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Synthesis of α,α-dichloroalcohols, α-hydroxyketones and 1-chloro-1-arylalkylene oxides via protonation of acyllithium reagents

George W. Kabalka *, Nan-Sheng Li, Su Yu

Department of Chemistry, The University of Tennessee, Knoxville, TN 37996-1600, USA
Department of Radiology, The University of Tennessee, Knoxville, TN 37996-1600, USA

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Abstract

The protonation of acyllithium reagents generated in situ from alkyllithiums and carbon monoxide in the presence of dichloromethane or dichloroarylmethanes produces α,α-dichloroalcohols in high yields. The reaction produces α-hydroxy-ketones in high yields when the aryl group of dichloroarylmethane contains a strong electron-donating group at the *ortho* or *para* position. The transformation of α,α-dichloro-α-aryl alcohols into 1-chloro-1-arylalkylene oxides is achieved in high yields by using sodium amide as a base.

Keywords: α,α-Dichloroalcohols; α-Hydroxyketone; 1-Chloro-1-arylalkylene oxide; Acyllithium; Carbon monoxide

1. Introduction

The transformation of organometallic reagents into useful synthetic intermediates has played an important role in organic synthesis for many years. One such transformation is the carbonylation of organometallic reagents with carbon monoxide. Studies involving acyllithium reagents generated via the carbonylation of organolithium with carbon monoxide have proven to be especially productive [1–7]. For example, Seyferth reported that acyllithium reagents, generated in situ from an alkyllithium and carbon monoxide, react with aldehydes [1], ketones [1], esters [8], lactones [9], isocyanates [10], isothiocyanates [10], carbodiimides [11], carbon disulfide [12], organic disulfides [13], and trimethylchlorosilanes [14] to give acylated products. Nudelman found that the acyllithium, generated from phenyllithium and carbon monoxide, in the presence of alkyl bromides gave diphenylalkylcarbinols [15,16]. In addition, attention has been paid to the carbonylation of lithium alkylamide with carbon monoxide [17–20], followed by the trapping of the acyl anion with electrophiles [21,22]. This reaction was used successfully in the synthesis of carbon-11 labelled carboxylic acid amides [23]. Recently, we found that trialkylboranes reacted with acyllithium reagents to afford ketones in modest yields [24]. We also found that acyllithium reagents could be protonated with dichloromethane [25], dichloroarylmethane [25], or acetonitrile [26] to produce α,α-dichloroalcohols or β-hydroxynitriles. α,α-Dichloroalcohols are important synthetic intermediates, which can be transformed into substituted chloroethylene oxides or α-chlorocarbonyl compounds [27–31]. The synthesis of α,α-dichloro alcohols is usually achieved via the reduction of α,α-dichloro ketones [27–29] or by the addition of the dichloromethyl anion to aldehydes or ketones [30,31]. However, no general method exists for the synthesis of α,α-dichloro-α-aryl alcohols [32]. We wish to report the details of the studies on the protonation of acyllithium reagents with dichlorocompounds. This reaction provides a useful synthetic method for the preparation of α,α-dichloroalcohols, α-hydroxyketones and 1-chloro-1-arylalkylene oxides.

* Corresponding author. Tel.: +1 423 9743260; fax: +1 423 9742997; e-mail: kabalka@utk.edu

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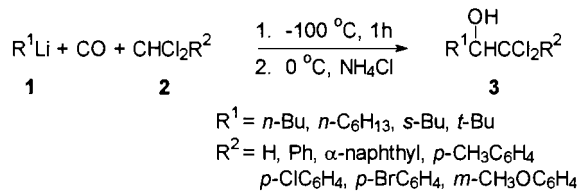


Scheme 1.

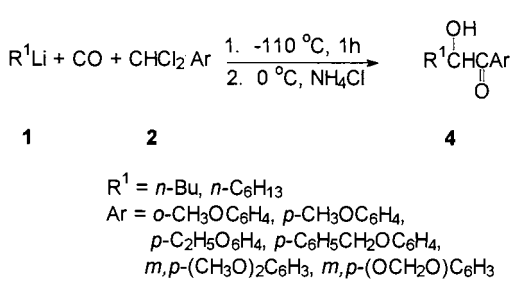
2. Results and discussion

The reaction of an alkyllithium reagent with carbon monoxide in the presence of dichloromethane or dichloroarylmethane generally produces α,α-dichloroalcohols, Scheme 1.

