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MEDICINAL CHEMISTRY RESEARCH

A FACILE SYNTHESIS OF 2-BENZYLOXY/2-(4-ISOPROPYLBENZYLOXY)-2-METHYL-3-(4-SUBSTITUTED PHENYL)PROPANOIC ACID BASED INSULIN SENSITIZING AGENTS: RSR_{13-15} AND PKR_{13-15}

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Abstract. the title compounds (RSR_{13-15}) and (PKR_{13-15}) were prepared by the etherification of benzyl alcohol and 4-isopropylbenzyl alcohol respectively with ethyl-2-bromo-2-methyl-3-(4-substituted phenyl)propanoates in the presence of sodium hydride in THF followed by alkaline hydrolysis of the ethyl esters. The substituted propanoic acids used in this synthetic sequence were prepared by magnesium-methanol reduction of correspondingly substituted propenoic acids, which in turn were prepared via 'Perkin Reaction' of 4-substituted benzaldehydes with propanoic anhydride. The details of the synthetic sequence followed for the preparation of all these compounds having almost all the structural features required for a compound to act as a potent insulin sensitizing agent are reported.

Introduction

Type 2 Diabetes is characterized by hyperglycemia and insulin resistance and/or impaired insulin action[1]. New therapies that normalize blood glucose levels without raising insulin levels as represented by thiazolidinedione class of drugs, after the pioneering discovery of Ciglitazone, still constitute an attractive alternative[2]. These glitazones[3-7] are reported to act by sensitizing peripheral

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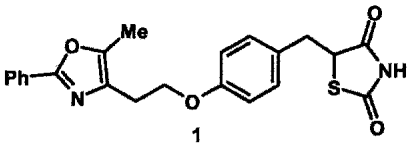
tissue to insulin and increasing the level of glucose transporter protein expression[8]. Compounds with (5-methyl-2-phenyloxazol-4-yl)ethyloxy chain (1) display particularly potent activity[9]. However, due to unsatisfactory efficacy and safety profile of these agents, there has been concern about thiazolidinediones as antidiabetic drugs[10], the hepatotoxicity associated with troglitazone etc.[11].

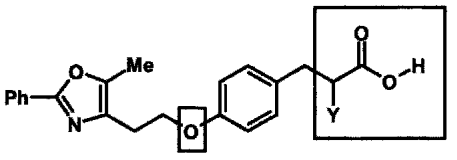
This activity as well as glucose transporter (GLUT 1 or GLUT 4) upregulation was further extended to acyclic acidic analogs[12] of thiazolidinedione and oxazolidinedione, such as (2) where the acidic role is being played by a carboxylic acid having an appropriate substituent at the α-position. Also the observed preference for larger groups at α-position, and the greater activity shown by compound (3) with benzyl substituent in the α-ether (alkoxy) series[12].

The relevance of targeting glucose transport enhancing activity as represented by α-tosylated carboxylic acids such as BM 13.0795 (4)[13] and α-aryloxy-β-arylpropionic acids[12] (5), which are reported to acutely stimulate the translocation of GLUT 4 to the plasma membrane[14], emerging as an efficacious means of restoring glycemic control in NIDDM, attracted our attention.

Chart 1



1



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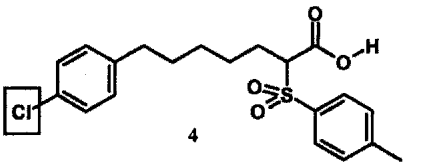

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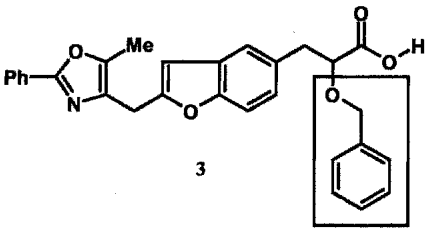

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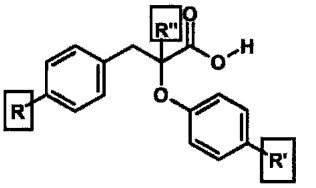


