Tartaric acid and its acyl derivatives. Part 5. Direct synthesis of monoacyltartaric acids and novel mono(benzoyl)tartaric anhydride: unusual findings in tartaric acid acylation

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Abstract

Practical acylation of unprotected tartaric acid **1** by acyl chlorides to the corresponding monoacyltartaric acids **2** has been shown. Several unusual cases in the acylation of **1** are observed; it has been found that two routes of acylation are possible. In the benzoylation of **1**, in addition to the expected products, the formation of a previously undescribed monobenzoyltartaric anhydride **7a** is reported. An unusual DME cleavage during the course of acylation was also observed.

Keywords: Acylation, chiral pool, hydroxycarboxylic acids, tartaric acid

Introduction

Tartaric acid **1** and both its mono- **2** and diacyl derivatives **3**, **4** (Figure 1) play an important role in the preparation of numerous chiral organic compounds.[1,2,3] Except for naturally occurring **1**, the most commonly used compounds from this group are *O*,*O*'-diacyltartaric acids **3**, which are common resolving agents both in the laboratory and in industry.[4,5] Both **3** as well as some of its derivatives (diesters, diamides[6]) also possess crystalline inclusion[7] and chiral recognition properties,[8] rendering them useful reagents for the resolution of non-basic racemates *via* enantioselective complexation.[9,10]

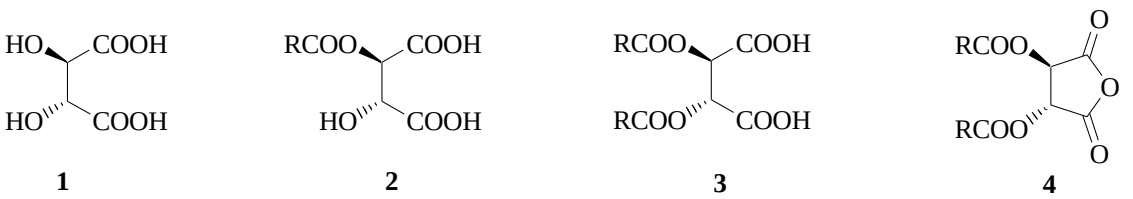


Figure 1. L-Tartaric acid and its *O*-acyl derivatives.

Due to their historical application, the synthesis of acids **3** is well known and described.[11,12] They are obtained by exhaustive acylation of tartaric acid **1** to the corresponding diacyltartaric anhydrides **4**, which is followed by hydrolysis.[13] According to this procedure, acids **3** are prepared in high yield both in academic and industrial laboratories. The last decade has seen a growing interest in the application of the mono-derivative *O*-acyltartaric acids **2**. They are used as ligands in chiral (acyloxy)boranes (CAB),[14-16] catalysts for enantioselective Diels-Alder,[17] hetero-Diels-Alder,[18] allylation,[19] and allylation polymerization[20] reactions. They are also applied in the synthesis of chiral depsipeptide dendrimers, a very promising class of peptide mimetics.[21,22] Recently, some naturally occurring derivatives of **2** were found in grapes: caftaric acid (caffeoyltartaric acid), p-coutaric acid (coumaroyltartaric acid) and fertaric acid (feruloyltartaric acid), all of which have received much attention due to their interesting pleiotropic biological activity (Figure 2).[23]

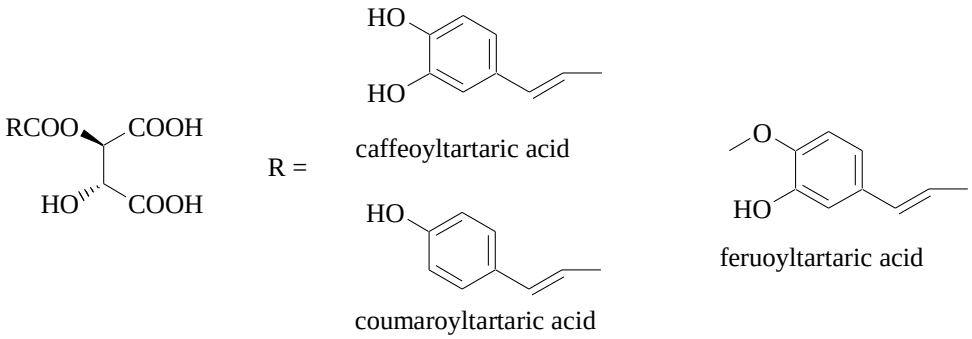
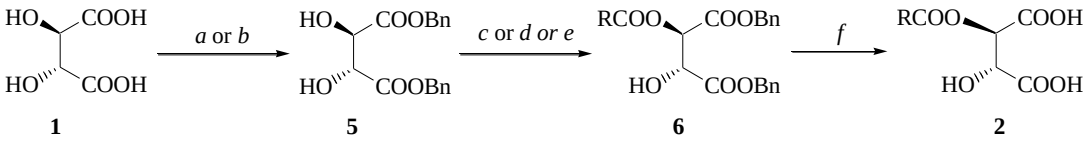


