Efficient Addition of Acid Enediolates to Epoxides

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We report new conditions to facilitate the addition of dianions of carboxylic acids to epoxides as an alternative method to the use of aluminum enolates. These conditions require the use of a sub-stoichiometric (10%) amount of amine for dianion generation and the previous activation of the epoxide with LiCl. Other Lewis acids have been shown to be less effective. Yields are good but only low diastereoselectivity is attained, which has not been controlled despite attempts at optimization.

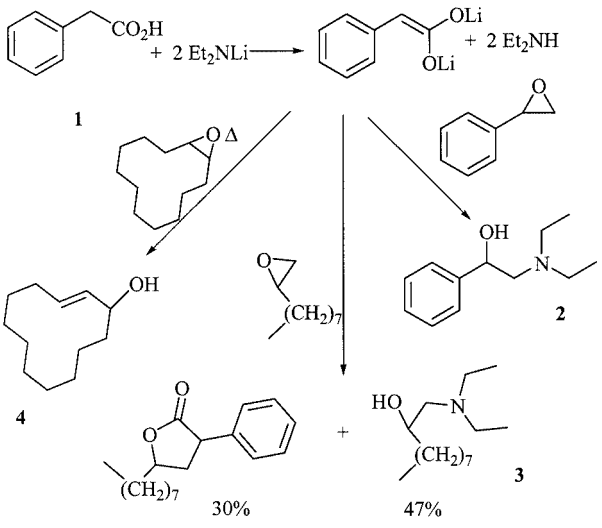
Introduction

The opening of epoxide rings by nucleophiles is a frequently required transformation for the synthesis of organic compounds,[1] usually in the formation of γ-lactones.[2] However, typical lithium enolates from esters do not satisfactorily react with epoxides [3] and high yields are generally only achieved by using the corresponding aluminum ester enolates.[1,4] It is likely that the presence of a Lewis acid such as the aluminum cation leads to an electrophilic assisted opening of the epoxide.[5]

Addition of the enediolates of carboxylic acids to epoxides was reported a few years ago with irregular results.[6] The lack of recently published results leads us to think that unsatisfactory results from other enolates and epoxides have discouraged a systematic study of the selectivity of these reactions.

Lithium dialkylamides are the bases usually used to generate lithium enediolates[7] owing to their strength as bases and their low nucleophilicity, especially when they are derived from sterically hindered amines, and to their solubility in non-polar solvents.[8,9] It is well known that, in these solvents, lithium enolates exist as complex ion-pair aggregate structures. The metal centre may be coordinated to solvent molecules or other chelating ligands, such as the amines resulting from the deprotonation of the acid by the lithium amide. The available data confirms the complexity present in these aggregated reactive species. Many different factors can affect those aggregates and consequently their reactivity.

These highly basic conditions are critical to the results of the addition of carboxylic acid dianions to epoxides. For instance, addition of phenylacetic acid **1** to two equivalents of LDE (lithium diethyl amide) affords the corresponding lithium enediolate (as an equilibrium system LDE/carboxylate enediolate/amine), which on treatment (Scheme 1):



Scheme 1

a) with a highly reactive epoxide, such as styrene oxide, yields the corresponding amino alcohol **2** in 77% yield, even though the amide is the only effective nucleophile present in the reaction medium.

b) with a less reactive epoxide, such as 1,2-epoxidecane, yields a mixture of amino alcohol **3** and γ-lactone from addition of the enediolate.

c) with a secondary epoxide, such as cyclododecene oxide, gives no addition products until it is heated for one hour under reflux. This treatment led to the isolation of allylic alcohol **4**, which results from the amide acting as a base, as has been already described.[10]

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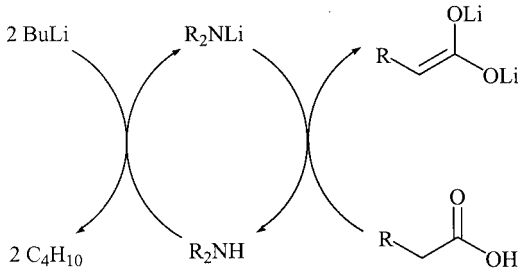
Previous studies by our group on reactions of enediolates with several electrophiles[11] led us to develop new conditions for the generation of dianions of carboxylic acids, which, in some cases, improved the yield and selectivity of the reaction.[12] We have optimized a complete generation of dianions of carboxylic acids by using an equimolecular amount of *n*BuLi combined with a less than stoichiometric amount of amine. As can be seen in Scheme 2, a catalytic cycle is possible because the carboxylate and the dianion can be held together without self-condensation. This is an advantage of diendiolate chemistry over the corresponding enolates. The amount and nature of the amine can be changed, but 0.6 equivalents of amine has evolved as a standard in our laboratory because it has proved to be an efficient method of generating dianions while avoiding addition of *n*BuLi to the acid or the appearance of any self-condensation products.