5:R=H,Cl,OMe; R'=H; R"=H
5a:R"=Me; R'=H
5b: R"=Me;R'=i-Pr

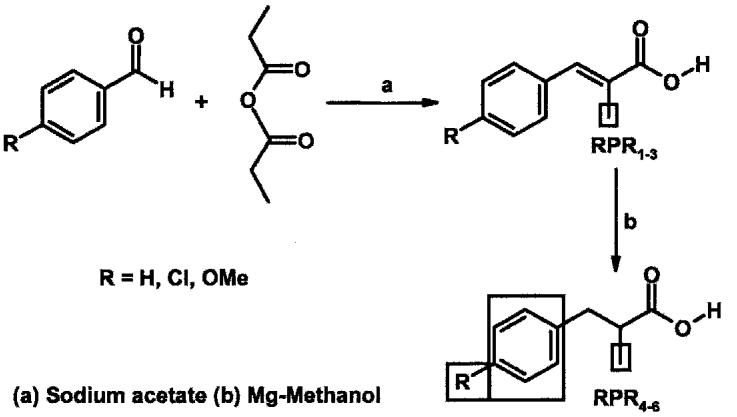
Also the greater potency of the ether series[12] and the enhanced in vivo glucose lowering activity shown by α-methyl substituted α-aryloxy-β-aryl propionic acid[13] (5a), which is reported to be further enhanced by placing a bulkier subsituent (isopropyl or benzyl etc.) at the para position of the α-aryloxy moiety of the (5b) type compounds[13,14], looked quite promising to us. Our goal in the present study was to synthesise 2-benzyloxy/2-(4-isopropylbenzyloxy)-2-methyl-3-(4-substituted phenyl)propanoic acids with an aim to incorporate all the important structural features required in general and the incorporation of 2-benzyloxy/2-(4-isopropylbenzyloxy) moieties in particular for a compound to act as potent insulin sensitizing agent, through a new and facile approach. Such compounds are not reported so far in the series of compounds, known to enhance the translocation of GLUT 4 across the plasma membrane, as per observations made and theoretical structure activity relationship shown in (chart 1) above.

Results and Discussion

2-Methyl-3-(4-substituted phenyl)propenoic acids (RSR_{1-3}) required in this synthetic sequence were prepared through 'Perkin Reaction' by refluxing 4-substituted benzaldehydes and propanoic anhydride.

These acids (RPR_{1-3}) were then reduced to corresponding 2-methyl-3-(4-substituted phenyl)propanoic acids (RPR_{4-6}) using magnesium-methanol methodology[15], in quantitative yields (Scheme 1) rather than the reported use of sodium borohydride,sodium amalgam-methanol and H_2-PtO_2 reagents to affect this reduction[12], because of the instability and cost of the reagent and complexity of workup and sometimes-poor yields.

Scheme 1



Since 2-methyl and 3-(4-substituted phenyl) moieties being intact in the 2-methyl-3-(4-substituted phenyl) propanoic acids (RPR_{4-6}) we prepared, the only structural feature left to be incorporated is to develop 2-benzyloxy/2-(4-isopropylbenzyloxy) linkage to obtain

the desired 2-benzyloxy/2-(4-isopropylbenzyloxy)-2-methyl-3-(4-substituted phenyl) propanoic acids ($RSR_{13\text{-}15}$/$PKR_{13\text{-}15}$).

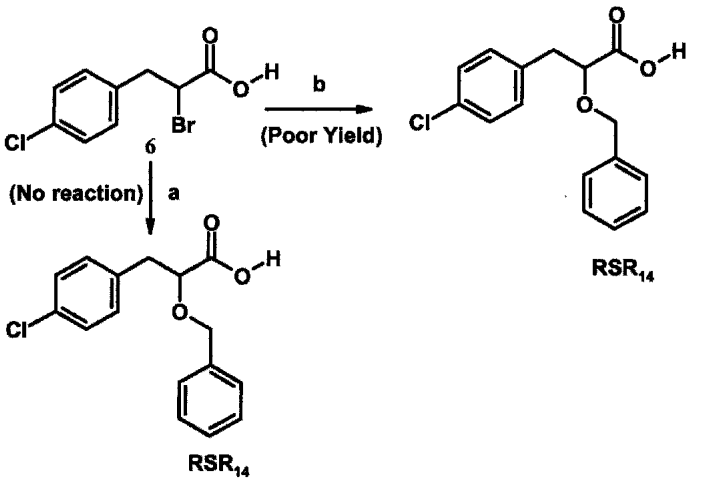
Most of the reported methods[13] to generate similar systems begin from α-bromo acetates/propionates and their condensation with phenoxides generated using K_2CO_3/DMF or NaH/THF to obtain α-aryloxyacetates/propionates and corresponding acetic/propionic acids, which was followed by their benzylation with variously substituted benzyl halides using lithiumcyclohexylisopropylamide (LICA), lithium bis(trimethylsilyl)-amide, lithium diisopropyl amide (LDA) and n-butyl lithium (nBuLi) etc. followed by their hydrolysis.

