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Synthesis of Optically Active 4-Hydroxymandelic Acid and Derivatives *via* Regio- and Stereoselective Friedel-Crafts Alkylation.

Franca Bigi*, Giovanni Sartori, Raimondo Maggi, Edo Cantarelli, Gianni Galaverna

Dipartimento di Chimica Organica e Industriale dell'Università
Viale delle Scienze, I-43100 Parma, Italy

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Abstract: Optically active 4-hydroxymandelic esters were prepared in good yields and very high diastereoselectivity (up to 96% d.e.) *via para*-hydroxyalkylation of phenolic ethers. Enantiomeric pure 4-hydroxymandelic acid is available by hydrolysis.

As part of our general program aimed at developing regio- and stereoselective electrophilic aromatic substitution, we have addressed the problem of the stereoselective *para*-functionalization of phenols.

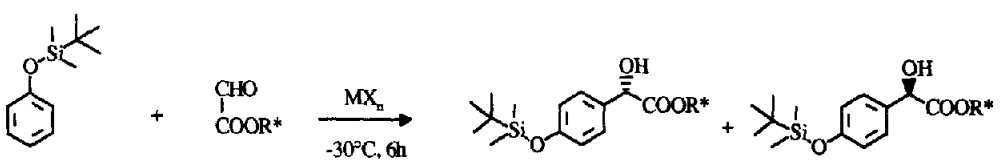
Amino alcohols, amino acids and hydroxy acids having a *para*-hydroxyaryl moiety occur as biologically active natural products, like adrenaline, and are useful building blocks for the synthesis of drugs[1].

Our interest in searching reaction methodology relevant to the synthesis of such target structures has prompted us to investigate the synthesis of chiral 4-hydroxymandelic acid (**6**).

This acid is used as intermediate for the synthesis of antibiotics[2] and sympathomimetic amino alcohols[3]. In addition it is employed as useful precursor of 4-hydroxyphenylglycine[4]. The synthesis of the racemic form of the 4-hydroxymandelic acid was previously reported in the literature[5] and recent examples of optical resolution in order to obtain single enantiomers were published[6,2b]. The chiral preparation of 3,4-dihydroxymandelic acid derivatives was reported two years ago by reduction of the corresponding ketonic precursors[7].

Therefore an efficient and stereoselective method for the synthesis of the acid **6** is a still open problem.

This communication presents a successful strategy for the synthesis of optically active 4-hydroxymandelic acid and its esters by reacting protected phenol **1** and chiral glyoxylates **2**.



1 **2** **3** **4**

i; R* = (-)-menthyl
j; R* = (-)-8-phenylmenthyl
k; R* = (-)-*trans*-phenylcyclohexyl

In order to avoid the ortho-alkylation[8] we used as protecting group on the phenolic oxygen the *tert*-butyldimethylsylyl group, which revealed itself to be a good protecting group, minimizing the electrophilic attack at the *ortho* position.

We examined the influence of the Lewis acid on the reaction outcome. The data reported in Table 1 show that the reaction is very sensitive to the nature of the Lewis acid regarding both the reactivity and the stereoselectivity.

Table 1. Synthesis of 4-hydroxymandelic esters **3i** and **4i**[a].

Entry	MX_n	R*	Major Product[b]	Total Yield(%)[c]	*Ortho/Para+Ortho* (%)[d]	**3i : 4i**[e]
1	$SnCl_4$	(-)-menthyl	**3i**	78	3	78 : 22
2	$TiCl_4$	(-)-menthyl	**3i**	46	13	75 : 25
3	$FeCl_3$	(-)-menthyl	**3i**	23	5	54 : 46
4	$AlCl_3$	(-)-menthyl		traces		
5	$C_6H_{11}OAlCl_2$	(-)-menthyl		no reaction		
6	$MgCl_2$	(-)-menthyl		no reaction		
7	$ZnCl_2$	(-)-menthyl		no reaction		
8	$Ti(OPr^i)_3Cl$	(-)-menthyl		no reaction		

[a] Experimental conditions, see Ref. 9. [b] All compounds reported were characterized by complete spectral and analytical data. [c] Isolated yield by silica gel chromatography. [d] Ratio of *ortho*-attack product to total amount of products determined by reversed-phase H.P.L.C. [e] Molar ratio of diastereoisomers **3** and **4** measured on the crude reaction mixture by reversed-phase H.P.L.C.

We chose tin tetrachloride as an acid promoter since it gave quite good *para*-regioselectivity as well as good yield and diastereocontrol (Table 1, entry 1).

In order to increase the diastereoselection we exploited a bulkier chiral auxiliary in the ester moiety (Table 2). Indeed using (-)-8-phenylmenthylglyoxylate (**2j**), a successful reagent in different kinds of reactions[11,8b], we reached excellent values of diastereoselection (d.e. >96%) and good yield.

Table 2. Synthesis of 4-hydroxymandelic esters **3** and **4**[a].