The reaction produces α-hydroxyketones when the aryl group of dichloroarylmethane contains a strong electron-donating group at the *ortho* or *para* position, Scheme 2.

The syntheses are straightforward. Commercially available alkyllithium reagents were utilized in this study. However, as demonstrated by Seyferth for the nucleophilic acylation of chlorosilane [14], other alkyllithium reagents may be used. The reaction is initiated by the slow addition of the alkyllithium reagent to a solution of dichloromethane (or a dichloroarylmethane) in a 4:4:1 (by volume) solvent system of THF:Et_2O:pentane which has been saturated with carbon monoxide at -110°C. After the alkyllithium addition, the mixture is stirred at -110°C for 1 h, and the reaction mixture is then hydrolyzed using saturated aqueous NH_4Cl at 0°C. The products are isolated by silica gel column chromatography. The results of the synthesis of α,α-dichloroalcohols and α-hydroxyketones are shown in Table 1 and Table 2, respectively.

As shown in the tables, generation of the acyllithium reagent in the presence of dichloromethane (Table 1, entry 1) was more efficient than generating the acyllithium prior to the addition of dichloromethane (Table 1, entry 2). In addition, product yields decreased at higher temperature (Table 1, entry 5). In most cases an excess dichloro reagent (**2**) resulted in an increased product yield; however, a large excess was not required.



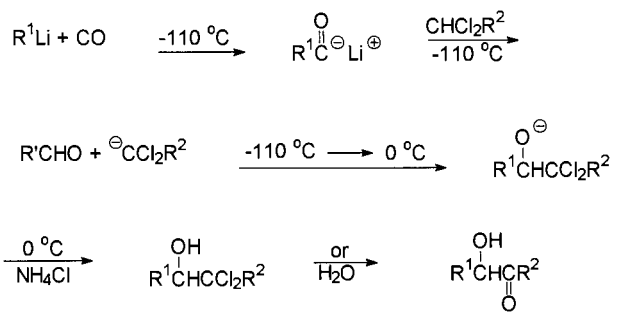
Scheme 2.

The reaction of a stoichiometric quantity of the dichloro compound (**2**) with the acyllithium also led to good yields of the product (Table 1, entries 7, 14, 16, 18, 20, 22 and 27; Table 2, entries 2, 3, 5, 9, 11, 12 and 13). The reaction is most efficient when R^1 is a primary alkyl group. Acyl anion reagents generated from secondary or tertiary alkyllithium reagents react with dichloromethane to give α,α-dichloroalcohols in only modest yields (Table 1, entries 8–12). The lower yields observed with secondary and tertiary alkyllithium reagents may be due to the steric interactions between the bulkier aldehyde intermediates and the chlorinated anion, Scheme 3. The reactions of acyl anion reagents generated from secondary or tertiary alkyllithium with dichloroarylmethane gave complex results.

The reaction of *n*-butyllithium with carbon monoxide in the presence of *p*-methyl-phenyldichloromethane produces 1,1-dichloro-1-(*p*-methylphenyl)-2-hexanol, along with a small amount of 1-(*p*-methylphenyl)-2-hydroxy-1-hexanone (Table 1, entries 17 and 18). The α-hydroxyketone is presumably generated by the hydrolysis of the corresponding α,α-dichloro-α-aryl alcohols. An electron-donating group at the *ortho* or *para* position of the aryl ring may enhance the hydrolysis of the corresponding α,α-dichloro-α-aryl alcohols via a S_N1 side reaction.

The reaction presumably occurs via the intermediate formation of an aldehyde generated by proton abstraction from the dichloro reagent by the initially formed acyl anion. The aldehyde then reacts with the chlorine-stabilized anion as outlined in Scheme 3. The low temperature (-110°C) is required for the formation of the intermediate anion and, presumably, minimizes formation of carbene intermediates. The α,α-dichloroalcohols are apparently hydrolyzed to generate α-hydroxyketones if R^2 is an aryl group with a strong electron-donating group at the *ortho* or *para* position.

α,α-Dichloro-α-aryl alcohols can be transformed into 1-chloro-1-arylalkylene oxides. Interestingly, no reaction occurred when α,α-dichloro-α-arylalcohols were treated with sodium hydroxide in DMF or DMSO. However, using aqueous sodium hydroxide in the presence of a phase transfer catalyst resulted in a partial



Scheme 3.