Scheme 2

Results and Discussion

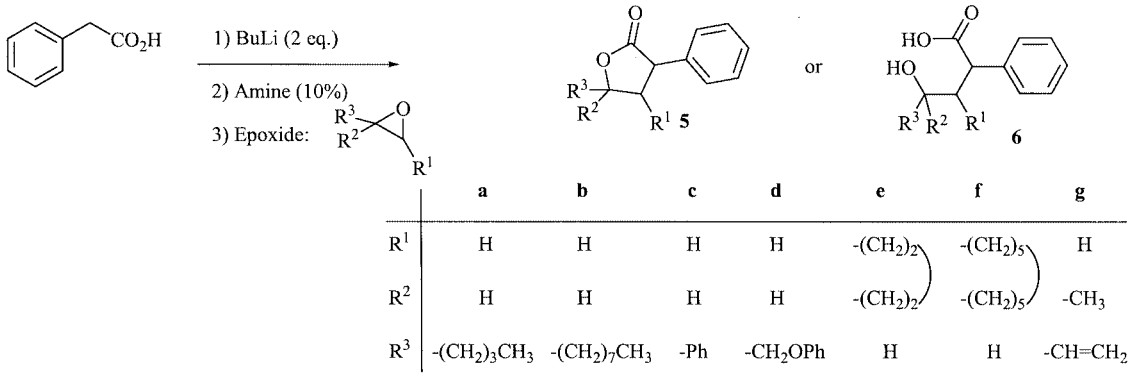
We report here the results obtained when a sub-stoichiometric amount of amine is tested with the addition of the phenylacetic acid (**1**) dianion to several epoxides (**a**−**g**). (Scheme 3). Factors that might have affected the yield were optimized, namely: the amount and nature of the lithium amide used as a base to generate the dianion, the temperature and the reaction time.

The optimized standard conditions were found to be 3 h at room temperature using 10 mol % of the corresponding amine. The corresponding yields along with any additives used are given in Table 1. In every case only one regioisomer, formed from addition to the most accessible epoxide site, was observed. Workup allows isolation of the γ-lactones **5** or of the corresponding hydroxy acid **6**, depending on the intermediate. In each case the hydroxy acids lead to the corresponding γ-lactones quantitatively by refluxing in toluene for 2 h.

Following the trend in our group, LDE was used as a base to generate the dianion except for reaction with epoxide **d** (Entry 10). LDA is slightly less basic than LDE but its greater bulk makes it more effective (see Entries 9 and 10) in the reaction of the dianion with epoxide **d**. Despite this, the corresponding amino alcohol is produced even when a sub-stoichiometric amount of LDE is used to generate the dianion. Using LDA may lower the amount of the unwanted side reaction, such as the attack of the amide on the epoxide to give the amino alcohol.

In the reaction of phenylacetic acid with styrene oxide (**c**) 30% of an additional product, 2,4-diphenyl-3-butenoic acid, was observed in the acidic fraction along with the expected γ-lactones **5c**. This product is formed on dehydration of hydroxy acid **6c**. Attempts to purify products **5c** and **6c** by column chromatography led to their total decomposition. As shown in Table 1, results were good for the addition of phenylacetic dianion to primary epoxides, with a noticeable increase in yield compared to those described previously.[1,2] Creger et al.[2] indicated that a stoichiometric amount of LDA was successfully used in some cases (steroidal transformations). More rigorous conditions (i.e. reflux for 18 h) were needed in order to achieve a 75% conversion, but this is not of general use.