Figure 2. A naturally occurring monoacylated acids **2**.

The most frequently used procedure to obtain acids **2** requires multi-step reactions (Scheme 1): the protection of the tartaric acid **1** carboxylic groups (usually by the benzyl esters using method *a* or *b*), an appropriate acylation (method *c* or *d* or *e*), and deprotection as the last step (method *f*).[18,22,24–30] However, the monoacylation of diester **5** itself remains challenging. It requires the addition of an amine and a catalyst when using an acid chloride (method *c*), or coupling agents (DCC or TFAA) in the acylation with an appropriate carboxylic acid (method *d* or *e*).



a: BnOH/TsOH,[22]
b: BnBr/DBU/DMF,[25]
c: RCOCl/Et_3N/DMAP,[26-28]
d: RCOOH/DCC/DMAP,[22,25]
e: RCOOH/TFAA,[29-31]
f: H_2/Pd/C.[26-28]

Scheme 1. The most frequently used procedure to obtain acids **2**.

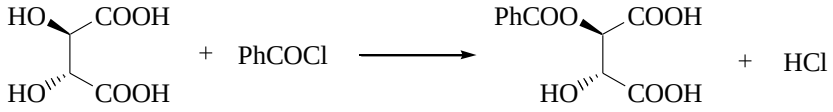
Iwasaki *et al*. observed considerably poorer selectivity in the monofunctionalization of tartrates (diethyl, 70%) as compared to other symmetrical 1,2-diols (>99%).[31] It should also be emphasized that the great differences between literature reports make the analysis and reliable evaluation of monoacylation procedures very difficult (Scheme 1, method *d*: R=Ph, 70% yield[25] or 38% yield[22]). An alternative approach towards the synthesis of monoacylated acids **2** entails their preparation *via* the partial aminolysis[32] or hydrolysis[33] of acids **3**, which is particularly useful if they are commercially available.

Result and Discussion

In an ongoing synthetic project, we required a simple, scalable, economically and ecologically *via*ble process for the preparation of monoacylated acids **2**. We examined the three-step method described by Furuta et al. (Scheme 1, method *a*, *c*, *f*, R=2,6-$(MeO)_2C_6H_3$, 78–82% yield)[26] using benzoyl chloride. Our yield of **2a** (R=Ph) (47%) was much lower than anticipated. Therefore, the complexity of the process was taken into account (the protection/deprotection of carboxylic functions). The need for using an amine and a catalyst, an additional hydrogenation step, as well as very laborious chromatographic purification of mono-derivative **6a** led us to recognize that this method for obtaining of **2** is not suitable for scale-up. We also rejected the methods *via* the partial deacylation, aminolysis or hydrolysis of diacyltartaric acid **3**. Deacylation procedures entail an initial preparation of **3**, additional reactions, and the use of increased quantities of acyl compounds, which remarkably raises the cost. Finally, our preliminary experiments of partial aminolysis and of hydrolysis of **3a** (R=Ph) did not yield encouraging results. Therefore, we decided to carry out a detailed investigation of a direct monoacylation of tartaric acid **1** with the goal of developing a simple protocol for the preparation of monoacylated derivatives **2**.

As a model for the optimization of monoacylation, we choose the reaction of tartaric acid **1** with benzoyl chloride (BzCl) (Table 1).