A combination of other methods to generate 2-methyl-3-phenylpropanoic acids using α-benzyl malonate, followed by their α-methylation using K_2CO_3-MeI and subsequent hydrolysis and decarboxylation, are also reported[13].

We planned to generate the α-benzyloxy/α-(4-sopropylbenzyloxy) linkage by carrying out α-bromination of 2-methyl-3-(4-substituted phenyl)propanoic acids via HVZ followed by coupling of the 2-bromo-2-methyl-3-(4-substituted phenyl)propanoic acids with benzyloxide/4-isopropylbenzyloxide generated from benzyl alcohol/4-isopropylbenzyl alcohol using K_2CO_3-DMF or NaH-THF.

We accordingly subjected 2-bromo-3-(4-chlorophenyl)propanoic acid (6) available in our laboratory to α-benzyloxylation as a trial experiment, by its addition to the benzyl alcohol in the presence of K_2CO_3 taken in DMF and also with NaH taken in THF (Scheme 2).

Scheme 2



(a) K_2CO_3-DMF, BnOH (b) NaH-THF, BnOH

The reaction did not proceed with K_2CO_3-DMF and the yield was very poor with NaH-THF. This may be because of the weaker nature of the base (K_2CO_3-DMF) and possible decarboxylation (NaH-THF) respectively.

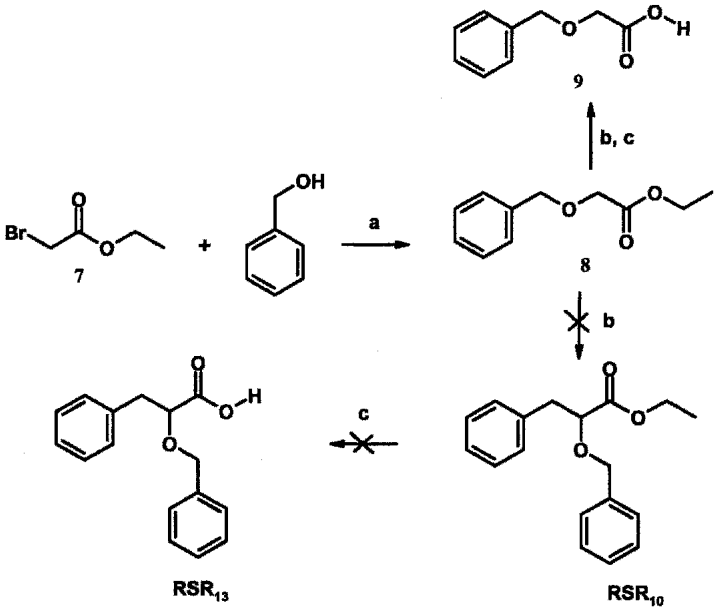
This prompted us to esterify the carboxylic acid function prior to ether formation using NaH-THF. The overall credit of developing this protocol (having α-methyl and β-phenyl or α-benzyl moiety being intact) goes to the availability, ease to handle and also the cost of NaH, which we used for the α-benzyloxylation of ethyl α-bromoacetate (7) with benzyl alcohol as another model experiment (Scheme 3).

The success of ether linkage developed was established from the PMR spectrum of the product (8), which showed the presence of two 2H singlet at δ 3.794 and at δ 4.619 for the CH_2 of the acetate and the CH_2 of benzyloxy moieties, respectively.

The ethyl-2-benzyloxy acetate (8) thus generated was subjected to undergo α-benzylation following the reported methodology[13] using NaH-THF and treating the reaction mixture with benzyl chloride, the product isolated upon alkaline hydrolysis of the ester do not gave the desired 2-benzyloxy-3-phenyl propanoic acid (RSR_{13}), rather it gave 2-benzyloxy acetic acid (9).