The relative configuration for products **5a**, **5b**, **5d** and **6g** were determined by NOE NMR experiments. The hydroxy acid **6g** was converted into the corresponding γ-lactone by refluxing it in toluene for 2 h in order to confirm its configuration. The diastereomeric ratio is very poor under these conditions (see Table 1). Taking into account that alkoxyamines can lead to an increase of the (*R**,*S**)-diastereoisomer in alkylations of dianions [9c] we tested the effect on the stereoselectivity of their addition to epoxides. In order to get good induction, larger amounts of amine are required but, on optimization, we reached the conclusion that not more than a 30% amount of amine may be used.



	a	b	c	d	e	f	g
R^1	H	H	H	H	-$(CH_2)_2$	-$(CH_2)_5$	H
R^2	H	H	H	H	-$(CH_2)_2$	-$(CH_2)_5$	-CH_3
R^3	-$(CH_2)_3CH_3$	-$(CH_2)_7CH_3$	-Ph	-CH_2OPh	H	H	-CH=CH_2

Scheme 3

Table 1. Addition of phenylacetic dianion to primary and secondary epoxides (Scheme 3)

Entry	Epoxide	Product	Yield	*RR*:*RS*	Amine (equiv.)	Observations
1	**a**	**5a**	76	55:45	LDE (0.2)	
2	**a**	**5a**	74	40:60	LDE (0.2)	DMI (2 equiv.)
3	**a**	**5a**	0	–	LDE (0.2)	DMI (10 equiv.)
4	**a**	**5a**	61	51:49	LDE (0.2)	DDOMG
5	**a**	**5a**	74	57:43	NBHPA (0.5)	
6	**b**	**5b**	76	55:45	LDE (0.2)	
7	**b**	**5b**	63	51:49	NBHPA (0.5)	
8	**c**	**5c**	77	[a]	LDE (0.2)	30% 2,4-diphenyl-3-butenoic acid
9	**d**	**5d**	71	–	LDE (0.2)	20% **2d**
10	**d**	**5d**	73	48:52	LDA (0.2)	
11	**d**	**5d**	73	45:55	NBHPA (0.5)	
12	**e**	**6e**	58		LDE (0.2)	74% starting material
13	**f**	–	–		LDE (0.2)	
14	**f**	**4**	60		LDE (0.2)	Reflux for 3 h

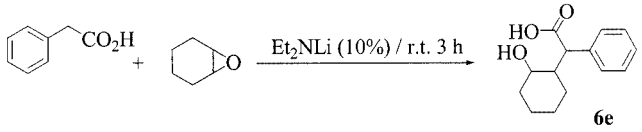
[a] Undetermined decomposes on purification.

Accordingly, a sub-stoichiometric amount of lithium *N*-benzyl-2-hydroxypropanamide (NBHPA) was used as a base (see Entries 5, 7 and 11).[11] Similar yields to those obtained with LDE were observed, but with no increase in diastereoselectivity.

On the other hand, α/γ-regioselectivity in the alkylation of dienediolates, from unsaturated carboxylic acids, may be controlled by the addition of specific lithium chelating compounds. This probably occurs by modification of the aggregation states.[12b] Here we have used 1,3-dimethylimidazolidin-2-one (DMI) and 1,4,3,6-tetrahydro-di-*O*-methyl-D-glucitol (DDOMG) but they did not affect this reaction (Entries 2, 3, 4). The amount of DMI used allows it to act as a lithium chelating agent (Entry 2) but when it was used as a co-solvent (Entry 3) no product was isolated.

The less reactive secondary epoxides do not react under these conditions and the elimination process described above prevents the use of higher temperatures.[13] In order to circumvent this problem we turned to the well-known use of Lewis acids for activating carbon–carbon bond for-

Table 2. Lewis acid-catalysed addition of phenylacetic dianion to cyclohexene oxide (**e**)



6e

Entry	Lewis acid	Lewis acid equivalents	Crude yield	Proportion **6e**	starting material
1	–	1 equiv.	58	26	74
2	$CeCl_3$·THF	1 equiv.	75	24	76
3	$CeCl_3$ (powder)	1 equiv.	82	35	65
4	$CeCl_3$ (granules)	1 equiv.	61	8	92
5	$GaCl_3$	1 equiv.	39	2	98
6	$TiCl_3$·THF	1 equiv.	34	0	100
7	$AlCl_3$·THF	1 equiv.	25	0	100
8	BF_3·OEt_2	1 equiv.	37	–	–
9	$MgCl_2$	1 equiv.	53	40	60
10	$MgCl_2$	2 equiv.	38	7	93
11	LiBr	1 equiv.	61	1	99
12	LiBr	2 equiv.	48	1	99
13	LiCl	1 equiv.	76	53	47
14	LiCl	2 equiv.	39	83	17
15	LiCl	1 equiv.[a]	95	87	13
16	LiCl	1 equiv.[a]	64	51	49
17	$LiClO_4$	2 equiv.[a]	32	77	23
18	$LiClO_4$	2 equiv.	51	69	31

[a] Inverse addition

mation through the ring opening of epoxides.[14] We then tested the compatibility of this method of epoxide activation with dienediolate chemistry.