Table 1. Optimization of monoacylation of **1** with benzoyl chloride



1 **2a**

Entry	Solvent	Temp. (°C)	Conc.[b] (mM)	BzCl (mol)	Cat.	Cat. (% mol)	Yield (%)[c]				
							2a	**3a**	**7a**	**4a**	PhCOOH
1	toluene	reflux	1.7	1	H_2SO_4	7	<1	1	1	22	42
2[d]	MeCN	reflux	1.7			7	29	16	8	2	35
3[e]	dioxane	reflux	1.7			7	41	8	2	<1	42
4[f]	DME	reflux	1.7			7	31	6	4	<1	51
5	MeCN	47	6.0			10	3	7	6	4	18
6	dioxane	52	1.3			10	<1	1	0	0	2
7	DME	64	0.75			20	<1	1	0	0	8
8[g]		reflux	1.7			7	22	5	1	0	43
9[h]		reflux	1.7			2,5	25	4	1	0	34
10[i]		40–60	0.3		Et_3N	150	2	0	0	0	0
11		reflux	1.7	1	(HCl)	-	40	10	4	<1	26
12[j]			1.2	1			34	5	2	<1	16
13			2.3	1			34	11	3	1	26
14			3.6	1			29	13	3	1	26
15			1.7	1.2			34	14	5	3	29
16			1.7	0.8			37	8	2	<1	17
17			1.0	0.5			23 (50)[k]	2	<1	0	9
18			1.7	1			39	9	4	2	22

[a] Standard procedure: reactions were carried out until evolution of HCl ceased (approximately 4 h); [b] As an initial suspension, [c] Unreacted **1** was detected (GC MS /(BSA) in the reaction mixtures, but its amount was not quantitatively established, [d] Reaction: temperature 85–86 °C, time: 2 h, [e] Reaction: temperature 100–102 °C, time: 3 h, [f] Reaction: temperature 94–95 °C, time: 3 h, [g] Slow warming of the reaction mixture, [h] with dropwise addition of BzCl, [i] addition of DMAP, reaction time 12 h, [j] Reaction mixture contains about 20% of unreacted BzCl, [k] yield of BzCl.

To follow the reaction course, we developed an original analytical HPLC method. The derivatization of the samples with benzylamine enables the quantitative determination of various similar polar reagents presented in the acylation system: acids, anhydrides and acid chlorides.[34] An appropriate derivatization procedure prevents the occurrence of side reactions (aminolysis of

O-acyl groups). We believe that due to the difficulties in the analysis of such a complex mixture, the reactions of both tartaric acid **1** as well as the other aldaric acids with acyl chlorides have not yet been investigated.[35]

Preliminary experiments showed that the solvent has a significant influence on the course of reaction (entries 1-4). In toluene, mainly diacyl anhydride **4a** was formed. In contrast, in polar solvents, we achieved encouraging yields of **2a**: 41% in dioxane and approximately 30% in MeCN and DME, in addition to other benzoylation products **3a**, **4a** and benzoic acid as a byproduct. Surprisingly, we noticed a significant amount of a previously unknown compound, which we identified as *O*-benzoyl-L-tartaric anhydride **7a**. Intrigued by this phenomenon, we examined the course of acylation of **1** by varying the quantity of BzCl added (Chart 1) and following the resulting concentration of **7a** and **2a**, **3a**, **4a**.

