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Manganese-Promoted Regioselective Ring-Opening of 2,3-Epoxy Acid Derivatives: A New Route to α-Hydroxy Acid Derivatives

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This paper is dedicated with best wishes to Professor Benito Alcaide on the occasion of his 60th birthday.

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Abstract: A simple and general methodology directed towards the synthesis 3-aryl-2-hydroxy amides, or esters with total regioselectivity from the easily available 2,3-epoxy amides or esters, promoted by active manganese is described. Utilizing enantiopure epoxy amides as starting materials, the corresponding 3-aryl-2-hydroxy amides in enantiopure form are also available. Some synthetic applications of selected examples of 3-aryl-2-hydroxy carboxylic acid derivatives are shown. A mechanism has been proposed to explain this novel reaction.

Keywords: amides; epoxides; esters; hydroxy acids; manganese

Introduction

Many synthetic applications of 2-hydroxy acid derivatives have been reported,[1] amongst these 2-hydroxy acid derivatives have also used as starting materials to obtain biologically active molecules.[2] In addition, the 2-hydroxy acid moiety is present in an important number of natural products,[3] and some derivatives possessing pharmacological applications.[4]

Several methods have been reported for obtaining 2-hydroxy acid derivatives,[5] and *inter alia*, the most direct access to these species could be considered to be the regioselective ring-opening[6] of 2,3-epoxy acid derivatives, involving the hydrogenation of the corresponding 2,3-epoxy acid derivatives, which generally has been applied to obtain 2-hydroxy esters.[7] To the best of our knowledge, only three papers reporting the transformation of epoxy amides into 2-hydroxy amides have been published. Thus, the treatment of 2,3-epoxy amides with samarium diiodide in the presence of H_2O[8] (aromatic amides) or MeOH (aliphatic amides) afforded 2-hydroxy amides.[9] However, this last method failed to obtain 2-hydroxy esters giving 3-hydroxy esters rather than the desired regioisomer. Recently, the catalytic hydrogenation of epoxy amides to obtain 2-hydroxy amides has also been described.[10] Taking into account these precedents, a novel and straightforward route to 2-hydroxy esters from the corresponding 2,3-epoxy esters avoiding the use of hydrogen gas, or the synthesis of 2-hydroxy amides promoted by a reagent cheaper than SmI_2 would be still of interest.

It has been shown that manganese is a non-toxic[11] and cheap[12] metal, with a reduction potential of the $Mn^{2+}/Mn(0)$ system of -1.03 V[13] [between the reduction potentials of $Zn^{2+}/Zn(0)$ and $Mg^{2+}Mg(0)$], adequate to reduce an important number of organic functions. However, in contrast to other metals, the applications of manganese in organic synthesis have been scarcely developed due to the inability of the commercially available manganese to react directly with organic compounds as consequence of its passivity.[14]

To overcome the lack of reactivity of manganese metal, different procedures to obtain active manganese (Mn*) have been described in 1996 by Rieke[15] and Fürstner[16] and in 1998 by Oshima.[17] After the appearance in the literature of the aforementioned procedures for the preparation of Mn*, the number of contributions reporting new synthetic applications of this metal has increased.[18] Recently, we reported the first sequential processes promoted by Mn*, in which, starting from aldehydes and 2,2-dichloro esters or amides, (*E*)-α,β-unsaturated esters[19] or amides,[20] were obtained, respectively, with complete or total

diastereoselectivity. In a similar manner we have also reported the synthesis of (*Z*)-α,β-unsaturated 2-halo esters or amides with high stereoselectivity,[21] promoted by Mn* from aldehydes and trihalo esters or amides.

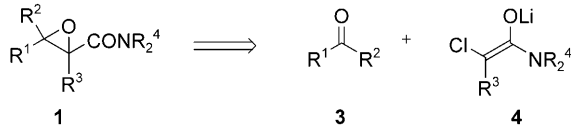
Herein we report the transformation of aromatic α,β-epoxy esters or amides into 2-hydroxy esters or amides, respectively, promoted by active manganese (Mn*). The homochiral version of this method is also reported starting from the corresponding enantiopure epoxy amides. All ring-opening reactions took place with complete regioselectivity. To explain the obtained results a mechanism is proposed.

