method **D**)*

This method is rarely used and may be of practical importance only to obtain of diacyl derivatives of acid **D-1**. Acid **D-4m** resulted from the resolution of acid ***rac*-4m** by means of cinchonine by the formation of diastereomeric salts.[67]

The enantio-separation of ***rac*-4j** is possible in a simple two-step crystallization procedure. In fact, a complex of the neutral calcium O,O'-dibenzoyl tartrate with two molecules of 2-methoxyethanol, which exists as a conglomerate, is the key compound. This salt crystallizes readily (crystallization is practically complete within 15-20 min.) in contrast to the hydrated salt, which crystallizes slowly and can be handled only with difficulty. Acid ***rac*-4j** obtained from the hydrolysis of anhydride ***rac*-2i**, was dissolved in a mixture of ethanol, water, methoxyethanol and calcium oxide. After seeding with crystals of **L-8** complex at 35-45ºC and cooling to 0ºC (15-20 min.), crystals of **L-8** precipitated (*Scheme 18*).



Scheme 18

Another portion of 2-methoxyethanol as well as ***rac*-4j** calcium oxide were then added to the mother liquor and the whole was seeded this time with complex **D-8** to afford crystals of **D-8** respectively. The procedure was repeated five times. The combined fractions of particular complexes were hydrolyzed with hydrochloric acid. The corresponding crystals of acids **L-4j** and **D-4j** (overall yields 80% and 81%, respectively) precipitated from the aqueous solutions.[114]

Table 4. Preparation and Properties O,O'-Diacyltartaric Acids

Cmpd	Conf.[a]	Yield (%)	Method[b]	mp. (ºC)	$[a]^{20}_{D}$	References
4a	L	----	**A**	118[89]	–24.6[c,89]	89, 111
4b	L	----	**A**	74-76	–58[d]	68
4b	D	----	**A**	73-75	+56.5[d]	68
4c	D	----	**A**	----	–3.95[e]	113
4d	L	97	**A**[f]	186-187	----	120[g]
4e	L	95	**A**[f]	194-195	----	120[g]
4f	L	61[h]	**A**	131-132	–61.5[c]	68
4f	D	66[h]	**A**	132-134	+63.7[c]	68
4g	L	98[74]	**A**	135[74]	–24.2[e,74]	74[g,i], 113
4h	L	----	**A**	----	–21.1[e]	113
4i	L	94[j]	**A**	----	----	83
4j	L	93[58]	A	88-90[j,56] 138-140[56]	–116[j,l,56] –118.5[l,56]	56, 58, 75[k], 104, 113
4j	*rac*	----	**A**	112-113[j,57] 112.5-114 and 169-172[j,114]	0	57, 59,114
4j	D	93[83]	**A**	88-90[j,66] 138-139[66]	+114[l,66]	66, 83, 112
4j	*meso*	----	**A**	208-212	0	63
4j	L	93	**D**	88-89.5[j]	–112[m]	114
4j	D	94	D	88-89[j]	+112[m]	114
4k	L	61[69]	**A**	65-68[69]	–29[e,69]	69, 113
4l	L	----	**A**	----	–24.4[e]	113
4m	L	96[j,83]	A	172[j,61]	–140[l,61]	2, 61, 75, 83
4m	D	79[87]	**A**	171-172[87]	+141[l,87]	61, 87
4m	*rac*	75	**A**	188	0	67
4m	D	----	**D**	168	+140[l]	67
4n	L	80[69]	**A**	133-135[69]	–31[e,69]	69, 113
4o	L	100	**B**	187	–115.3[c]	121
4p	L	----	**A**	186	–162.8[l]	119

Table 4. Continued...

