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HIGHLY REGIO- AND DIASTEREOSELECTIVE FRIEDEL-CRAFTS ALKYLATION OF PHENOLS. SYNTHESIS OF 2-HYDROXYMANDELIC ESTERS.

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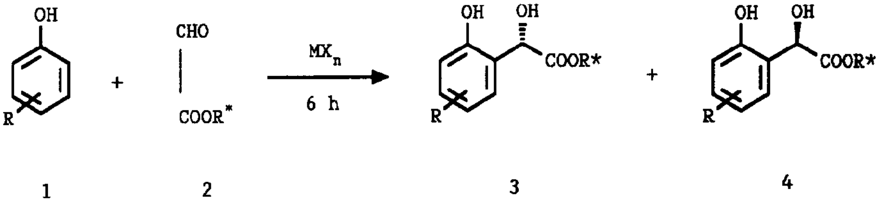
Abstract - Ortho-hydroxyalkylation of phenol substrates was performed via coordinative complexes of metal phenolates with chiral glyoxylates: optically active 2-hydroxymandelic esters have been obtained with good yields and very high diastereoselectivity (up to 94% d.e.).

In recent years a special attention has been paid to asymmetric induction in the formation of carbon-carbon bonds[1], since syntheses generally involve the gradual elaboration of a carbon skeleton. We have been aimed at developing asymmetric electrophilic aromatic substitution as an important tool of carbon-carbon bond construction.

During our studies on the selective functionalization of phenolic systems we have pointed out that highly coordinating metal phenolates promote regio- and stereocontrolled reactions.[2] According to this approach this communication describes a successful strategy for the synthesis of chiral 2-hydroxymandelic esters.

Mandelic acid and some derivatives, such as cyclandelate and eucatropine, are used as drugs[3] and were usually prepared as racemic mixtures by multistep syntheses.[4] Stereoselective syntheses of mandelic acid and derivatives gave low values of diastereomeric excess and/or lacked general validity for preparation of 2-hydroxymandelic derivatives.[5]

We present here the diastereoselective hydroxyalkylation of phenols with chiral glyoxylates leading to optically active 2-hydroxymandelic esters. The reaction of metal phenolates 1 with (-)-menthylglyoxylate 2i was the first to be studied.



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

The reaction occurs with complete *ortho*-regioselectivity with mono-attack on the phenol ring and the absence of by-products, like dimeric derivatives.[6] The data reported in Table 1 show that the diastereoselection depends on the nature of the phenoxy derivatives obtained with different Lewis acids, as well as on the temperature.

In all the cases examined the same distereoisomer **3ia** is formed preferentially.

Table 1. Synthesis of 2-hydroxymandelic esters **3i** and **4i**.[a]

Run	Phenol	R	MXn	Major Compd[b]	Temp °C	$[\alpha]_D^{25c}$	% Total Yield[d]	3i:4i[e]
1	**1a**	3-Bu^t	Et_2AlCl	**3ia**	0	-24.9(0.4)[f]	28	60:40
2	**1a**	3-Bu^t	$EtAlCl_2$	**3ia**	0		34	56:44
3	**1a**	3-Bu^t	EtMgBr	**3ia**	0		40	56:44
4	**1a**	3-Bu^t	EtMgBr	**3ia**	-30		28	70:30
5	**1a**	3-Bu^t	$InCl_3$	**3ia**	-30		18	70:30
6	**1a**	3-Bu^t	$\frac{1}{2}SnCl_4$	**3ia**	0		50	71:29
7	**1a**	3-Bu^t	BCl_3	**3ia**	20		35	50:50
8	**1a**	3-Bu^t	$\frac{1}{2}TiCl_4$	**3ia**	20		65	70:30
9	**1a**	3-Bu^t	$\frac{1}{2}TiCl_4$	**3ia**	0		60	71:29
10	**1a**	3-Bu^t	$\frac{1}{2}TiCl_4$	**3ia**	-30		53	75:25
11	**1a**	3-Bu^t	$\frac{1}{2}TiCl_4$	**3ia**	-60		28	79:21
12	**1a**	3-Bu^t	$TiCl_4$	**3ia**	0		63	74:26
13	**1a**	3-Bu^t	$TiCl_4$	**3ia**	-30		58	75:25
14	**1b**	4-OMe	$\frac{1}{2}TiCl_4$	**3ib**	-30	-10.7(0.4)	50	76:24
15	**1c**	H	$\frac{1}{2}TiCl_4$	**3ic**	-30	+ 4.5(0.8)	43	73:27

[a] Experimental conditions, see Ref.7. [b] All compounds reported were characterized by complete spectral and analytical data. [c] Ethanol. *c* values in parenthesis. Reported values refer to the major product. [d] Isolated yield by silica gel chromatography. [e] Molar ratio refer to diastereoisomers **3** and **4** measured on the crude reaction mixture by reversed-phase H.P.L.C. [f] Methylene chloride.

On the basis of these results we investigated the influence of the ring substituent in titanium phenolates, as titanium revealed to be an efficient metal promoting the stereocontrol of the process. The reactions were carried out at -30 °C in order to obtain a good level of diastereoselection as well as good yields.

The nature of the phenolic substituent does not affect the degree of stereoselection, which is about 50%. The major isomers **3i** are easily isolated by simple crystallization.