Results and Discussion

Synthesis of Aromatic 2-Hydroxy Amides

Initially we tested the transformation of epoxy amides **1** into 2-hydroxy amides **2**, as a cheaper alternative procedure to that previously reported with SmI_2.

The starting epoxy amides **1** were readily prepared by reaction of various aldehydes or ketones **3** with the lithium enolates of chloro amides **4**[22] for 2 h and further stirring overnight at room temperature (Scheme 1).

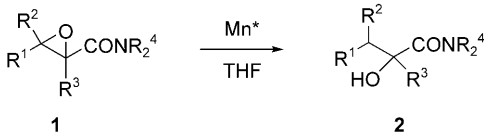


Scheme 1. Preparation of epoxy amides **1**.

Treatment of aromatic α,β-epoxy amides **1** with 3 equivalents of Mn*[23] at room temperature for 2.5 h afforded the corresponding aromatic 2-hydroxy amides **2** in high yields and with complete regioselectivity. When consumption of the starting epoxy amide was not complete, the reaction was performed at room temperature for 12 h (Table 1, entries 1–3).

This proposed methodology to obtain aromatic or unsaturated 2-hydroxy amides **2** seems to be general. Thus, the reaction was carried out with electron-rich (Table 1, entries 2 and 5) or electron-deficient (Table 1, entries 3, 6–8 and 10) groups on the aromatic ring. This process also allowed the employment of disubstituted (Table 1, entries 1–3), or trisubstituted (Table 1, entries 4–12) oxirane rings, and amides derived from different amines, including bulky amines such as diisopropylamine (Table 1, entries 2, 5, 6, 9, and 13). The method tolerated various organic functions such as ethers, nitriles, or chlorine atoms. The reaction could be carried out from epoxy amides de-

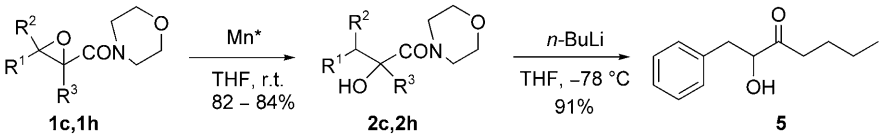
Table 1. Synthesis of 2-hydroxy amides **2** by regioselective ring-opening of 2,3-epoxy amides **1**.



1 **2**

Entry	**1**	**2**[a]	R^1	R^2	R^3	NR_2^4	Yield [%][b]
1	**1a**	**2a**[c]	Ph	H	H	NEt_2	78 (60)
2	**1b**	**2b**[c]	*p*-$MeOC_6H_4$	H	H	$N(i\text{-}Pr)_2$	81
3	**1c**	**2c**[c]	*p*-ClC_6H_4	H	H	[d]	82
4	**1d**	**2d**	Ph	H	Me	NEt_2	81 (64)
5	**1e**	**2e**	*p*-$MeOC_6H_4$	H	Me	$N(i\text{-}Pr)_2$	79 (70)
6	**1f**	**2f**	*p*-ClC_6H_4	H	Me	$N(i\text{-}Pr)_2$	83
7	**1g**	**2g**	*p*-CNC_6H_4	H	Me	NEt_2	85 (69)
8	**1h**	**2h**	*p*-CNC_6H_4	H	Me	[d]	84
9	**1i**	**2i**	(*E*)-MeCH=CH	H	Me	$N(i\text{-}Pr)_2$	80
10	**1j**	**2j**	*p*-ClC_6H_4	H	*n*-Bu	NEt_2	70
11	**1k**	**2k**	(*E*)-PhCH=CH	H	*n*-Bu	NEt_2	65
12	**1l**	**2l**[e]	Ph	Me	H	NEt_2	73
13	**1m**	**2m**[e]	Ph	Et	H	$N(i\text{-}Pr)_2$	76