Cmpd	Conf.[a]	Yield (%)	Method[b]	mp. (ºC)	$[a]^{20}_{D}$	References
4q	L	83	**A**	125.5-126	–26[e]	69
4r	L	----	**A**	166-167[54]	–207.4[e,113]	1, 54, 113
4s	L	----	**A**	206	–384.2[m]	115
4s	D	----	**A**	206	+384.6[m]	115
4s	*rac*	----	[n]	206	0	115
4s	*meso*	----	**A**	225	0	115
4s	L	90	**B**	204-206	-333[m]	116[g]
4s	D	----	**B**	204-206	+340[m]	116[g]
4t	L	96	**A**	----	----	83
4u	D	----	**A**	----	–25.5	113
4v	L	100	**A**	82-85	–54[e]	69
4w	L	72	**A**	195-196	+150[e]	68
4w	D	----	**A**	195-196	–151[e]	68
4x	D	100	**A**	189-199[j]	-89[c/d]	65
4y	L	96[74]	**A**	273[74] decomp.	–26.1[e,74]	74[g,i], 113
4z	L	98[120]	**B**	200-202[120] 186-188[116]	–159[m,116]	116[g], 120[g]
4aa	L	25	**C**	150-152	----	122
4ab	*rac*	----	**C**	49-50	0	123
4ac	L	----	**A**	----	----	117
4ad	L	----	**A**	28-30[118]	----	117, 118

a) Configuration; b) In text; c) In acetone; d) In water; e) In dioxane; f) Hydrolysis with 80% AcOH; g) NMR data; h) After twice crystallization with benzene; i) IR data; j) As hydrate; k) After acylation of **1** hydrolysis of **2** without isolation; l) In ethanol; m) In methanol; n) Mixing enantiomers and crystallization.

IV. Summary

Methods of preparation and basic physical properties of isomers of acid **1** as well as of anhydrides **2** and acyl acids **3** and **4** have been presented. The compounds obtained have been tabulated according to their molecular formula.

The natural acid (+) **L-1**, formed as a by-product of wine production, is one of the cheapest chiral products of two asymmetric centers. Acid (-) **D-1** became also a valuable product of industrial importance, due to the discovery of a simple and efficient method to obtain ***rac*-1** by catalytic oxidation of maleic acid in the presence of WO_3 and effective resolution of the racemate into both diastereoisomers. Methods to prepare ***meso*-1** are not very efficient and it is the most expensive compound and is of only laboratory importance.

Anhydrides **2** are obtained mainly from acid **1** and acid chlorides ,or less often from acid anhydrides. The addition of a chlorinating agent, *e. g.* $SOCl_2$, is one of the most important modifications of the process, because of the resulting considerable decrease in the consumption of the acylating agent achieved.

The acylation of dibenzyl tartrate followed by catalytic debenzylation with hydrogen in the presence of palladium is the basic method of obtaining acids **3**.

The most important method of obtaining acids **4** consists in the hydrolysis of corresponding anhydrides; however, the synthesis "*via* esters" or "*via* salts" with amines, especially in the case of complicated and expensive substituents, is also of importance.

Acid **1** and its diacyl derivatives **2** and **4** are most often used for the resolution of racemic mixtures of amines, alcohols and compounds of a basic character. Monoacyl acids **3** are gaining increasing importance fulfilling an important role, *e. g.* as a selective chiral ligand in borate complexes used in asymmetric Diels-Alder reactions, aldol condensations or allylation of aldehydes. The application of chicoric acid **4s** and its derivatives in studies of the HIV virus inhibitors is also interesting.

In summary, although tartaric acid **1** and its derivatives **2**-**4** have been known for over 150 years, they are still very attractive compounds which enjoy wide applications in organic chemistry and technology.

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REFERENCES

1. J. Gawroński and K. Gawrońska, *"Tartaric and Malic Acids in Synthesis"*, J. Wiley & Sons, New York, NY, 1999.

2. D. A. A. Kidd, *J. Chem. Soc.*, 4675 (**1961**).

3. M. Ács, W. Fogassy, and F. Faigl, *Tetrahedron*, **41**, 2465 (1985).

4. K. Nemak, M. Ács, Z. M. Jaszay, D. Kozma and E. Fogassy, *Tetrahedron*, **52**, 1637 (1996).

5. A. K. Ghosh, E. S. Koltun and G. Bilcer, *Synthesis*, **9**, 1281 (2001).

6. K. Furuta, Y. Miwa, K. Iwanaga and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 6254 (1988).

7. H. U. Blaser, *Chem. Rev.*, **92**, 935 (1992).

8. M. Yatagi and T. Ohnuki, *J. Chem. Soc. Perkin Trans. 1*, 1826 (**1990**).

9. a) *Merck Index*, 13th edn., Merck & Co., Inc.: New Jersey, (**2001**); b) T. Rosenberg, *Acta*