Table 1
The synthesis of α,α,-dichloroalcohols

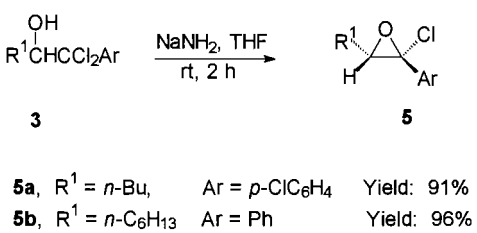
Entry[a]	Product[b]	R^1	R^2	Molar equivalent ratio of 2:1	Yield (%)[c]
1	**3a**	*n*-Bu	H	15:1	81
2[d]	**3a**	*n*-Bu	H	15:1	58
3	**3a**	*n*-Bu	H	6:1	84
4	**3a**	*n*-Bu	H	4:1	81
5[e]	**3a**	*n*-Bu	H	4:1	59
6	**3a**	*n*-Bu	H	2:1	74
7	**3a**	*n*-Bu	H	1:1	62
8	**3b**	*s*-Bu	H	6:1	23
9	**3b**	*s*-Bu	H	4:1	34
10	**3c**	*t*-Bu	H	15:1	32
11	**3c**	*t*-Bu	H	6:1	40
12	**3c**	*t*-Bu	H	4:1	36
13	**3d**	*n*-Bu	Ph	2:1	97
14	**3d**	*n*-Bu	Ph	1:1	89
15	**3e**	*n*-Bu	α-naphthyl	2:1	90
16	**3e**	*n*-Bu	α-naphthyl	1:1	87
17[f]	**3f**	*n*-Bu	*p*-$CH_3C_6H_4$	2:1	74
18[g]	**3f**	*n*-Bu	*p*-$CH_3C_6H_4$	1:1	62
19	**3g**	*n*-Bu	*p*-ClC_6H_4	2:1	90
20	**3g**	*n*-Bu	*p*-ClC_6H_4	1:1	80
21	**3h**	*n*-Bu	*p*-BrC_6H_4	2:1	90
22	**3h**	*n*-Bu	*p*-BrC_6H_4	1:1	86
23	**3i**	*n*-Bu	*m*-$CH_3OC_6H_4$	2:1	90
24	**3j**	*n*-C_6H_{13}	H	6:1	78
25	**3j**	*n*-C_6H_{13}	H	2:1	73
26	**3k**	*n*-C_6H_{13}	Ph	2:1	99
27	**3k**	*n*-C_6H_{13}	Ph	1:1	86

[a] Acyllithium reagents were generated in the presence of the dichloro compounds at −110°C except where noted. [b] All new products were characterized by spectral and elemental analyses. All known compounds were characterized by comparing their spectral and physical properties with literature values. [c] Isolated yields based on alkyllithium reagent. [d] Acyllithium reagent was generated prior to the addition of dichloromethane. [e] Experiment was carried out at −78°C. [f] 6% yield of α-hydroxyketone was also isolated. [g] 7% yield of α-hydroxyketone was also isolated.

transformation of α,α-dichloro-α-aryl alcohols into 1-chloro-1-arylalkylene oxides. The dichloroalcohols are readily transformed into alkylene oxides by reacting them with sodium amide in THF as shown in Scheme 4. The ^{1}H- and ^{13}C-NMR spectra of the product alkylene oxides reveal that only one isomer is produced. Assuming that this isomer is formed via an internal S_N2 reaction which proceeds through the lowest energy configuration. The structure of the epoxides should be that in which the R^1 group and the chloro substituent are *cis*.

3. Conclusion

The first example of protonation of alkyl acyllithium reagents with dichloro compounds is reported. The reaction provides a new method for the preparation of α,α-dichloroalcohols, α-hydroxyketones and 1-chloro-1-arylalkylene oxides in high yields.



Scheme 4.