In order to study this, secondary epoxides were reacted with dianions in the presence of a variety of Lewis acids. Only those Lewis acids compatible with the basic conditions of the reaction were used which has not been previously reported.

As a model reaction, we present here the result of the addition of the enediolate of phenylacetic acid to cyclohexene oxide (**e**) in the presence of several Lewis acids (Table 2) under the optimized conditions described above.

Very irregular results were obtained. As expected, some of the Lewis acids produced a complete reprotonation of the dianion and only starting material was recovered. Others, usually lithium salts, led to an increase in the yield of the addition product. The best results were obtained with LiCl under inverse addition. Inverse addition involved the addition of the dianion solution to a mixture of the epoxide with LiCl in THF (Entry 15, Table 2). Surprisingly, LiBr had no effect under similar conditions (Entries 11 and 12).

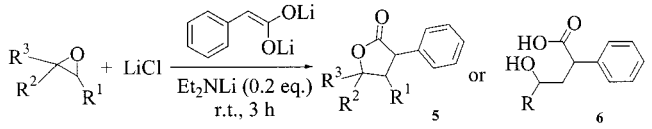
It is well known that LiCl is a disaggregating agent of enolates[15] and that lithium amides form mixed dimers with LiCl, this being the species responsible for the highly enantioselective deprotonation of ketones by chiral lithium amides.[10a] Similar behaviour is observed with LiBr. Thus in the intramolecular alkylation of cyclohexanones the use of LiBr as the additive in place of LiCl leads to slightly better results.[16] Taking this into account, the big difference that LiCl and LiBr exhibit in the activation of the addition of dienolates to epoxides may be related to the LiCl playing a double role. It could be acting firstly as a disaggregating agent of the enolate and secondly as an activating agent in the opening of the epoxide through its coordination to the oxygen. Thus, the different behaviours of the two salts could be related to the second role, but we have no explanation for such a large difference in reactivity with such a small change in the nature of the Lewis acid.

In addition, the dependence of the yield on the relative concentrations of the enediolate, the epoxide and the salt (see Entries 13 to 16) and the higher yield obtained when the dianion is added to a mixture of epoxide and LiCl suggests that activation of the epoxide by the LiCl prior to the addition of the dianion is crucial.

At this point, we want to show the results of the addition of the dienediolate of phenylacetic acid **1** to several epoxides under the combined optimized conditions: sub-stoichiometric amount of amine for base generation and previous addition of LiCl to the epoxide. The results shown in Table 3 indicate that this combination may represent an efficient procedure for the direct addition of dianions of carboxylic acids to epoxides, in a way not described before.

Under these conditions, the use of lithium *N*-benzyl-2-hydroxypropanamide had no effect on the diastereoselectivity of the addition, except for the addition to 1,2-epoxy-2-methyl-3-butene (**g**), the most hindered epoxide used in this study.

Table 3. LiCl catalysed addition of phenylacetic dianion to epoxides under inverse addition conditions



Epoxide	Product	Yield	*R*R**:*R*S**	Amine
a	**5a**	71	47:53	Et_2NH
a	**5a**	71	57:43	NBHPA
d	**5d**	82	38:62	Et_2NH
d	**5d**	65	38:62	NBHPA
g	**6g**	63	57:43	Et_2NH
g	**6g**	78	28:72	NBHPA
e	**6e**	71		Et_2NH
e	**6e**	52		NBHPA

Conclusion

We present new conditions for the addition of dianions of carboxylic acid to epoxides as an alternative to aluminum enolate chemistry. The changes involved are the use of a sub-stoichiometric (10%) amount of amine for dianion generation and activation of the epoxide with LiCl. These modifications show that this reaction has a much wider range than was previously reported.[1]

Experimental Section

General: Melting points were determined with a Cambridge Instruments Hot Plate Microscope and are uncorrected. IR spectroscopic data were obtained for liquid film or KBr discs; the measurements were carried out by the SCSIE (Servei Central de Suport a la Investigació Experimental de la Universitat de Valencia) with a Matteson Satellite FTIR 3000 model spectrophotometer. NMR spectra were recorded for $CDCl_3$ solutions, with Varian Unity 300 or Bruker Unity AC-300, AC-400 or AC-500 spectrometers. High-resolution mass spectra were determined with a Fison VG Autospec spectrometer. Flash Column Silica Gel of 230−400 mesh (manufacturer: Scharlau) was used for flash column chromatography, with hexane/ethyl acetate mixtures for elution.