Chem. Scand., **2**, 748 (1948); c) J. M. Albahary, *C. R. Hebd. Seances Acad. Sci.*, **144**, 1232 (1907); d) H. Schiff, *Justus Liebigs Ann. Chem.*, **113**, 189 (1860); e) N. Gregg-Wilson and R. Wright, *J. Chem. Soc.*, 3112 (**1928)**; f) F. Trimble, *Ind. Eng. Chem.*, **33**, 661 (1941); g) L. Synoradzki and P. Ruśkowski, Unpublished data; h) J. Timmermans and M. Dumont, *Bull. Soc. Chim. Belges*, **40**, 694 (1931); i) D. H. Wester, *Chem. Zentralbl.*, **86(I)**, 248 (1915); j) A. Findlay and A. N. Campbell, *J. Chem. Soc.*, 1769 (**1928**).

10. I. Dabul, *US Patent 3114770*, 1963; *Chem. Abstr.*, **60**, P11901c.

11. Catalogue: *Scientific Research Fluka and Riedel-de Haën, 2003-2004 International*.

12. P. Präve, U. Faust, W. Sittig and D. A. Sukatsch, *"Fundamentals of Biotechnology"*, VCH Verlagsgesellschaft, Weinheim, 1987.

13. Y. Minota, T. Kodama, U. Kotera and K. Yamada, *JP Patent 7233154*, 1972, *Chem. Abstr.*, **77**, 138350k.

14. Y. Kamatani, H. Okazaki, K. Imai, N. Fujita, Y. Yamazaki and K. Ogino, *GO Patent 2605311*, 1976, *Chem. Abstr.*, **86**, 105953s.

15. Y. Miura, K. Yutani, H. Takesue, K. Fujii and Y. Izumi, *GO Patent 2605921*, 1976; *Chem. Abstr.*, **86**, 70103k.

16. Y. Kawabata and S. Ichikura, *JP Patent 77102496*, 1977, *Chem. Abstr.*, **87**, 199200q.

17. J. Rabaté and A. Gourevitch, *J. Pharm. Chim.*, **28**, 386 (1938).

18. E. G. Kellett, *J. Soc. Chem. Ind.*, 204 (**1932**).

19. M. Umiński, L. Synoradzki, B. Filipiak, Z. Czarnocki and M. Panasiewicz, *PL Patent 166042*, 1991; *Chem. Abstr.*, **125**, 300469q.