4. Experimental section

All reagents and solvents were transferred using techniques designed to eliminate contact with air. All glassware and syringes were oven-dried for 24 h prior to use. THF and ethyl ether were distilled from sodium benzophenone ketyl. Pentane and dichloromethane were dried by distillation from calcium hydride. *n*-Butyllithium (1.6 M in hexane), *s*-butyllithium (1.3 M in cyclohexane), *t*-butyllithium (1.7 M in pentane), *n*-hexyllithium (2.0 M in hexane), sodium amide (95%) and aryl aldehydes were purchased from Aldrich. α,α-Dichlorotoluene, Aldrich, was dried and purified by distillation from phosphorus pentoxide. Other α,α-dichloroarylmethanes were prepared by the reaction of phosphorus pentachloride with the corresponding aryl aldehydes according to the literature procedure [33]. ^{1}H- and ^{13}C-NMR spectra were obtained using a

Table 2
The synthesis of α-hydroxyketones

Entry[a]	Product[b]	R^1	Ar	Molar equivalent ratio of 2:1	Yield (%)[c]
1	**4a**	*n*-Bu	*p*-$CH_3OC_6H_4$	2:1	93
2	**4a**	*n*-Bu	*p*-$CH_3OC_6H_4$	1:1	88
3	**4b**	*n*-Bu	*p*-$CH_3CH_2OC_6H_4$	1:1	81
4	**4c**	*n*-Bu	*p*-$C_6H_5CH_2OC_6H_4$	2:1	96
5	**4c**	*n*-Bu	*p*-$C_6H_5CH_2OC_6H_4$	1:1	91
6	**4d**	*n*-Bu	*o*-$CH_3OC_6H_4$	2:1	31
7	**4d**	*n*-Bu	*o*-$CH_3OC_6H_4$	1:1	21
8	**4e**	*n*-Bu	*m,p*-$(CH_3O)_2C_6H_4$	2:1	88
9	**4e**	*n*-Bu	*m,p*-$(CH_3O)_2C_6H_4$	1:1	72
10	**4f**	*n*-Bu	*m,p*-$(OCH_2O)C_6H_4$	2:1	95
11	**4f**	*n*-Bu	*m,p*-$(OCH_2O)C_6H_4$	1:1	88
12	**4g**	*n*-C_6H_{13}	*p*-$CH_3CH_2OC_6H_4$	1:1	77
13	**4h**	*n*-C_6H_{13}	*p*-$C_6H_5CH_2OC_6H_4$	1:1	87

[a] Acyllithium reagents were generated in the presence of the dichloro compounds at −110°C. [b] All products were characterized by spectral and elemental analyses. [c] Isolated yields based on alkyllithium reagent.

Bruker AC-250 (250 MHz) NMR spectrometer. Elemental analysis were performed by Atlantic Microlab, Inc. Norcross, GA. HRMS were performed by the mass spectrometry laboratory at The University of Tennessee-Knoxville.

4.1. Synthesis of α,α-dichloroalcohols and α-hydroxyketones

*4.1.1. The preparation of 1,1-dichloro-1-phenyl-2-hexanol (**3d**) is representative*

To a three-necked, 250 ml, round bottomed flask equipped with a magnetic stirrer, glass-enclosed thermocouple probe, and a fritted-glass gas dispersion tube were added α,α-dichlorotoluene (1.61 g, 10.0 mmol) and 150 ml of a 4:4:1 (by volume) mixture of THF, diethyl ether, and pentane. The solution was cooled to −110°C by means of a low temperature bath. Carbon monoxide was then continuously bubbled into the solution. After 30 min of carbon monoxide addition, *n*-butyllithium (5.0 mmol, 3.1 ml of a 1.6 M solution in hexane) was added slowly via syringe over a period of approximately 45 min. After the addition was complete, the reaction was stirred at −110°C for 1 h and then allowed to warm to 0°C. Hydrolysis was achieved by adding saturated aqueous ammonium chloride (40 ml). The two phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 ml). The organic phases were combined, washed with a saturated NaCl solution (20 ml) and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was isolated by silica gel chromatography [hexane/ethyl acetate = 9/1 (v/v) as eluent] to give **3d** [32] [1.2 g, 97% (Table 2, entry 13)]. ^{1}H-NMR ($CDCl_3$/TMS): δ 7.79–7.67 (*m*, 2H), 7.45–7.32 (*m*, 3H), 4.08 (*dd*, 1H, $J = 1.9$, $J = 9.4$ Hz), 2.38 (*brs*, 1H), 1.67–1.17 (*m*, 6H), 0.84 (*t*, 3H, $J = 7.1$ Hz). ^{13}C-NMR ($CDCl_3$): δ 139.8, 129.2, 128.2, 127.3, 97.6, 81.1, 31.2, 28.3, 22.3, 13.8 ppm.