[a] Unless otherwise noted, all reactions were performed at room temperature for 2.5 h.
[b] Isolated yield after column chromatography based on compounds **1**; the yield of the same reaction carried out using SmI_2 instead of Mn* is shown in parentheses.
[c] This reaction was performed at room temperature for 12 h.
[d] From morpholine amide.
[e] Diastereoisomeric ratios of the starting epoxides **1l,m** ($dr > 98/2$ in both cases) were the same to those observed for α-hydroxy amides **2l,m**.



Scheme 2. Preparation of hydroxy ketone **5**.

rived from α,β-unsaturated aldehydes (Table 1, entries 9 and 11).

The complete regioselectivity (>98%) of the ring-opening reaction was established by ^{1}H and ^{13}C NMR analysis of the crude reaction products, which revealed the presence of only one regioisomer.

The regiochemistry of the ring-opening reaction was established by analysis of ^{1}H and ^{13}C NMR spectra and DEPT experiments of the 2-hydroxy amides **2** prepared, showing that the hydroxy group is bonded to a tertiary carbon atom in compounds **2d–k**, and to the secondary carbon atom in amides **2l–m**. To confirm the structures of **2a–c**, HMBC NMR experiments were carried out.

Interestingly, the reaction could be carried out with aromatic epoxy amides derived from morpholine **1c**, and **1h**, the corresponding 2-hydroxy amides **2c**, and **2h** being obtained in high yields (Scheme 2). Amides derived from morpholine can be readily transformed into ketones by reaction with organolithium reagents.[24] Thus, amide **2c**, was allowed to react with *n*-butyllithium at −78 °C for 3 h, obtaining the expected 1-aryl-2-hydroxyheptan-3-one **5**, in 91% yield (Scheme 2).

In addition to the low price of manganese with respect to SmI_2, the use of Mn* instead of SmI_2 to open the epoxide ring presents other additional advantages. Manganese afforded higher yields of 2-hydroxyamides than SmI_2. Thus, some yields of 2-hydroxy amides reported when using SmI_2 are shown in Table 1 in parentheses. In all of these cases, the yields obtained in the ring-opening of epoxy amides promoted by Mn* were higher than using SmI_2.

When the reaction was performed on aliphatic 2,3-epoxy amides under the same reaction conditions (2.5 h at room temperature), a mixture of the starting material and the corresponding α,β-unsaturated amide was obtained and no trace of 2-hydroxy amides was observed. Modifications to the reaction conditions only allowed the synthesis of α,β-unsaturated amides. Thus, after refluxing for 3 h a mixture of Mn* and 2,3-epoxy-*N,N*-diethyl-2-methyldecanamide **1n** or 3-cyclohexyl-*N,N*-diethyl-2-methylpropanamide **1o** the corresponding (*E*)-*N,N*-diethyl-2-methyldecan-2-enamide **6a** (*E/Z* 80/20, 70% yield) or (*E*)-3-cyclohexyl-*N,N*-diethyl-2-methylprop-2-enamide **6b** (*E/Z* 90/10, 75% yield) were isolated, respectively. The *E*-relative configuration of the C=C double bond was established by comparison with the spectroscopic data of unsaturated amides **6a**, and **6b** with the same compounds previously reported in the literature.[25] It is noteworthy that this is first example reported in the literature of a deoxygenation reaction promoted by active manganese.[26] Hence, studies concerning the synthetic applications of this novel reaction are being carried out in our laboratory.