20. E. Walton, *J. Soc. Chem. Ind.*, **64**, 219 (1945).

21. D. Kozma, G. Pokol and M. Ács, *J. Chem. Soc. Perkin Trans. 2*, 435 (**1992**).

22. W. T. Haskins and C. S. Hudson, *J. Am. Chem. Soc.*, **61**, 1266 (1939).

23. J. M. Church and R. Blumberg, *Ind. Eng. Chem.*, **43**, 1780 (1951).

24. M. E. Jungfleisch, *Compt. Rend.*, **75**, 439 (1872).

25. S. Tanatar, *Ber.*, **12**, 2293 (1879).

26. A. Kekule and R. Anschütz, *Ber.*, **13**, 2150 (1880).

27. G. Meissner, *Ber.*, **30**, 1574 (1897).

28. A. F. Holleman, *Rec. Trav. Chim.Pays-Bas*, **17**, 66 (1898).

29. K. A. Hofmann, O. Ehrhart and O. Schneider, *Ber.*, **46**, 1657 (1913).

30. N. Milas and E. M. Terry, *J. Am. Chem. Soc*., **47**, 1412 (1925).

31. N. Milas, *J. Am. Chem. Soc*., **49**, 2005 (1927).

32. G. Braun, *J. Am. Chem. Soc*., **51**, 228 (1929).

33. A. N. Campbell, L. Slotin and S. A. Johnston, *J. Am. Chem. Soc*., **55**, 2604 (1933).

34. N. Milas and S. Sussman, *J. Am. Chem. Soc*., **58**, 1302 (1936).

35. A. F. Holleman, *Org. Synth. Coll. Vol. I*, 497 (**1941**).

36. F. S. Head, *J. Chem. Soc*., 1136 (**1948**).

37. J. C. Bailar, H. B. Jonassen and A. D. Gott, *J. Am. Chem. Soc*., **74**, 3131 (1952).

38. W. Lossen, *Justus Liebigs Ann. Chem.*, **300**, 24 (1898).

39. T. Higuchi, H. Uno and I. Shimada, *J. Pharm Sci.*, **54**, 302 (1965).

40. G. P. Liesen and C. N. Sukenik *J. Org. Chem.*, **52**, 455 (1987).

41. V. N. Pankratova, T. F. Goreva and Yu. N. Krasnov, *Khim. Elementoorg. Soedin.*, **6**, 20 (1978); *Chem. Abstr.*, **91**, 221691g.

42. E. Peynaud, *Bull. Soc. Chim. Fr.*, 574 **(1961**).

43. R. Beutel and M. Tishler, *J. Am. Chem. Soc*., **9**, 1463 (1946).

44. K. H. Bell, *Australian J. Chem.*, **32**, 2625 (1979).

45. K. H. Bell, *Australian J. Chem.*, **34**, 671 (1981).

46. K. H. Bell, *Australian J. Chem.*, **40**, 399 (1987).

47. E. Várkonyi-Schlovicskó, K. Takács and I. Hermecz, *J. Heterocyclic Chem.*, **34**, 1065 (1997).

48. P. Kafarski, B. Lejczak and J. Szewczyk, *Can. J. Chem.*, **61**, 2425 (1983).

49. B. Lejczak, P. Kafarski, M. Soroka and P. Mastalerz, *Synthesis*, 577 (**1984**).

50. D. A. Miljkovic, N. Sharaf El Din and K. M. Gasi, *J. Serb. Chem. Soc.*, **50**, 277 (1985); *Chem. Abstr.*, **109**, 72978.

51. A. Abiko, W. M. Davis and S. Masamune, *Tetrahedron Asymm.*, **6**, 1295 (1995).

52. R. Anschütz and A. Pictet, *Ber.*, **13**, 1175 (1880).

53. A. Wohl and C. Oesterlin, *Ber.*, **34**, 1139 (1901).

54. E. Erlenmeyer and G. Higendorff, *Biochem. Z.*, **77**, 55 (1916).

55. F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, **123**, 663 (1923).

56. F. Zetzsche and M. Hubacher, *Helv. Chim. Acta*, **9**, 291 (1926).

57. P. Brigl and H. Grüner, *Ber.*, **65**, 641 (1932).

58. C. L. Butler and L. H. Cretcher, *J. Am. Chem. Soc.*, **55**, 2605 (1933).

59. N. A. Soerensen, J. Stene and E. Samuelsen, *Justus Liebigs Ann. Chem.*, **543**, 132 (1940).

60. H. J. Lucas and W. Baumgarten, *J. Am. Chem. Soc.*, **63**, 1653 (1941).

61. A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922 (1943).

62. C. F. Fuchs, *US Patent 2520139*, 1950; *Chem. Abstr.*, **44**, 10733i, *Brit. Patent 674710*, 1952; *Chem. Abstr.*, **47**, 4904c.