All other α,α-dichloroalcohols and α-hydroxyketones were prepared via the procedure outlined for **3d**. Yields of these compounds are indicated in Table 1 and Table 2. The characteristics of these compounds are as follows:

*4.1.2. 1,1-Dichloro-2-hexanol (**3a**)*

B.p. 82°C/10 mm Hg (lit. [30] b.p. 86°C/12 mm Hg). ^{1}H-NMR ($CDCl_3$/TMS): δ 5.70 (*d*, 1H, $J = 4.0$), 3.86 (*m*, 1H), 2.36 (*brs*, 1H), 1.87–1.19 (*m*, 6H), 0.93 (*t*, 3H, $J = 7.0$ Hz); ^{13}C-NMR ($CDCl_3$): δ 76.8, 76.4, 32.0, 27.5, 22.5, 13.9 ppm.

*4.1.3. 1,1-Dichloro-3-methyl-2-pentanol (**3b**)*

The ratio of the two diastereomers was 65:35, based on ^{1}H-NMR data. ^{1}H-NMR ($CDCl_3$ /TMS): δ 5.89 (*d*, 0.65H, $J = 3.5$), 5.75 (*d*, 0.35H, $J = 6.3$), 3.72 (*dd*, 0.35H, $J = 6.3$, $J = 4.7$), 3.61 (*dd*, 0.65H, $J = 3.5$, $J = 7.1$ Hz), 2.42 (*brs*, 1H), 1.96–1.02 (*m*, 3H), 1.01–0.83 (*m*, 6H); ^{13}C-NMR ($CDCl_3$): δ 80.1, 79.0, 76.1, 75.8, 37.2, 36.3, 26.3, 24.0, 14.9, 12.6, 11.3, 10.8 ppm. Anal. Found: C, 42.40; H, 7.09. $C_6H_{12}Cl_2O$ Calc.: C, 42.13; H, 7.07.

*4.1.4. 1,1-Dichloro-3,3-dimethyl-2-butanol (**3c**)*

B.p. 55°C/4 mmHg (Lit. [30] b.p. 71–73°C/12mmHg). ^{1}H-NMR ($CDCl_3$/TMS):δ 6.04 (*d*, 1H, $J = 1.6$), 3.69 (*dd*, 1H, $J = 5.2$ $J = 1.6$), 2.66 (*d*, 1H, $J = 5.2$ Hz), 1.04 (*s*, 9H); ^{13}C-NMR ($CDCl_3$): δ 83.2, 74.8, 35.7, 26.4 ppm.

*4.1.5. 1,1-Dichloro-1-(1-naphthyl)-2-hexanol (**3e**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 8.75 (*d*, 1H, $J = 8.6$), 8.15–8.09 (*d*, 1H, $J = 7.5$), 7.91–7.83 (*m*, 2H), 7.62–7.37 (*m*, 3H), 4.82 (*t*, 1H, $J = 5.7$), 2.40 (*s*, 1H), 1.75–1.11 (*m*, 6H), 0.80 (*t*, 3H, $J = 7.1$ Hz); ^{13}C-NMR ($CDCl_3$): δ 134.9, 134.6, 131.4, 129.5, 129.4, 126.3, 126.2, 125.9, 125.7, 124.2, 98.2, 78.3, 32.3, 28.4, 22.3, 13.8 ppm. Anal. Found: C, 64.85; H, 6.13. $C_{16}H_{18}Cl_2O$ Calc.: C, 64.66; H, 6.10.

*4.1.6. 1,1-Dichloro-1-(4-methylphenyl)-2-hexanol (**3f**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.61 (*d*, 2H, $J = 8.3$), 7.18 (*d*, 2H, $J = 8.3$), 4.06 (*dd*, 1H, $J = 1.6$, $J = 9.4$), 2.52 (*s*, 1H), 2.36 (*s*, 3H), 1.67–1.18 (*m*, 6H), 0.84 (*t*, 3H, $J = 7.1$ Hz); ^{13}C-NMR ($CDCl_3$): δ 139.3, 137.0, 128.8, 127.1, 97.8, 81.1, 31.2, 28.4, 22.3, 20.9, 13.9 ppm. Anal. Found: C, 59.67; H, 6.90. $C_{13}H_{18}Cl_2O$ Calc.: C, 59.78; H, 6.95.