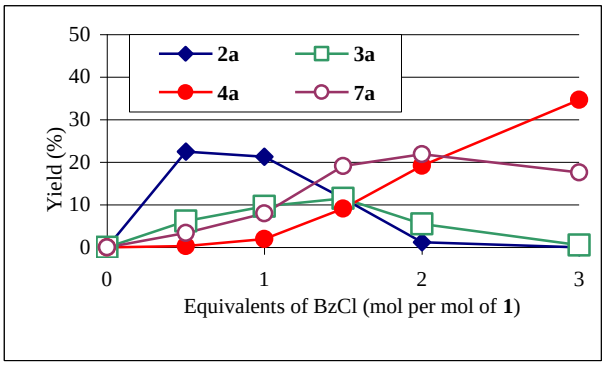
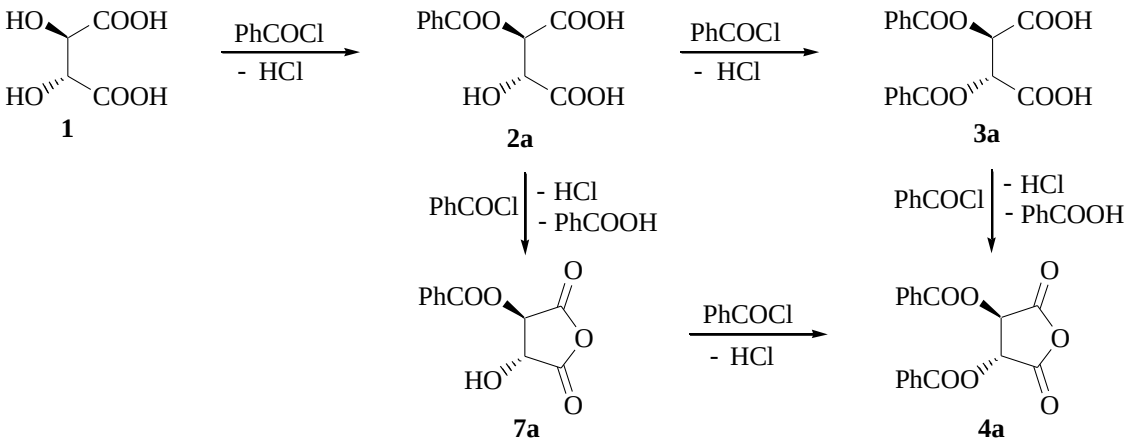


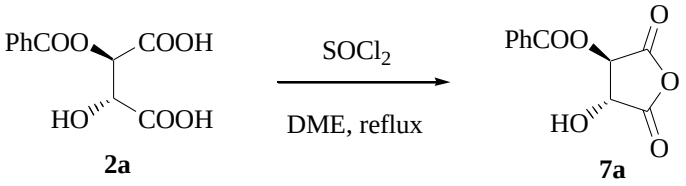
Chart 1. Products contribution **2a**–**4a**, **7a** in the reaction of **1** with BzCl (subsequent dropping in of the latter) in MeCN (HPLC yield).

It was found that the product of di-acylation, acid **3a**, occurs together with the monoacylated anhydride **7a**, which shows that acylation of tartaric acid **1** proceeds *via* two routes (Scheme 2). The formation of tartaric anhydride itself in the first step is not to be excluded, but neither we nor other authors[12,36] were able to isolate it or synthesize until now.

After the formation of **2a**, the next mole of BzCl is competitively used for the benzoylation of its free hydroxy group with the formation of **3a** or its dehydration and cyclization to the anhydride **7a**. The presence of **7a** confirmed our earlier assumptions that both the hydroxy and carboxylic groups of **2a** are reactive towards acyl carbon of BzCl. We successfully obtained **7a** from **2a** in good yield (75%) from an independent experiment entailing cyclization with thionyl chloride (Scheme 3).[37]



Scheme 2. Two routes of the reaction of **1** with BzCl.



Scheme 3

The cyclic anhydride of tartaric acid with free hydroxy groups was not previously synthesized or characterized; therefore, anhydride **7** constitutes a transitional derivative between tartaric and the well-known diacyltartaric anhydrides **4**.

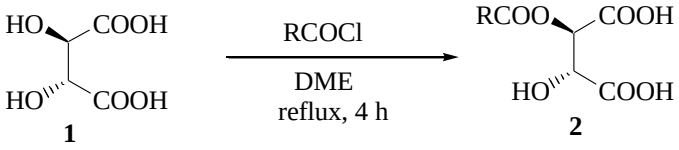
Further experiments of the monoacylation of **1** were carried out at reflux, because attempts to increased yields by lowering the temperature failed (entries 5–7). Due to the greater selectivity and easier product isolation, the reaction conditions were optimized in DME despite slightly higher HPLC yields of **2a** obtained in dioxane (entry 3). A full conversion of BzCl in the optimized reaction was required because its presence decreased the isolation yield of **2a** and increased the formation of impurities during concentration of the reaction mixture.

Neither slow heating of the reaction mixture (entry 8) nor dropwise addition of BzCl (entry 9) increased the yield of **2a**. The acylation of **1** in the presence of Et_3N and DMAP, which has been shown to be advantageous in the case of diols (as compared with the Furuta procedure[26]), was not succesful. Using acid **1** with unprotected carboxylic groups, when mixed with the amine, formed an insoluble salt that showed very little reaction in the desired direction. Both the higher dilution of the reaction mixture and the longer reaction time did not improve the results. In turn, at higher temperatures (above 60 °C), the debenzoylation of acid **2a** occurred.