Synthesis of Aromatic 2-Hydroxy Esters 8

The reaction conditions to carry out the ring opening reaction of α,β-epoxy esters **7**, in general terms, depend on the substitution pattern of the starting epoxy ester. Thus, the synthesis of **8a–c**, and **8g** (from disubstituted epoxy esters **7a–c** and trisubstituted ester **7g**) was attained by the treatment with Mn* at room temperature for 12 h; compounds **8d–f** and **8h** were prepared after reaction with Mn* at reflux for 3 h.[27]

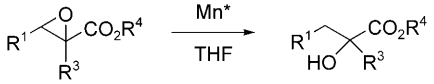
As is summarized in Table 2, 2-hydroxy esters **8** were obtained in good to high yields and with complete regioselectivity. Similarly to amides, the transformation of aromatic epoxy esters into 2-hydroxy esters seems to be general and the aromatic ring can be substituted with electron-donor or electron-withdrawing substituents. Moreover, esters **8** can be derived from bulky alcohols as, for example, isopropyl alcohol (Table 2, entry 5), or from heteroaromatic α,β-epoxy esters such as the furan derivative (Table 2, entry 8) and from γ,δ-unsaturated α,β-epoxy esters (Table 1, entry 3).

In a similar manner to what is indicated in the case of amides, the regioselectivity in the ring-opening process of compounds **7a–h** was examined based on the spectroscopic data of the crude reaction products. These studies have shown the presence of only one regioisomer. The regiochemistry of the final products was similar to that of product **2** and was established by ^{1}H, ^{13}C, DEPT and HMBC NMR experiments.

Some synthetic applications of α-hydroxy ester **8a** have been carried out. Thus, the hydrolysis and reduction of **8a** readily afforded the corresponding α-hydroxy acid **9** and 1,2-alkanediol **10** in high yields (Scheme 3).

When the reaction was performed from **7i**, and **7j**, under the same reaction conditions, the corresponding 3-hydroxy esters **11a**, and **11b** were obtained rather than the desired 2-hydroxy esters in high yields

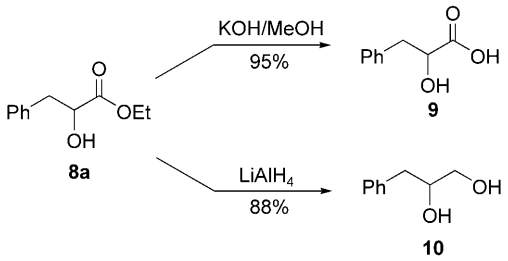
Table 2. Synthesis of 2-hydroxy esters **8** by regioselective ring-opening of 2,3-epoxy esters **7**.



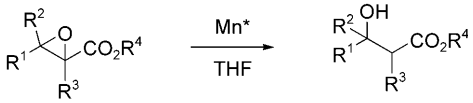
7 **8**

Entry	7	8[a]	R^1	R^3	R^4	Yield [%][b]
1	**7a**	**8a**	Ph	H	Et	77
2	**7b**	**8b**	*p*-ClC_6H_4	H	Me	60
3	**7c**	**8c**	(*E*)-MeCH=CH	H	Me	65
4	**7d**	**8d**	Ph	Me	Et	75
5	**7e**	**8e**[c]	*p*-$MeOC_6H_4$	Me	*i*-Pr	73
6	**7f**	**8f**[c]	*p*-CNC_6H_4	Me	Et	80
7	**7g**	**8g**	*p*-CNC_6H_4	*n*-C_5H_{11}	Et	76
8	**7h**	**8h**[c]	2-furyl	Me	Et	61

[a] Unless otherwise noted these reactions were performed at room temperature for 12 h.
[b] Isolated yield after column chromatography based on compounds **1**.
[c] This reaction was performed at reflux for 3 h.



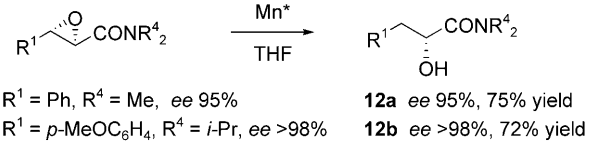
Scheme 3. Transformation of α-hydroxy ester **8a** into α-hydroxy acid **9** and 1,2-alkanediol **10**.