*4.1.7. 1,1-Dichloro-1-(4-chlorophenyl)-2-hexanol (**3g**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.68 (*d*, 2H, $J = 8.7$), 7.36 (*d*, 2H, $J = 8.7$), 4.05 (*dd*, 1H, $J = 1.8$, $J = 7.6$), 2.40 (*brs*, 1H), 1.72–1.43 (*m*, 2H), 1.43–1.15 (*m*, 4H), 0.85 (*t*, 3H, $J = 7.1$ Hz); ^{13}C-NMR ($CDCl_3$): δ 138.4, 135.4, 128.8, 128.3, 96.6, 81.0, 31.2, 28.3, 22.3, 13.9 ppm. Anal. Found: C, 51.29; H, 5.30. Calc.: $C_{12}H_{15}Cl_3O$ C, 51.18; H, 5.37.

*4.1.8. 1,1-Dichloro-(4-bromophenyl)-2-hexanol (**3h**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.66–7.46 (*m*, 4H), 4.05 (*dd*, 1H, $J = 1.6$, $J = 7.7$), 2.40 (*brs*, 1H), 1.71–1.44 (*m*, 2H), 1.44–1.17 (*m*, 4H), 0.85 (*t*, 3H, $J = 7.1$ Hz); ^{13}C-NMR ($CDCl_3$): δ 138.9, 131.3, 129.1, 123.7, 96.6, 81.0, 31.2, 28.3, 22.3, 13.8 ppm. Anal. Found: C, 44.34; H, 4.60. $C_{12}H_{15}BrCl_2O$ Calc.: C, 44.20; H, 4.64.

*4.1.9. 1,1-Dichloro-1-(3-methoxyphenyl)-2-hexanol (**3i**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.35–7.27 (*m*, 3H), 6.94–6.85 (*m*, 1H), 4.08 (*d*, 1H, $J = 9.0$), 3.83 (*s*, 3H), 2.49–2.38 (*brs*, 1H), 1.69–1.17 (*m*, 6H), 0.85 (*t*, 3H, $J = 7.1$ Hz); ^{13}C-NMR ($CDCl_3$): δ 159.3, 141.3, 129.3, 119.5, 114.4, 113.6, 97.3, 81.0, 55.4, 31.2, 28.4, 22.3, 13.9 ppm. Anal. Found: C, 56.49; H, 6.58. $C_{13}H_{18}Cl_2O_2$ Calc.: C, 56.33; H. 6.55.

*4.1.10. 1,1-Dichloro-2-octanol (**3j**) [34]*

^{1}H-NMR ($CDCl_3$/TMS): δ 5.70 (*d*, 1H, $J = 4.2$), 3.95–3.80 (*m*, 1H), 2.60 (*brs*, 1H), 1.83–1.15 (*m*, 8H), 0.89 (*t*, 3H, $J = 6.5$ Hz); ^{13}C-NMR ($CDCl_3$):δ 76.8, 76.3, 32.2, 31.6, 29.0, 25.3, 22.5, 14.0 ppm.

*4.1.11. 1,1-Dichloro-1-phenyl-2-octanol (**3k**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.78–7.69 (*m*, 2H), 7.45–7.32 (*m*, 3H). 4.07 (*dd*, $J = 6.0$, $J = 4.0$), 2.50 (*brs*, 1H), 1.67–1.47 (*m*, 2H), 1.47–1.13 (*m*, 8H), 0.85 (*t*, 3H, $J = 6.7$ Hz); ^{13}C-NMR ($CDCl_3$): δ 139.8, 129.2, 128.2, 127.3, 97.6, 81.1, 31.6, 31.5, 28.9, 26.2, 22.5, 14.0 ppm. Anal. Found: C, 61.19; H, 7.34. $C_{14}H_{20}Cl_2O$ Calc.: C, 61.10; H, 7.32.

*4.1.12. 2-Hydroxy-1-(4-methoxyphenyl)-1-hexanone (**4a**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.91 (*d*, 2H, $J = 8.8$), 6.97 (*d*, 2H, $J = 8.8$), 5.09–4.97 (*m*, 1H), 3.89 (*s*, 3H), 3.79 (*brs*, 1H), 1.96–1.19 (*m*, 6H), 0.87 (*t*, 3H, $J = 7.1$ Hz); ^{13}C-NMR ($CDCl_3$): δ 200.4, 164.1, 130.8, 126.5, 114.0, 72.6, 55.5, 36.0, 27.1, 22.4, 13.9 ppm. Anal. Found: C, 70.32; H, 8.22. $C_{13}H_{18}O_3$ Calc.: C, 70.24; H, 8.16.