Surprisingly, the highest yield of monobenzoyltartaric acid **2a** was obtained in a reaction that was autocatalyzed by the evolved HCl, which is soluble in the reaction mixture (in DME 3–5%) (entries 11 and 18, 40% and 39% HPLC yield, respectively; 30% of isolated yield, without

H_2SO_4 as a cat.). Next, we conducted the synthesis of several monoacylated tartaric acids **2b**–**d** under the optimized conditions for benzoyl derivative **2a** (Table 2).[38]

Table 2. Synthesis of monoacylated tartaric acid **2a-d**



1 **2**

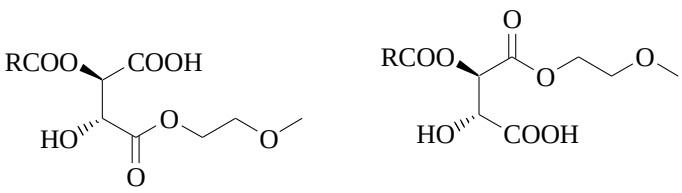
Product	R	Yield % (HPLC)	Yield %[a]
2a	Ph	41	30
2b	4-$MeOC_6H_4$[b]	46	12[c]
2c	2,6-(*i*-PrO)$_2C_6H_3$[b]	37	27
2d	9-anthryl[b]	50	18

[a] Yields of the isolated products. [b] An appropriate acid chloride was generated immediately prior to the reaction using $SOCl_2$. [c] Very laborious work-up.

Two novel compounds, *O*-p-anisoyl-L-tartaric acid **2b** and *O*-9-anthroyl-L-tartaric acid **2d**, were synthesized and characterized. The HPLC yield of monoacylation reached 37–50%, whereas isolation of the pure compound was very difficult and time-consuming. The search for an appropriate solvent for efficient crystallization is currently under investigation.

Choosing the method of direct acylation of free acid **1**, we were aware that achieving very high yields would be difficult, if not impossible. Nevertheless, we managed to obtain several monoacylated derivatives **2** in moderate yield by a simple procedure (single step, without catalyst), which is well suited for scale-up. With the ability to completely hydrolyze the residue and recover most of the waste, the process is more environmentally friendly. For expensive acyl chlorides in which the price dictates the cost of the process, it is favorable to carry out the acylation in a deficiency of acid chloride (Table 1, entry 17). The monoacylation of **1** is then relatively selective, and the presence of other acylation products is small.

Detailed analysis of the reaction products led to the observation of an interesting and rare phenomenon: dimethoxyethane cleavage. Initially, it was indirectly shown using LC MS and GC MS, as we detected esters **8a** and **8b** in the reaction mixtures (Figure 3). We suppose that they were formed as a result of the esterification of **7a** with 2-methoxyethanol, which was produced in the course of DME decomposition. This phenomenon was easy to overlook due to the very similar retention times of **8a** and acid **3a**.



8a, R = Ph
9a, R = 4-$MeOC_6H_4$

8b, R = Ph
9b, R = 4-$MeOC_6H_4$

Figure 3

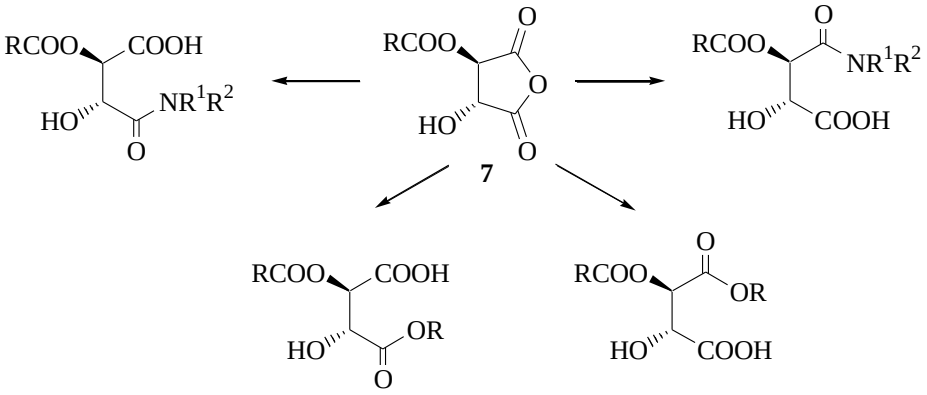
Both the isomeric structures of **8a** and **8b** as well as earlier results were confirmed by the direct preparation of **8a** and **8b** by the reaction of anhydride **7a** with 2-methoxyethanol and their HMBC analysis. It should be clearly stated that the DME used was not contaminated with 2-methoxyethanol, as confirmed by GC MS analysis.