Entry	MX_n	R*	Major Prod.[b]	Total Yield(%)[c]	*Ortho/Para+Ortho* (%)[d]	**3 : 4**[e]	$[\alpha]_D$[f] (c)	Config.
1	$SnCl_4$	(-)-menthyl	**3i**	78	3	78 : 22	- 2.6(0.5)	S
2	$SnCl_4$	(-)-8-phenyl menthyl	**3j**	70	-	> 98 : 2	+28.1(0.5)	S
3	$SnCl_4$	(-)-*trans*-2-phenyl-cyclohexyl	**4k**	62	-	6 : 94	-57.1(0.3)	R

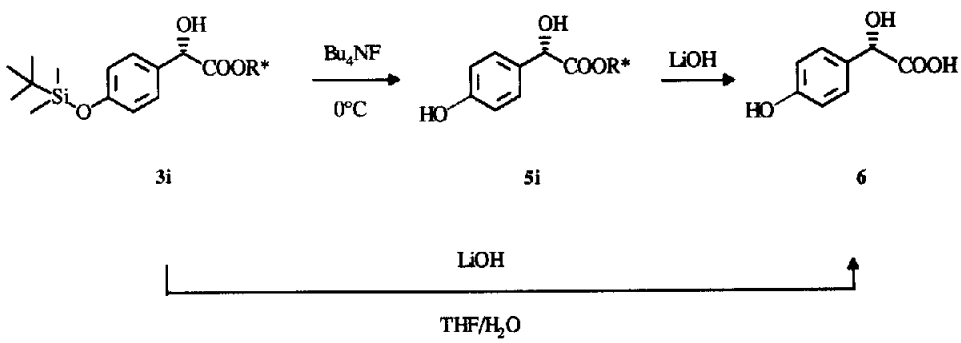
[a,b,c,d,e] See notes a,b,c,d,e in Table 1. [f] Ethanol 95%. Reported values refer to the major product.

It is worthy of note that a stereochemical reversal was obtained with high level of diastereoselectivity (up to 88%) by employing (-)-*trans*-2-phenylcyclohexanol as chiral auxiliary[12].

Furthermore the reactions occur with complete *para*-regioselectivity together with the absence of dimeric by-product[13].

The attribution of the S configuration at C-2 of the major isomer **3i** was made on the basis of ^{1}H NMR studies[14,8a] and it was successively confirmed by the positive optical rotation[16] of the acid obtained after deprotection and hydrolysis. The S configuration of the new stereogenic centre is in accordance with a chelation mechanism.

Finally we studied the deprotection of the reaction products. The desylylation of compound **3i** was carried out with tetrabutylammonium fluoride[17] in THF at 0°C; it gave 4-hydroxymandelic ester **5i** in practically quantitative yield without affecting the diastereomeric ratio, as checked by ^{1}H NMR at 400 MHz. Then the hydrolysis of the ester **5i** with lithium hydroxide in THF/H_2O (2:1) at room temperature afforded the corresponding (+)-(S)-4-hydroxymandelic acid (+)-**6**, $[\alpha]_D$ = +123.6 in ethanol (c=0.16). Moreover, the use of lithium hydroxide resulted in simultaneus desylylation and hydrolysis of **3i**, giving directly the acid (+)-**6**.



This hydrolysis procedure does not cause any racemization. Indeed H.P.L.C. analysis, carried out by using chiral ligand exchange chromatography[18] showed that enantiomerically pure (+)-S-4-hydroxymandelic acid was obtained from isomer **3i**. In the same way the levorotatory acid **6** was obtained by reacting **4k**.

In conclusion we have accomplished the synthesis of optically active 4-hydroxymandelic acid derivatives via highly diastereoselective Friedel-Crafts hydroxyalkylation of phenol. According to this approach the 4-hydroxymandelic acid is now available in both the enantiomeric forms by a suitable choice of the chiral auxiliary in the reagent **2**.

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This paper is dedicated to the memory of Professor Giuseppe Casnati.

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9. *General Procedure*: a solution of (-)-menthyl glyoxylate (5 mmol) in anhydrous CH_2Cl_2 (18 ml) was added to a solution of $SnCl_4$ (5 mmol) in CH_2Cl_2 (5 ml) cooled to -30°C, while a stream of dry nitrogen was passed. After stirring for 30 min, a solution of *tert*-butyldimethylsylylphenyl ether (prepared from phenol and *tert*-butyldimethylsylylchloride)[10] (5 mmol) in CH_2Cl_2 (10 ml) was added. The reaction was stirred for 6 h at -30 °C and then quenched with saturated aqueous NH_4Cl solution. After normal work up, pruducts **3i** and **4i** were separated by silica gel chromatography (CH_2Cl_2).
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12. Actually there is no rationale for such stereochemical result.
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14. The minor isomer **4i** shows two methyl groups of the (-)-menthyl moiety shielded ($\delta = 0.43, 0.63, 0.91$), as expected for 2R configuration, and the isomer **3i** shows signals at $\delta = 0.77, 0.82, 0.89$[15,8a].
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