Scheme 4. Transformation of **7i,j** into **11a,b**.

(Scheme 4). The regiochemistry in the ring-opening reaction was established by comparison of the spectroscopic data of hydroxy esters **11a**, and **11b** to the thos eof same compounds previously reported in the literature.[28]

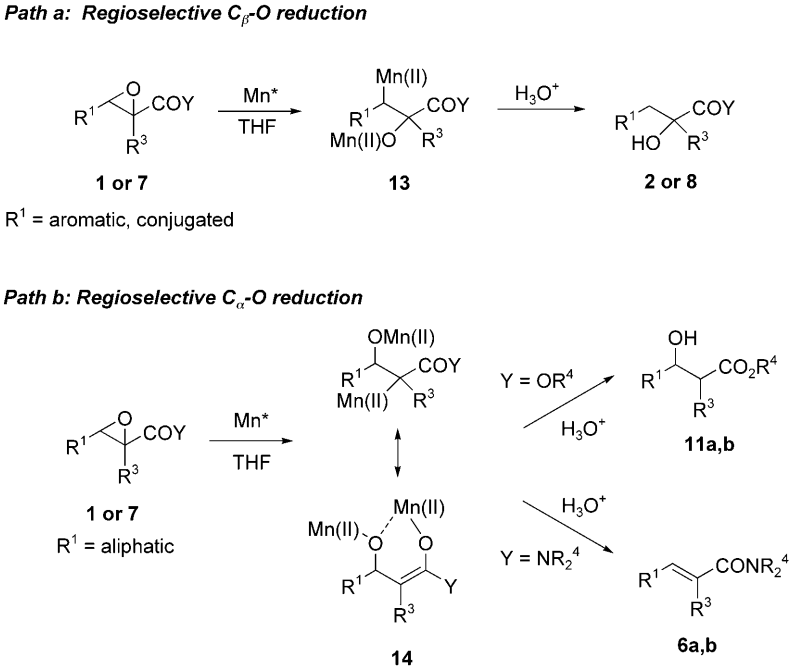
This methodology is also useful to obtain enantiomerically enriched 3-aryl-2-hydroxy amides **12**. Thus, starting from optically active (2*R*,3*S*)-2,3-epoxy-*N,N*-dimethyl-3-phenylpropanamide **1p** or (2*R*,3*S*)-2,3-epoxy-*N,N*-diisopropyl-3-(4-methoxyphenyl)propanamide **1q** the corresponding enantiopure (2*R*)-2-hydroxy-*N,N*-dimethyl-3-phenylpropanamide **12a**[29] or (2*R*)-2-hydroxy-*N,N*-diisopropyl-3-(4-methoxyphenyl)-propanamide **12b** could be prepared, with same *ee* to that shown by the starting materials (95 and >98%, respectively; Scheme 5). Both chiral epoxy amides



Scheme 5. Transformation of enantiopure epoxy amides into optically active α-hydroxy amides **12**.

were readily obtained by enantioselective epoxidation of the corresponding (*E*)-α,β-unsaturated amides being obtained with *ee* 95 and >98%, for **1p** and **1q**, respectively.[29b] The *ee* were determined by HPLC analysis.[30]

The synthesis of aromatic 2-hydroxyamides **2** and 2-hydroxy esters **8** might be explained by assuming the regioselective reduction of the C–O bond promoted by Mn* (Scheme 6). Thus, we could initially surmise that the reduction of the oxirane ring on amides **1** or esters **7** could take place through two different paths: a) the reduction of the C_β–O bond to afford the 2-hydroxy acid compound; and b) the reduction of the C_α–O to yield the 3-hydroxy acid derivative (Scheme 6). We could consider that the cleavage of the C_β–O bond in 3-aryl-2,3-epoxy amides or esters is favoured, in comparison to the C_α–O bond, due to a benzylic anion **13** (or conjugated anion in the case of epoxy compounds **1i**, **1k**, and **7c**) being obtained, since this anion is stabilized by resonance. In order to justify the anionic or radical pathway, we have examined the treatment of 3-(4-chlorophenyl)-*N,N*-diisopropyl-2,3-epoxypropanamide **1f** with Mn*: i) in the absence of light; and ii) in the presence of AIBN. In both cases, no differences were observed in the reaction products when compared with the data described in Table 1 so, an anionic mechanism is suggested.