All reactions were carried out under argon, using standard conditions for exclusion of moisture, in oven-dried glassware, in THF freshly distilled from blue benzophenone ketyl and with diethylamine and diisopropylamine distilled from CaH_2. 1-Benzylamino-2-propanol[9c] was placed under vacuum and left for 24 h before use. The DMI was distilled (106 °C at 17 Torr) and collected over 3/4-Å molecular sieves. The distilled DMI was stored over molecular sieves and kept under Ar.

The BuLi used was 1.6 M in hexane. Exact determination of the solution's concentration was periodically checked before use. Usually, the molarity quoted is not the true concentration of the solution (e.g. 1.18 M for fresh new Aldrich bottles and 1.19 M for Merck ones).

The reaction temperature (−78 °C) was achieved by cooling with a CO_2/acetone bath and 0 °C with an ice/water bath. Organic extracts were dried with anhydrous $MgSO_4$, and solutions were evaporated under reduced pressure with a rotary evaporator and a bath at 40 °C.

General Procedure for Addition Reactions: Carboxylic acid (2.25 mmol) in THF (2 mL) was slowly added to stirred lithium amide (4.8 mmol for stoichiometric amount, 0.5 mmol for sub-stoichiometric LDE or LDA or 1.3 mmol for sub-stoichiometric 1-benzylamino-2-propanol) in THF (2 mL) at −78 °C, according to the method already described.[9c][12a] The solution was stirred for 30 min at 0 °C and cooled again to −78 °C. Epoxide (2.25 mmol) in THF (2 mL) was added dropwise (5 min), and the solution stirred for 1 h at room temperature. The reaction was quenched with water (20 mL) and the mixture extracted with diethyl ether (3 × 15 mL). The aqueous layer was acidified under ice-bath cooling by careful addition of conc. hydrochloric acid, and then extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine and dried ($MgSO_4$). Evaporation of solvent gave the crude acid reaction mixture. For analytical purposes the products were isolated by column chromatography.

Standard Addition Procedure Modifications

Using the Lewis Acid BF_3·Et_2O: BF_3·Et_2O (0.3 mL, 2.25 mmol) was added to the solution of epoxide (2.25 mmol) in THF (1 mL) affording a blood-red complex. This solution was then introduced dropwise into the reaction vessel at −78 °C and the general procedure continued as described.

Using a Solid Lewis Acid: The solution of epoxide (2.25 mmol) in THF (1 mL) was added dropwise to the dianion solution at −78 °C. The reaction flask was opened and the solid Lewis acid (2.25 mmol) was added via a solids funnel (as one sample). The reaction flask was then resealed and the general procedure continued as described.

Using a Chelating Agent: Before addition of the epoxide to the dianion, a solution of the ligand (number of equivalents stated in Table 1) in THF (2 mL) was added to the dianion solution at 0 °C. The solution was maintained at 0 °C, stirring for 15 min. The solution was cooled to −78 °C and the addition of the epoxide continued as described.

Using a Chelating LiCl and Inverse Addition: Instead of adding the LiCl (94.4 mg, 2.25 mmol) to the reaction flask at the beginning of the reaction it was added to a clean flask. The dianion mixture was diluted with THF (4 mL), as the concentrated dianion mixture was too viscous to pass easily through the needle, and then transferred at −78 °C on top of the epoxide mixture under $Ar_{(g)}$. Each reaction was extracted in the same way after being quenched.