Thus α-benzylation has not taken place, was very clear from the PMR spectrum of the product isolated, which do not show any up field 2H signal for the second benzylic methylene in addition to the methylene protons of the benzyloxy moiety which appeared at δ 4.640. The only change in the PMR spectrum was the absence of triplet and the quartet of the ester ethyl.So, no benzylation but only hydrolysis of the ester has taken place.

Scheme 3

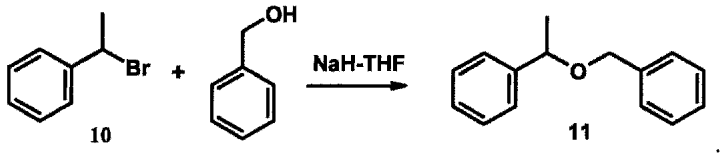


(a) NaH-THF (b) NaH-THF, BnCl (c) EtOH, 4N-NaOH

Thus the required 2-benzyloxy-3- phenylpropanoic acid (RSR_{13}) system could not be generated through this methodology[13]. Therefore, α-benzylation in case of 2-benzyloxy propanoates, is not expected to take place through this methodology (NaH-THF) may be because of the presence of electron releasing α-methyl, we therefore, did not try that.

We additionally tried α-benzyloxylation of α-bromo ethyl benzene(10) available with us using benzyl alcohol and NaH-THF to further explore the possibility of developing the ether linkage on a carbon bearing a methyl group as another model (Scheme 4).

Scheme 4

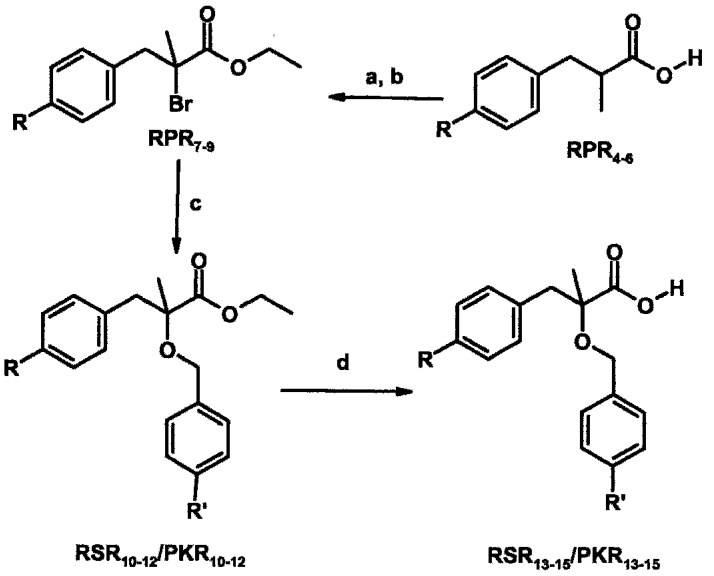


10 11

The PMR spectrum of the product (11) thus obtained showed a 1H quartet at δ 4.519 and a 3H doublet at δ 1.476 along with a 2H singlet for the benzylic CH_2 at δ 4.672 confirming the structure and establishing the formation of ether linkage.

We accordingly, generated the required Ethyl 2-Bromo-2-methyl-3-(4-substituted phenyl)propanoates (RPR_{7-9}) directly and in quantitative yields via HVZ of (RPR_{4-6}) and subsequent quenching of the α-bromo acid chlorides thus obtained in absolute ethanol to achieve α-bromination as well as esterification of the 2-Methyl-3-(4-substituted phenyl)propanoic acids simultaneously (Scheme 5).

Scheme 5



R = H, Cl, OMe; R' =H, i-Pr

(a) Thionyl chloride,Red-P and Bromine (b) Absolute EtOH
(c) NaH/THF, BnOH/4-i-PrBnOH (d) EtOH,4N-NaOH

Formation of ether linkage at α-position being the final and most important step of this synthetic sequence was successfully carried out by treating the Sodium salt of benzyl alcohol/4-isopropylbenzyl alcohol, generated from benzyl alcohol/4-isopropylbenzyl alcohol and NaH taken in THF, with ethyl-2-bromo-2-methyl-3-(4-substituted phenyl)propanoates (RPR_{7-9}) leading to corresponding ethyl-2-benzyloxy/2-(4-isopropylbenzyloxy)-2-methyl-3-(4-substitutedphenyl)propanoates (RSR_{10-12}/PKR_{10-12}), (Scheme 5).