Although compounds **8a** and **8b** were only found in trace amounts in the reaction mixtures, they contaminated **2a** after crystallization from MeCN at a level of 2–3%. Fortunately, an efficient recrystallization from water provided **2a** in high purity.

We also noticed that during the synthesis of anisoyl derivative **2b**, compounds **9a** and **9b** were formed. This is analogous to the formation of esters **8a** and **8b** in the synthesis of **2a** (Figure 3). It clearly indicates the presence of *O*-p-anisoyltartaric anhydride in a system. This observation confirmed that the proposed mechanism of the reaction of tartaric acid with acyl chloride is of general importance (Scheme 2).

Conclusions

In conclusion, the results show that the direct acylation of unprotected tartaric acid **1** by acyl chlorides to give the corresponding acids **2** is of practical importance. Using original but classical analytical tools, we observed two possible routes of acylation of **1** with BzCl, one of which proceeds *via* the previously unknown compound *O*-benzoyl-L-tartaric anhydride **7a**, and the second *via* **3a** acid. The anhydride **7a**, which may be efficiently obtained by the cyclization of **2a** with thionyl chloride, opens a facile route to the novel tartaric acid derivatives by a simple ring-opening reaction with various nucleophiles (Scheme 4). Such studies of regioselective ring-opening of monoacyltartaric anhydrides are currently in progress.



Scheme 4

Additionally, we noticed a rare phenomenon of O-CH_3 bond cleavage in an essentially stable solvent such as DME.

Experimental Section

General. The commercial-grade L-tartaric acid **1** was used without further purification. Thionyl chloride and BzCl were freshly distilled. Solvents were dried over molecular sieves 4Å. HPLC were done with a HP 1100 Agilent Technologies model on a RP column LiChrospher 100 RP-18, using UV-Vis detector (measurement at 230 nm), with AcOH aq/MeCN (1:1) as the eluent. ^{1}H NMR spectra were recorded with a Varian Mercury 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) and measured in DMSO-d_6 with TMS as an internal standard. The optical rotations were measured with PolAAr 32 Optical Activity Ltd. IR spectra were recorded using KBr pellets. Melting points were uncorrected.

General procedure for the synthesis of *O*-acyl-L-tartaric acids (2a-d)
31.5 g (0.21 mol) of **1**, 29.5 g (0,21 mol) of appropriate acyl chloride and 120 mL of DME were placed in a round-bottom flask. The reaction mixture was mechanically stirred and refluxed until no gaseous HCl was observed for about 4h. After reaction completion, most of DME was evaporated. Crude **2a** and **2b** were twice recrystallized, first from water then from MeCN. Crude **2c** was isolated as an oil by the extraction from water and ether. Crude **2d** was purified by the column chromatography.
***O*-Benzoyl-L-tartaric acid (2a).** Yield 30%; white crystals; mp 206–208 ºC, (lit.[1] mp 211 ºC); $[\alpha]_D^{25}$ –5.70 (c 1.00, MeOH), (lit.[1] –5.8 (MeOH)). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 4.68 (d, *J* = 2.4 Hz, 1H), 5.48 (d, *J* = 2.4 Hz, 1H), 6.01 (s, 1H), 8.05–7.54 (m, 5H), 13.24 (s, 1H).
***O-p*-Anisoyl-L-tartaric acid (2b).** Yield 12%; white crystals; mp 187–193ºC; $[\alpha]_D^{25}$ = –9.9 (c 1.00, MeOH). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 3.83 (s, 3H), 4.64 (d, *J* = 2.4 Hz, 1H), 5.42

(d, *J* = 2.4 Hz, 1H), 7,06 (q, *J* = 4.8 Hz, 2H), 7.99 (q, *J* = 4.8 Hz, 2H). Anal. Calcd. for $C_{12}H_{12}O_8$: C, 50.71; H, 4.26. Found C, 50.53, H, 4.49.