63. R. K. Ness H. G. Fletcher and C. S. Hudson, *J. Am. Chem. Soc.*, **73**, 4759 (1951).

64. J. C. Roberts, *J. Chem. Soc.*, 3315 (**1952**).

65. Sandoz Ltd. *Swiss Patent 307322*, 1955; *Chem. Abstr.*, **51**, P7422h.

66. M. Semonský, A. Černý and V. Zikán, *Coll. Czechoslov. Chem. Commun.*, **21**, 382 (1956).

67. J. H. Hunt, *J. Chem. Soc.*, 1926 (**1957)**.

68. Cilag Ltd. *Brit. Patent 772215*, 1957; *Chem. Abstr.*, **52**, P1216f.

69. L. Vrba and M. Semonský, *Coll. Czechoslov. Chem. Commun*., **27**, 1732 (1962).

70. R. L. Shriner and C. L. Furrow, *Org. Synth. Coll. IV*, 242 (**1963**).

71. K. H. Bell, *Australian J. Chem.*, **32**, 65 (1979).

72. R. E. Ireland and W. J. Thompson, *J. Org. Chem.*, **44**, 3041 (1979).

73. T. Teramoto, M. Deguchi and T. Kurosaki, *Tetrahedron*, **22**, 1109 (1981).

74. L. Duhamel and J. C. Plaquevent, *Org. Prep. Proc. Int.*, **14**, 347 (1982).

75. F. Faigl, I. Miskolczi and K. Szathmari, *HU Patent 34720*, 1985; *Chem. Abstr.*, **104**, 109235.

76. R. Kluger, J. F. Chow and J. J. Croke, *J. Am. Chem. Soc.*, **106**, 4017 (1984).

77. M. M. Kayser, L. Breau, S. Eliev and P. Morand, *Can. J. Chem.*, **64**, 104 (1986).

78. Y. Dobashi and S. Hara, *J. Org. Chem.*, **52**, 2490 (1987).

79. B. Kopenhoefer, H. Allmendinger and B. Peters, *Justus Liebigs Ann. Chem.*, 991 (**1987**).

80. J. M. Dener, D. J. Heart and S. Ramesh, *J. Org. Chem.*, **53**, 6023 (1988).

81. L. Szotyori, F. Kovacs, O. Gyorvari, G. Megyesi and I. Suto, *HU Patent 55770*, 1991; *Chem. Abstr.*, **155**, 255981f.

82. J. Serwatowski, L. Synoradzki, H. Hajmowicz, T. Dłużniewski and A. Smyk, *PL Patent 153299*, 1991; *Chem. Abstr.*, **117**, 48319.

83. S. Nakai, H. Sato and T. Fujino, *JP Patent 6166683*, 1992 (*EP Patent 600714*, 1993); *Chem. Abstr.*, **121**, 108498.

84. N. Huh and C. M. Thompson, *Tetrahedron*, **51**, 5935 (1995).

85. A. Mravik, Z. Böcskei, S. Keszei, F. Elekes and E. Fogassy, *Tetrahedron Asymm.*, **7**, 1477 (1996).

86. L. I. Monser, G. M. Greenway and D. F. Ewing, *Tetrahedron Asymm.*, **7**, 1189 (1996).

87. H. Yunpu, J. Zhongliang, L. Jiaguo, G. Zhengsong, S. Xianfa, Z. Fumin and G. Aihua, *Huaxue Shiji*, **21**, 106 (1999); *Chem. Abstr.*, **131**, 18817.