*4.1.13. 2-Hydroxy-1-(4-ethoxyphenyl)-1-hexanone (**4b**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.89 (*d*, 2H, $J = 8.8$), 6.95 (*d*, 2H, $J = 8.8$), 5.07–4.97 (*m*, 1H), 4.11 (*q*, 2H, $J = 7.0$), 3.75–3.42 (*brs*, 1H), 1.97–1.16 (*m*, 9H), 0.87 (*t*, 3H, $J = 7.0$ Hz); ^{13}C-NMR ($CDCl_3$): δ 200.3, 163.5, 130.8, 126.2, 114.4, 72.6, 63.8, 36.0, 27.0, 22.4, 14.6, 13.8 ppm. Anal. Found: C. 71.26; H, 8.57. $C_{14}H_{20}O_3$ Calc.: C, 71.16; H, 8.53.

*4.1.14. 2–Hydroxy-1-(4-benzyloxyphenyl)-1-hexanone (**4c**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.90 (*d*, 2H, $J = 8.8$), 7.52–7.30 (*m*, 5H), 7.04 (*d*, 2H, $J = 8.8$), 5.14 (*s*, 2H), 5.06–4.96 (*m*, 1H), 3.20–3.70 (*brs*, 1H), 1.94–1.17 (*m*, 6H), 0.87 (*t*, 3H, $J = 7.0$ Hz); ^{13}C-NMR ($CDCl_3$): δ 200.4, 163.2, 135.9, 130.9, 128.7, 128.3, 127.5, 126.6, 114.9, 72.7, 70.2, 36.0, 27.1, 22.5, 13.9 ppm. Anal. Found: 76.59; H, 7.51. $C_{19}H_{22}O_3$ Calc.: C, 76.48; H, 7.43.

*4.1.15. 2-Hydroxy-1-(2-methoxyphenyl)-1-hexanone (**4d**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.84–7.77 (*m*, 1H), 7.58–7.47 (*m*, 1H), 7.09–6.93 (*m*, 2H), 5.16–5.05 (*m*, 1H), 3.91 (*s*, 3H), 3.88–3.78 (*m*, 1H), 1.94–1.15 (*m*, 6H), 0.86 (*t*, 3H, $J = 7.0$ Hz); ^{13}C-NMR ($CDCl_3$): δ 203.5, 158.6, 134.5, 131.0, 124.4, 120.9, 111.6, 76.6, 55.4, 34.1, 27.6, 22.4, 13.8 ppm. HRMS, Found: 221.1180. $C_{13}H_{17}O_3$ ($M-H^+$) Calc.: 221.1178.

*4.1.16. 2-Hydroxy-1-(3,4-dimethoxyphenyl)-1-hexanone (**4e**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.58–7.38 (*m*, 2H), 6.93 (*d*, 1H, $J = 8.8$), 5.12–4.95 (*m*, 1H), 3.97 (*s*, 3H), 3.95 (*s*, 3H), 3.63–3.36 (*brs*, 1H), 1.96–1.17 (*m*, 6H), 0.88 (*t*, 3H, $J = 6.9$ Hz); ^{13}C-NMR ($CDCl_3$/TMS): δ 200.5, 153.9, 149.3, 126.6, 123.1, 110.6, 110.1, 72.5, 56.05, 55.96, 36.2, 27.0, 22.4, 13.8 ppm. Anal. Found: C, 66.52; H, 7.87. $C_{14}H_{20}O_4$ Calc.: C, 66.65; H, 7.99.

*4.1.17. 2-Hydroxy-1-(3,4-methylenedioxyphenyl)-1-hexanone (**4f**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.51 (*dd*, 1H, $J = 1.5$, $J = 8.2$), 7.40 (*d*, 1H, $J = 1.5$), 6.89 (*d*, 1H, $J = 8.2$), 6.07 (*s*, 2H), 5.02–4.92 (*m*, 1H), 3.70–3.26 (*brs*, 1H), 1.94–1.16 (*m*, 6H), 0.87 (*t*, 3H, $J = 7.0$ Hz); ^{13}C-NMR ($CDCl_3$): δ 200.5, 152.4, 148.3, 128.2, 124.8, 108.2, 106.9, 102.0, 72.7, 36.0, 27.0, 22.4, 13.8 ppm. Anal. Found: C, 66.16; H, 6.79. $C_{13}H_{16}O_4$ Calc.: C, 66.09; H, 6.83.