Scheme 6. Mechanistic proposal for the conversion of **1** or **7** into **2**, **6**, **8**, or **11**.

Another indirect probe of this mechanism is the result obtained from aliphatic esters (Path b). In these compounds, the absence of a stabilization of the anionic intermediate, after the oxiraneopening, afforded the corresponding 3-hydroxy regioisomer instead of the 2-hydroxy derivative. In this latter case, the stabilization is due to the resonance with the carbonyl group in **14**. Hydrolysis of enolate **14** would afford 3-hydroxy esters **11**. A similar intermediate **14** has been proposed in the previously reported synthesis of (*E*)-α,β-unsaturated amides promoted by active manganese. Hence this intermediate **14** would also explain the formation of compounds **6** from aliphatic α,β-epoxy amides **1n–o**.[20]

Conclusions

In conclusion, a simple and general methodology has been developed to synthesize aromatic 3-aryl-2-hydroxycarboxylic derivatives, with total regioselectivity, from the readily available 2,3-epoxy esters or amides, promoted by active manganese. The synthesis of 3-aryl-2-hydroxy amides in enantiopure form has been described to demonstrate that this method can be also used to obtain optically active 2-hydroxy derivatives. A mechanism has been proposed to explain this reaction.

Experimental Section

Characterization data for all new compounds are available in the Supporting Information file.

Preparation of 2,3-Epoxy Amides 1

To a −78 °C stirred solution of the corresponding 2-chloro amide (4.5 mmol) in dry THF (4 mL) was added dropwise lithium diisopropylamide [prepared from MeLi (3.2 mL of 1.5 M solution in diethyl ether, 5 mmol) and diisopropylamine (0.8 mL, 5 mmol) in THF 25 mL at 0 °C]. After stirring for 10 min, a solution of the corresponding aldehyde or ketone (3.5 mmol) in dry THF (4.5 mL) was added dropwise at −78 °C and the mixture was stirred for 2 h. Then, the resulting mixture was allowed to warm to room temperature and stirred for 12 h at this temperature. Then this was quenched with aqueous saturated solution of NH_4Cl (20 mL) and extracted with diethyl ether (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuuum. The crude 2,3-epoxy amides **1** were purified by flash column chromatography on silica gel (hexane:EtOAc, 3:1) provided pure compounds.

Preparation of 2,3-Epoxy Esters 7

To a stirred solution of the corresponding 2-halo ester (2.5 mmol) at −78 °C in dry THF (4 mL) was added dropwise potassium hexamethyldisilazide (6.5 mL of 0.5 M solution in toluene, 3.25 mmol). After the stirring for 10 min, a solution of the corresponding aldehyde or ketone (2.5 mmol) in dry THF (4 mL) was added dropwise at −78 °C, and the resulting mixture was allowed to warm to room temperature. The resulting solution was quenched with a saturated aqueous solution of NH_4Cl (20 mL). Usual

work-up provided crude 2,3-epoxy esters **7**, which were purified by column flash chromatography over silica gel (hexane:EtOAc, 5:1).

Preparation of Highly Active Manganese (Mn*)

A mixture of lithium (26 mmol) and 2-phenylpyridine (4 mmol) in THF (20 mL) under a nitrogen atmosphere was stirred for 1 h. In a separate flask a solution of the Li_2MnCl_4 complex was prepared by stirring a suspension of anhydrous $MnCl_2$ (13 mmol) and LiCl (26 mmol) in THF (20 mL) for 30 min. Then, this yellow solution was added at room temperature *via* syringe to the 2-phenylpyridine/lithium solution previously prepared and was stirred, under a nitrogen atmosphere at room temperature for 1 h. The black slurry was allowed to stir at room temperature for 3 h further.