The S configuration is attributed to the new stereogenic centre of the major diastereoisomers **3i** on the basis of ^1H NMR studies. Crews and coworkers[8] have recently published a ^1H NMR study showing characteristic methyl chemical shifts of the (-)-menthyl moiety of (R)- and (S)-O-methylmandelate esters, in which the substituents in the vicinity of the O-methylmandelate aryl group are shielded.

This conclusion is valid also for 2-hydroxyatrolactic esters, ^{1}H NMR data and X-ray structures for which we recently published. The (2S)-compounds have only one methyl group shielded ($\delta \approx 0.76, 0.89, 0.90$) whereas (2R)-compounds have two.

Now we observe the same pattern: the major isomers 3i show one methyl group shielded ($\delta \approx 0.76$, 0.85 and 0.88) and diastereoisomers 4i show two methyl groups shielded ($\delta \approx 0.45, 0.59, 0.91$). In view of the different shielding effects, the assignment of S absolute configuration can be made at C-2 for compounds 3i.

With the aim at improving the diastereoselectivity we turned our attention to a bulkier chiral moiety in the reagent 2.

In particular we used (-)-8-phenylmenthylglyoxylate (2j) in which the presence of the phenyl ring induces high level of diastereoselection in different kinds of reaction.[9] By reacting 3-t.butylphenol (1a) and glyoxylate 2j we have explored the stereochemical consequences of the presence of different Lewis acids (Table 2).

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

Run	Phenol	R	MXn	Major Compd[b]	Temp °C	$[\alpha]_D^{25°C}$	%Total Yield[d]	3j:4j[e]
1	1a	3-Bu^t	$EtAlCl_2$	3ja	20	+19.2(0.8)	40	93: 7
2	1a	3-Bu^t	BCl_3[f]	3ja	20		41	79:21
3	1a	3-Bu^t	$Ti(OPr^i)_4$[f]	3ja	20		23	65:35
4	1a	3-Bu^t	$\frac{1}{2}SnCl_4$	3ja	20		60	96: 4
5	1a	3-Bu^t	$TiCl_4$	3ja	20		95	97: 3
6	1a	3-Bu^t	$\frac{1}{2}TiCl_4$	3ja	20		90	97: 3
7	1a	3-Bu^t	$\frac{1}{2}TiCl_4$	3ja	0		68	97: 3
8	1a	3-Bu^t	$TiCl_4$	3ja	-30		65	98: 2
9	1a	3-Bu^t	$\frac{1}{2}TiCl_4$	3ja	-30		57	98: 2
10	1a	3-Bu^t	$\frac{1}{2}TiCl_4$	3ja	-60		35	98: 2
11	1b	4-MeO	$TiCl_4$	3jb	20	+16.5(0.3)	97	97: 3
12	1d	4-Cl	$TiCl_4$	3jd	20	+26.5(0.4)	62	97: 3

[a,b,c,d,e] See notes a,b,c,d,e in Table 1. [f] Reaction time 48 h.

Excellent values of diastereoselection have been obtained even at room temperature matched with pratically quantitative yield in the case of $TiCl_4$. Phenoxy derivatives obtained from phenol and BCl_3 or $Ti(OPr^i)_4$, that present a lower diastereoselection, let us to identify the minor isomer.

The temperature influenced the diastereoselection in a negligible way, whereas it remarkably affected the yield.

Finally the reaction, carried out at room temperature for 6h, was extended to activated and poorly reactive phenols, affording 2-hydroxymandelic derivatives **3j** with very high stereocontrol (94% d.e.) as well as good yields (Table 2).[10]

The assignment of S configuration at C-2 of isomer **3ja** was made on the basis of chemical correlation with compound **3ia**. Convergent reduction of (2S)-**3ia** and **3ja** to the same diol (-)-1-(2-hydroxy-4-t.butylphenyl)-1,2-dihydroxyethane ensured the 2S attribution to **3ja**. This absolute configuration of the new chiral carbon atom is in accordance with the observed bias of (-)-8-phenylmentylglyoxylate to react on the *si*-face,[9,11] possibly via a chelate mechanism.

In conclusion we have achieved the first and straightforward synthesis of chiral 2-hydroxymandelic esters *via* coordinated Friedel-Crafts *ortho*-hydroxyalkylation of phenols under mild conditions with good yields and good to excellent diastereoselectivity (up to 97 % d.e.).

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7. *General Procedure*: To a solution of 3-*tert*-butylphenol (5 mmol) in anhydrous CH_2Cl_2 (17 ml), 2.5 ml of 1M solution of $TiCl_4$ in anhydrous CH_2Cl_2 freshly prepared were added at -30 °C, while a stream of dry nitrogen was passed. After stirring for 30 min, anhydrous (-)-menthylglyoxylate (**2i**) (5mmol) was added as a solution in CH_2Cl_2 (5 ml). The reaction was stirred for 6h at -30 °C and then quenched with saturated aqueous NH_4Cl solution. Extractive work-up (CH_2Cl_2) and chromatography on silica gel gave **3ia** and **4ia**.
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10. Diastereomeric compounds **3j** and **4j** were easily distinguished by ^1H NMR spectroscopy. Major isomers **3j** show benzylic methine signals at lower chemical shift ($\delta \approx$ 4.1 ppm, $\Delta\delta \approx$ 0.7 ppm).
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