***O*-(2,6-Diisopropoxybenzoyl)-L-tartaric acid (2c).** Yield 27%; as oil; $[\alpha]_D^{25}$ = –24,7; (c = 1, MeOH), (lit.[1] –28.5 (EtOH)). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 1.20 (dd, *J* = 6.0 Hz, *J* = 2.0 Hz, 12H), 4.50 (d, *J* = 2.4 Hz, 1H), 4.54 (m, 2H), 5.51 (d, *J* = 2.4 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 2H), 7.25 (t, *J* = 8.6 Hz, 1H).

***O*-9-Anthroyl-L-tartaric acid (2d).** Yield 18%; brown powder; mp 121-124 ºC; $[\alpha]_D^{25}$ = –41.7 (c = 1, MeOH). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 4.78 (d, *J* = 2.4 Hz, 1H), 5.87 (d, *J* =2.4 Hz, 1H), 7.54–7.63 (m, 4H), 8,16–7,18 (m, 4H), 8.79 (s, 1H). Anal. Calcd. for $C_{19}H_{14}O_7$: C, 64.41, H, 3.98. Found: C, 64.00, H, 4.00.

Synthesis of *O*-benzoyl-L-tartaric anhydride (7a)

20 g (0.079 mol) of **2a**, 5.9 mL (0,082 mol) of thionyl chloride and 35 mL of DME were placed in a round-bottom flask. The reaction mixture was stirred mechanically and refluxed until no gaseous HCl and SO_2 was observed. After reaction completion, most of DME was evaporated. Crude product was recrystallized from DME at –10 ºC to give **7a** as white crystals (13.9 g, 75%); mp 178–180 ºC; $[\alpha]_D^{25}$ +122.14 (c 1.00, DME anhydrous). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 5.38 (dd, *J* = 6.8 Hz, 1H), 6.33 (d, *J* = 6.8 Hz, 1H), 6.921 (d, *J* = 6.8 Hz, 1H), 8.05–7.58 (m, 5H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 71.64, 74.73, 127.88, 129.11, 129.67, 134.45, 164.67, 165.98, 168.86 ppm. Anal. Calcd for $C_{11}H_8O_6$: C, 55.94; H, 3.41. Found: C, 55.92; H, 3.46.

2-methoxyethyl *O*-benzoyltartrate, Isomer I (8a). mp 121–124 ºC; $[\alpha]_D^{25}$ = +16.9 (c 1.00, MeOH). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 2.99 (s, 3H), 3.32–3.43 (m, 2H), 4.06–4.11 (m, 1H), 4.22–4.28 (1H), 4.77 (br, 1H), 5.44 (d, *J* = 2.4 Hz, 1H), 6.28 (br, 1H), 7.54 (t, 2H), 7.68 (t, 1H), 8.01 (d, 2H), 13.08 (br, 1H). Anal. Calcd. for $C_{14}H_{16}O_8$: C, 53.85, H, 5.16. Found C, 53.48, H, 5.28.

2-methoxyethyl *O*-benzoyltartrate, Isomer II (8b). mp 154–158 ºC; $[\alpha]_D^{25}$ = +0.0 (c 1.00, MeOH).^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 3,23 (s, 3H,), 3,53 (t, *J* = 4,6 Hz, 2H), 4,18-4,30 (m, 2H), 4,67 (d, *J* = 2,6 Hz, 1H), 5,54 (d, *J* = 2,6 Hz, 1H), 6,10 (br, 1H), 8,05–7,54 (m, 5H), 13,08 (br, 1H); ^{13}C NMR (400 MHz, DMSO-*d*$_6$): δ = 58,16 (CH_3), 64,64 (CH_2), 69,50 (CH_2), 70,14 (CH), 74,06 (CH), 128,56 (Ph), 128,85 (Ph), 129,63 (Ph), 134,04 (Ph), 164,98 (COOPh), 166,84 ($COOCH_2$), 171,59 (COOH) ppm. Anal. Calcd. for $C_{14}H_{16}O_8$: C, 53.85, H, 5.16. Found C, 53.39, H, 5.30.

Acknowledgements

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