*4.1.18. 2-Hydroxy-1-(4-ethoxyphenyl)-1-octanone (**4g**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.89 (*d*, 2H, $J = 8.8$), 6.95 (*d*, 2H, $J = 8.8$), 5.07–4.97 (*m*, 1H), 4.11 (*q*, 2H, $J = 7.0$), 3.75 (*brs*. 1H), 1.97–1.16 (*m*, 13H), 0.85 (*t*, 3H, $J = 7.0$ Hz); ^{13}C-NMR ($CDCl_3$): δ 200.4, 163.5, 130.8, 126.2, 114.5, 72.7, 63.8, 36.3, 31.6, 29.0, 24.9, 22.5, 14.6, 14.0 ppm. Anal. Found: C, 72.79; H, 9.25. $C_{16}H_{24}O_3$ Calc.: C, 72.69; H, 9.15.

*4.1.19. 4.1.19. 2-Hydroxy-1-(4-benzyloxyphenyl)-1-octanone (**4h**)*

^{1}H-NMR ($CDCl_3$/TMS): δ 7.90 (*d*, 2H, $J = 9.0$), 7.49–7.29 (*m*, 5H), 7.04 (*d*, 2H, $J = 9.0$), 5.15 (*s*, 2H), 5.05–4.97 (*m*, 1H), 1.93–1.13 (*m*, 10H), 0.85 (*t*, 3H, $J = 6.5$ Hz); ^{13}C-NMR ($CDCl_3$): δ 200.4, 163.2, 135.9, 130.9, 128.7, 128.3, 127.5, 126.6, 114.9, 72.7, 70.2, 36.3, 31.6, 29.0 24.9, 22.5, 14.0 ppm. Anal. Found: C, 77.18; H, 8.05. $C_{21}H_{26}O_3$ Calc.: C, 77.27; H, 8.03.

*4.1.20. Synthesis of 1-chloro-1-(4-chlorophenyl)-1-hexylene oxide (**5a**)*

To a solution of 1,1-dichloro-1-(4-chlorophenyl)-2-hexanol (**3g**) (100 mg, 0.357 mmol) in dry THF (2 ml) at 0°C, was added under argon, sodium amide (300 mg, 7.7 mmol). The mixture is stirred at room temperature for 2 h. TLC analysis showed no starting material alcohol remained. The reaction was quenched with saturated aqueous NH_4Cl (1 ml) and H_2O (2 ml). The product was extracted into ether (3 × 10 ml) and dried over anhydrous $MgSO_4$. The solution was evaporated to give **5a**, 79 mg (90% yield). ^{1}H-NMR ($CDCl_3$/TMS): δ 7.43 (*d*, 2H, $J = 8.6$), 7.34 (*d*, 2H, $J = 8.6$), 2.95 (*t*, 1H, $J = 6.0$), 2.00–1.86 (*m*, 2H) 1.62–1.34 (*m*, 4H), 0.96 (*t*, 3H, $J = 7.1$ Hz); ^{13}C-NMR (CCl_3): δ 137.8, 135.0, 128.6, 127.2, 81.3, 67.2, 28.9, 27.9, 22.4, 13.9 ppm. HRMS, Found: 244.0420. $C_{12}H_{14}Cl_2O$ (M) Calc.: 244.0422.

*4.1.21. Synthesis of 1-chloro-1-phenyl-1-octylene oxide (**5b**)*

Compound **5b** was prepared according to the procedure outlined for **5a**. Yield: 96%. ^{1}H-NMR ($CDCl_3$/TMS): δ 7.54–7.29 (*m*, 5H), 2.98 (*t*, 1H, $J = 6.0$), 2.00–1.87 (*m*, 2H), 1.63–1.20 (*m*, 8H), 0.90 (*t*, 3H, $J = 6.6$ Hz); ^{13}C-NMR ($CDCl_3$): δ 139.2, 128.9, 128.4, 125.7, 82.0, 67.0, 31.6, 29.3, 29.0, 25.8, 22.5, 14.9 ppm. HRMS, Found: 238.1140. $C_{14}H_{19}ClO$ (M) Calc.: 238.1124.

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