5-Butyl-3-phenyltetrahydrofuran-2-one (5a): M.p. 26−31 °C. IR: $\tilde{\nu}_{max.}$ = 3064 (Ar-H), 2958 (C−H), 1769 (C=O), 1603, 1498, 1467 (Ar−H), 1355, 1180, 1002, 935, 754, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): (*R*S**): δ = 7.31 (m, 5 H, Ar-H), 4.63 (m, 1 H, CH-O), 3.92 (m, 1 H, CHC=O), 2.50 (ddd, *J* = 6, 9.2, 13.2 Hz, 1 H, C*H*$_2$CHC=O), 2.38 (ddd, *J* = 6.8, 7.2, 13.6 Hz, 1 H, C*H*$_2$CHC=O), 1.79 (m, 1 H, CHC*H*$_2$CH$_2$), 1.64 (m, 1 H, CHC*H*$_2$CH$_2$), 1.50 (m, 2 H, CHCH$_2$C*H*$_2$), 1.40 (m, 2 H, C*H*$_2$CH$_3$), 0.94 (t, *J* = 6.6 Hz, 3 H, CH_3) ppm; (*R*R**): δ = 7.31 (m, 5 H, Ar-H), 4.48 (m, 1 H, CH−O), 3.88 (m, 1 H, CHC=O), 2.75 (ddd, *J* = 5.2, 8.8, 13.6 Hz, 1 H, C*H*$_2$CHC=O), 2.05 (ddd, *J* = 6, 10.4, 13.6 Hz, 1 H, C*H*$_2$CHC=O), 1.83 (m, 1 H, CHC*H*$_2$CH$_2$), 1.68 (m, 1 H, CHC*H*$_2$CH$_2$), 1.50 (m, 2 H, CHCH$_2$C*H*$_2$), 1.40 (m, 2 H, C*H*$_2$CH$_3$), 0.94 (t, *J* = 6.6 Hz, 3 H, 4′-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (*R*S**): δ = 177.1 (C=O), 136.9 (CAr), 129.1 (2 CHAr) 128.3 (2 CHAr), 127.8 (CHAr), 79.2 (CH−O), 45.9 (*C*HC=O), 36.7 (*C*H$_2$CHC=O), 35.4 (CH*C*H$_2$CH$_2$), 27.7 (CHCH$_2$*C*H$_2$), 22.7 (*C*H$_2$CH$_3$) 14.2 (CH_3) ppm; (*R*R**): δ = 177.5 (C=O), 136.9 (CAr), 129.1 (2 × CHAr) 128.3 (2 × CHAr), 127.8 (CHAr), 78.9 (CH−O), 47.5 (*C*HC=O), 38.4 (*C*H$_2$CHC=O), 35.3 (CH*C*H$_2$CH$_2$), 27.6 (CHCH$_2$*C*H$_2$), 22.7 (*C*H$_2$CH$_3$), 14.2 (CH_3) ppm. MS (EI): *m/z* (%) = 218 (1.4) [M^+], 174 (28), 104 (100) [PhCHCH_2^+], 77 (12) [$C_6H_5^+$]. HRMS: *m/z* calcd. for $C_{14}H_{18}O_2$ = 218.1307, found M^+ = 218.1306.

5-Octyl-3-phenyltetrahydrofuran-2-one (5b): M.p. 44−45 °C. IR: $\tilde{\nu}_{max.}$ = 3075 (Ar−H), 2922 (C−H), 1760 (C=O), 1610, 1522, 1450 (Ar−H), 1388, 1185, 1012, 752, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): (*R*S**): δ = 7.20 (m, 5 H, Ar-H), 4.63 (m, 1 H, CH−O), 3.89 (m, 1 H, CHC=O), 2.49 (ddd, *J* = 6.0, 9.6, 12.8 Hz, 1 H, C*H*$_2$CHC=O), 2.39 (ddd, *J* = 6.4, 6.8, 13.2 Hz, 1 H, C*H*$_2$CHC=O), 1.79 (m, 1 H, CHC*H*$_2$CH$_2$), 1.64 (m, 1 H, CHC*H*$_2$CH$_2$), 2.85−1.15 (m, 12 H, 6CH_2), 0.89 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm; (*R*R**): δ = 7.20 (m, 5 H, Ar-H), 4.48 (m, 1 H, CH−O), 3.88 (m, 1 H, CHC=O), 2.77 (ddd, *J* = 5.2, 8.8, 12.4 Hz, 1 H, C*H*$_2$CHC=O), 2.01 (ddd, 1 H, *J* = 10.4, 12.0, 12.4 Hz, C*H*$_2$CHC=O), 1.82 (m, 1 H, CHC*H*$_2$CH$_2$), 1.68 (m, 1 H, CHC*H*$_2$CH$_2$), 2.85−1.15 (m, 12 H, 6CH_2), 0.89 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (*R*S**): δ = 177.2 (C=O), 137.5 (CAr), 129.2 (2 × CHAr), 128.3 (2 × CHAr), 127.8 (CHAr), 79.3 (CH−O), 45.9 (CHC=O), 36.6 (*C*H$_2$CHC=O), 35.6 (CH*C*H$_2$CH$_2$), 32.1 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 22.9 (*C*H$_2$CH$_3$), 14.3 (CH_3)ppm; (*R*R**): δ = 177.5 (C=O), 136.9 (CAr), 129.0 (2 × CHAr), 127.8 (2 × CHAr), 127.7 (CHAr), 78.9 (CH-O), 45.5 (CHC=O), 38.4(*C*H$_2$CHC=O), 35.7 (CH*C*H$_2$CH$_2$), 32.1 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 22.9 (*C*H$_2$CH$_3$), 14.3 (CH_3) ppm. MS (EI): *m/z* (%) = 274 (1.1) [M^+], 230 (27), 117 (45), 104 (100) [PhCHCH_2^+], 91 (16) [$C_7H_7^+$]. HRMS: *m/z* calcd. for $C_{18}H_{26}O_2$ = 274.1933, found M^+ = 274.1942.