88. J. Oxelbark and S. Claeson, *Tetrahedron Asymm.*, **13**, 2235 (2002).

89. P. C. Austin and J. R. Park, *J. Chem. Soc.*, **127**, 1926 (1925).

90. D. G. Ray and G. F. Koser, *J. Org. Chem.*, **57**, 1607 (1992).

91. K. Furuta, S. Shimizu, Y. Miwa and H. Yamamoto, *J. Org. Chem.*, **54**, 1481 (1989).

92. K. Ishihara, Q. Gao and H. Yamamoto, *J. Org. Chem.*, **58**, 6917 (1993).

93. K. Furuta, Q. Gao and H. Yamamoto, *Org. Synth.*, **72**, 86 (1993).

94. Y. Hu, K. A. Yamada, D. K. Chalmers, D. P. Annavajjula and D. F. Covey, *J. Am. Chem. Soc.*, **118**, 4550 (1996).

95. Q. Gao, T. Maruyama, M. Mouri and H. Yamamoto, *J. Org. Chem.*, **57**, 1951 (1992).

96. Q. Gao, K. Ishihara, T. Maruyama, M. Mouri and H. Yamamoto, *Tetrahedron*, **50**, 979 (1994).

97. K. Furuta, T. Maruyama and H. Yamamoto, *J. Am. Chem. Soc.*, **113**, 1041 (1991).

98. K. Furuta, T. Maruyama and H. Yamamoto, *Synlett*, 439 (**1991**).

99. K. Ishihara, T. Maruyama, M. Mouri, Q. Gao, K. Furuta and H. Yamamoto, *Bull. Chem. Soc. Jpn*, **66**, 3491 (1993).

100. M. Sato, S. Sunami, Y. Sugita and C. Kaneko, *Chem. Pharm. Bull.*, **42**, 839 **(**1994).

101. A. G. M. Barett and A. Kamimura, *J. Chem. Soc., Chem. Commun.*, 1755 (**1995**).

102. K. Furuta, M. Mouri and H. Yamamoto, *Synlett*, 561 (**1991**).

103. K. Ishihara, M. Mouri, Q. Gao, T. Maruyama, K. Furuta and H. Yamamoto, *J. Am. Chem. Soc.*, **115**, 11490 (1993).

104. W. Langenbeck and O. Herbst, *Chem. Ber.*, **86**, 1524 (1953).

105. K. H. Bell, *Australian J. Chem.*, **40**, 1723 (1987).

106. A. Cambell, A. H. J. Houston and J. Kenyon, *J. Chem. Soc.*, 93 (**1947**).

107. Y. Hamada and S. Mukai, *Tetrahedron Asymm.*, **7**, 2671 (1996).

108. F. J. Kearly and A. W. Ingersoll, *J. Am. Chem. Soc.*, **73**, 5783 (1951).

109. J. C. Clark, G. H. Phillipps and M. R. Steer, *J. Chem. Soc. Perkin Trans. 1*, 475 (**1976**).

110. D. Kozma, Z. Bocskei, C. Kassai, K. Simon and E. Fogassy, *Chem. Commun*., 753 (**1996**).

111. P. C. Austin, *J. Chem. Soc.*, **130**, 1825 (1928).

112. J. Mezei, I. Orosz and A. Spitzar, *HU Patent 22147*, **1982**; *Chem. Abstr.*, **97**, 215901h.

113. L. Duhamel J. and C. Plaquevent, *J. Am. Chem. Soc.*, **100**, 7415 (1978).

114. A. Mravik, Z. Lepp and E. Fogassy, *Tetrahedron Asymm*., **7**, 2387 (1996).

115. M. L. Scarpati and G. Oriente, *Tetrahedron*, **4**, 43 (1958).

116. H. Zhao and T. R. Burke, *Synth. Commun.*, **28**, 737 (1998).

117. B. R. Harris, *US Patent 2025984*, **1935**; *Chem. Abstr.*, **30**, 1144.

118. P. A. Pottier, *Fr Patent M3000*, **1963**; *Chem. Abstr.*, **62**, 14505f.

119. P. Rabe, *Justus Liebigs Ann. Chem.*, **492**, 242 (1932).

120. R. A. Reinke, P. J. King, J. G. Victoria, B. R. McDougall, G. Ma, Y. Mao, M. G. Reinecke and W. E. Robinson, *J. Med. Chem.*, **45**, 3669 (2002).

121. H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa and Y. Kita, *J. Org. Chem.*, **64**, 3519 (1999).

122. Z. Kolodyńska and W. Wieniawski, *Acta Pol. Pharm.*, **24**, 261 (1967); *Chem. Abstr.*, **69**, 18800v.

123. T. Kunitake and Y. Okahata, *Bull. Chem. Soc. Jpn*, **51**, 1877 (1978).

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