General Procedure for the Synthesis of 2-Hydroxy Amides 2 and 12

In the case of 2-hydroxy amides **2a–c** and **12a,b**, the slurry of Mn* (1.5 mmol, 4.5 mL) in THF was added to a stirred solution of 2,3-epoxy amides **1** (0.5 mmol) in THF (2 mL) under an inert atmosphere. The mixture was stirred at room temperature for 12 h before it was quenched with 3 M HCl. The organic material was extracted with diethyl ether (3 × 20 mL), the combined organic extracts were washed successively with HCl 3 M (2 × 10 mL), saturated $NaHCO_3$ (2 × 20 mL), and water (2 × 20 mL) and dried over Na_2SO_4. Solvents were removed under vacuum. Purification by flash column chromatography on silica gel (hexane:EtOAc, 3:1) provided pure compounds. However, for the case of the synthesis of compounds **2d–m** instead of at room temperature for 12 h, the reaction was carried out at room temperature for 2.5 h.

General Procedure for the Synthesis of Butyl [2-(4-Chlorophenyl)-1-hydroxy-1-ethyl] Ketone 5

n-Butyllithium (3.0 mmol) was added dropwise to the corresponding 2-hydroxy amide **2c** (1.0 mmol) in THF (4 mL) at −78 °C. After stirring for 3 h the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), followed by extraction with diethyl ether (3 × 10 mL). Usual work-up provided crude product **5**, which were purified by flash column chromatography on silica gel (hexane:EtOAc, 3:1)

General Procedure for the Synthesis of 2-Hydroxy Esters 8 and 3-Hydroxy Esters 11

The procedure for the synthesis of **8a–c**, **8g and 11a,b** consists of the addition of the slurry of Mn* (2 mmol, 6.8 mL) in THF to a stirred solution of 2-hydroxy ester **7** (0.5 mmol) in THF (2 mL) under an inert atmosphere. The mixture was stirred at room temperature for 12 h before it was quenched with HCl 3 M. The organic material was extracted with diethyl ether (3 × 20 mL), the combined organic extracts were washed sequentially with HCl 3 M (2 × 10 mL), saturated $NaHCO_3$ (2 × 20 mL), saturated $Na_2S_2O_3$ (2 × 20 mL), brine (2 × 20 mL) and dried over Na_2SO_4. Solvents were removed under vacuum. Purification by flash column chromatography on silica gel (hexane:EtOAc 10:1) provided the pure compounds **8** and **11**.

In the case of 2-hydroxy esters **8d–f** and **8h**, they was prepared after reaction with Mn* at reflux for 3 h.

General Procedure for the Synthesis of 2-Hydroxy-3-phenylpropanoic Acid 9

To a solution of the corresponding α-hydroxy ester **8a** (1.0 mmol) in MeOH (2 mL) under a nitrogen atmosphere was added KOH (3.0 mmol). After stirring the mixture for 12 h at room temperature the reaction was quenched by the addition of HCl 1 M (5 mL). The organic material was then extracted with diethyl ether (3 × 10 mL) and dried over Na_2SO_4. Solvents were removed under vacuum. Purification by flash column chromatography on silica gel (hexane: EtOAc, 1:1) afforded pure compound **9.**

Procedure for the Synthesis of the 1,2-Alkanediol 10

To a suspension of $LiAlH_4$ (1.0 mmol) in THF a solution of the corresponding α-hydroxy ester **8a** (1.0 mmol) in THF (1 mL) was added dropwise at 0 °C. After stirring of the mixture for 12 h at room temperature, the reaction was quenched by addition of a mixture of water/ice and extracted with ether. The combined organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude products **10** were purified by flash column chromatography on silica gel (hexane:EtOAc, 1:1).

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