(3*RS*,5*SR*)-5-Phenoxymethyl-3-phenyltetrahydrofuran-2-one (5d): M.p. 119−120 °C. IR: $\tilde{\nu}_{max.}$ = 3059 (Ar−H), 2916 (C−H), 1756 (C=O), 1600, 1585, 1497 (Ar−H), 1244, 1061, 939, 752, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 7 H, Ar-H), 7.00 (t, *J* = 7.6 Hz, 1 H, Ar-H), 6.92 (d, *J* = 8.0 Hz, 2 H, 2 Ar−H), 4.87 (m, 1 H, CH−O), 4.26 (dd, *J* = 3.6, 10.4 Hz, 1 H, C*H*$_2$−O), 4.20 (dd, *J* = 4.4, 10.4 Hz, 1 H, C*H*$_2$−O), 3.97 (dd, *J* = 9.6, 12.3 Hz, 1 H, CHC=O), 2.84 (ddd, *J* = 6.0, 9.2, 12.8 Hz, 1 H, C*H*$_2$CHC=O), 2.48 (ddd, *J* = 10, 12.4, 12.4 Hz, 1 H, C*H*$_2$CHC=O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5 (C=O), 158.4 (CAr′), 136.7 (CAr), 129.8 (2 CHAr′), 129.2 (2 × CHAr), 128.3 (2 × CHAr), 128.0 (CHAr), 121.8 (CHAr′), 114.9 (2 × CHAr′), 76.1 (CH−O), 68.8 (CH_2−O), 46.8 (*C*HC=O), 33.7 (*C*H$_2$CHC=O) ppm. MS (EI): *m/z* (%) = 268 (83) [M^+], 174 (100), 131 (78), 103 (84), 77 (59) [$C_6H_5^+$]. HRMS: *m/z* calcd. for $C_{17}H_{16}O_3$ = 268.1100, found M^+ = 268.1091.

(3*RS*,5*RS*) 5-Phenoxymethyl-3-phenyltetrahydrofuran-2-one (5d): M.p. 90−91 °C. IR: $\tilde{\nu}_{max.}$ = 3036 (Ar−H), 2923 (C−H), 1749 (C=O), 1589, 1547, 1494 (Ar−H), 1235, 1156, 1078, 742, 684 cm^{-1}; δ = 7.33 (m, 7 H, Ar-H), 7.01 (t, *J* = 7.6 Hz, 1 H, Ar-H), 6.94 (d, *J* = 8.0 Hz, 2 H, 2 Ar−H), 4.95 (m, 1 H, CH−O), 4.25 (dd, *J* = 3.3, 10.2 Hz, 1 H, C*H*$_2$−O), 4.17 (m, 1 H, C*H*$_2$−O), 4.16 (m, 1 H, CHC=O), 2.81 (ddd, *J* = 3.6, 9.6, 13.2 Hz, 1 H, C*H*$_2$CHC=O), 2.60 (ddd, *J* = 8.4, 8.4, 13.2 Hz, 1 H, C*H*$_2$CHC=O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4 (C=O), 158.0 (CAr′), 137.6 (CAr), 129.9 (2 × CHAr′), 129.3 (2 × CHAr), 128.1 (2 × CHAr), 127.9 (CHAr), 121.9 (CHAr′), 114.9 (2 CHAr′), 76.1 (CH−O),

69.6 (CH_2−O), 45.8 (*C*HC=O), 33.7 (CH_2*C*HC=O) ppm. MS (EI): *m*/*z* (%) = 268 (100) [M^+], 131 (40), 120 (35), 105 (46), 91 (31) [$C_7H_7^+$], 77 (29) [$C_6H_5^+$]. HRMS: *m*/*z* calcd. for $C_{17}H_{16}O_3$ = 268.1100, found M^+ = 268.1092.

(2-Hydroxycyclohexyl)phenylacetic Acid (6e): M.p. 164−166 °C. IR: $\tilde{\nu}_{max.}$ = 3274 (OH), 2921 (C−H), 2855 (C−H), 1672 (C=O) cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 7.40−7.20 (m, 5 H, Ar-H), 4.93 (s, 2 H, O*H*), 3.85 (d, *J* = 7.2 Hz, 1 H, CHC=O), 3.20 (dt, *J* = 4.2, 9.9 Hz, 1 H, C*H*-OH), 2.11 (m, 1 H, C*H*CHC=O), 1.92 (m, 1 H, HCH_{eq}CHOH), 1.73 (m, 1 H, HCH_{eq}CHCHOH), 1.64 (m, 2 H, CH_2), 1.4 (m, 1 H, HCH_{ax}CHOH), 1.2 (m, 2 H, CH_2), 0.7 (m, 1 H, CH_2) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 167.4 (COOH), 129.3 (CAr), 128.8 (2 × CHAr), 127.9 (2 × CHAr), 126.6 (CHAr), 72.5 (C−OH), 53.4 (Ar-*C*H−CO_2H), 46.7 (*C*HCHOH), 35.1, 27.2, 24.8 and 24.3 (4 × CH_2) ppm. MS (EI): *m*/*z* (%) = 234 (0.2) [M^+], 216 (11) [$M^+ - H_2O$], 173 (15), 172 (100) [$M^+ - H_2O - CO_2$], 143 (12), 136 (33) [$PhCCO_2H_2]^+$, 104 (41) [$PhCHCH_2^+$], 91 (24) [$C_7H_7^+$].

4-Hydroxy-4-methyl-2-phenylhex-5-enoic Acid (6g): Pale yellow oil. IR: $\tilde{\nu}_{max.}$ = 3381 (OH), 2946 (C−H), 2834 (C−H), 1762 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): (*R***S**): δ = 7.30 (m, 5 H, Ar-H), 6.04 (dd, *J* = 11.2, 16.8 Hz, 1 H, CH_2=C*H*), 5.35 (d, *J* = 16.8 Hz, 1 H, CH_2=CH), 5.19 (d, *J* = 11.2 Hz, 1 H, CH_2=CH), 4.04 (dd, *J* = 9.2, 11.2 Hz, 1 H, PhC*H*), 2.60 (dd, *J* = 9.2, 11.2 Hz, 1 H, CH_2COH), 2.36 (t, *J* = 11.2 Hz, 1 H, CH_2COH), 1.56 (s, 3 H, CH_3) ppm; (*R***R**): δ = 7.30 (m, 5 H, Ar-H), 5.93 (dd, *J* = 10.8, 17.2 Hz, 1 H, CH_2=C*H*), 5.38 (d, *J* = 17.2 Hz, 1 H, CH_2=CH), 5.22 (d, *J* = 10.8 Hz, 1 H, CH_2=CH), 3.89 (dd, *J* = 8.8, 12.8 Hz, 1 H, PhC*H*), 2.67 (dd, *J* = 8.8, 12.8 Hz, 1 H, CHCH_2), 2.26 (t, *J* = 12.8 Hz, 1 H, CHCH_2), 1.58 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (*R***S**): δ = 176.8 (CO_2H), 141.0 (*C*H=CH_2), 136.6 (CAr), 130.4 (2 CHAr), 126.2 (2 CHAr), 114.4 (CHAr), 112.4 (CH=*C*H_2), 83.5 (*C*OH), 46.7 (Ph*C*H), 43.1 (CH*C*H_2), 25.5 (CH_3) ppm; (*R***R**): δ = 177.2 (CO_2H), 139.7 (*C*H=CH_2), 136.6 (CAr), 130.4 (2 CHAr), 126.2 (2 CHAr), 114.4 (CHAr), 114.3 (CH=*C*H_2), 83.4 (*C*OH), 46.5 (Ph*C*H), 43.3 (CH*C*H_2), 27.3 (CH_3) ppm. MS (EI): *m*/*z* (%) = 220 (0.5) [M^+], 202 (17) [$M^+ - H_2O$], 158 (55) [$M^+ - H_2O - CO_2$], 157 (29), 143 (20) [$M^+ - C_6H_5$], 143 (100) [$M^+ - CO_2 - H_2O - CH_3$], 129 (38), 128 (38), 118 (20) [$PhCH_2CO^+$], 91 (26) [$C_7H_7^+$], 77 (19) [$C_6H_5^+$]. HRMS: *m*/*z* calcd. for $C_{13}H_{16}O_3$ = 220.1676, found M^+ = 220.1672.

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