The ethyl- 2- benzyl/2 - (4-isopropylbenzyloxy) – 2 – methyl – 3 - (4-substituted phenyl) propanoates (RSR_{10-12},PKR_{10-12}) thus obtained were subjected to alkaline hydrolysis to generate the desired 2-benzyloxy/2-(4-isopropylbenzyloxy)-2-methyl-3-(4-substituted phenyl) propanoic acids (RSR_{13-15}, PKR_{13-15}) having almost all the structural features required for a compound to act as potent insulin sensitizing agent.

Experimental

The melting and boiling points reported here (Table 1) were recorded using an open concentrated sulphuric acid bath and are uncorrected. The Infrared spectra of these compounds were recorded on Perkin-Elmer Spectrum RX FT-IR Spectrophotometer at RSIC, Panjab University, Chandigarh and Nuclear Magnetic Resonance Spectrum on AC300F, 300MHz Bruker and AC200F, 200MHz respectively at RSIC, Panjab University, Chandigarh and RRL Jammu. Mass Spectral analysis was carried out on GCMS-QP 5000 Shimadzu at NIPER, SAS Nagar, Mohali, Punjab. 2-methyl-3-(4-substituted phenyl)propenoic acids (RSR_{1-3}) required in this synthetic sequence were prepared through standard 'Perkin Reaction' by refluxing 4-substituted benzaldehydes and propanoic anhydride (as shown in scheme 1). These acids (RPR_{1-3}) were then reduced to corresponding 2-methyl-3-(4-substituted phenyl)propanoic acids (RPR_{4-6}) using magnesium-methanol methodology[26] (as shown in scheme 1).The structure of all these compounds were confirmed from their spectral analysis.

Table 1. Characterization data of compounds RPR_{1-9}, RSR_{10-15} and PKR_{10-15}

Compound	Molecular Formula	R	R'	mp / bp* (°C)	Yield g (%)
RPR_1	$C_{10}H_{10}O_2$	H		79-81	9.92 (61.24%)
RPR_2	$C_{10}H_9O_2Cl$	Cl		160-161	15.00 (76.60%)
RPR_3	$C_{11}H_{12}O_3$	OMe		157-159	11.60 (60.40%)
RPR_4	$C_{10}H_{12}O_2$	H		270-273*	4.26 (86.50%)
RPR_5	$C_{10}H_{11}O_2Cl$	Cl		274-275*	4.76 (80.03%)
RPR_6	$C_{11}H_{14}O_3$	OMe		268-270*	5.00 (85.91%)
RPR_7	$C_{12}H_{15}O_2Br$	H		225-228*	5.02 (93.00%)
RPR_8	$C_{12}H_{14}O_2BrCl$	Cl		235-238*	5.18 (85.00%)
RPR_9	$C_{13}H_{17}O_3Br$	OMe		233-236*	5.18 (86.38%)

(Continued next page.)

RSR_{10}	$C_{19}H_{22}O_3$	H	H	143-145*	2.27 (76,10%)
RSR_{11}	$C_{19}H_{21}O_3Cl$	Cl	H	133-135*	2.60 (85.50%)
RSR_{12}	$C_{20}H_{24}O_4$	OMe	H	160-162*	2.34 (71.40%)
PKR_{10}	$C_{22}H_{28}O_3$	H	i-Pr	210-212*	2.55 (75.00%)
PKR_{11}	$C_{22}H_{27}O_3Cl$	Cl	i-Pr	224-226*	2.89 (77.20%)
PKR_{12}	$C_{23}H_{30}O_4$	OMe	i-Pr	218-220*	2.82 (76.20%)
RSR_{13}	$C_{17}H_{18}O_3$	H	H	115-117	1.23 (60.80%)
RSR_{14}	$C_{17}H_{17}O_3Cl$	Cl	H	119-121	1.51 (66.20%)
RSR_{15}	$C_{18}H_{20}O_4$	OMe	H	138-140	1.28 (56.80%
PKR_{13}	$C_{20}H_{24}O_3$	H	i-Pr	174-176	1.42 (60.80%)
PKR_{14}	$C_{20}H_{23}O_3Cl$	Cl	i-Pr	177-179	1.62 (62.30%)
PKR_{15}	$C_{21}H_{26}O_4$	OMe	i-Pr	173-175	1.61 (63.14%)

(Continued from previous page.)

Ethyl-2-bromo-2-methyl-3-(4-substitutedphenylpropanoate (RPR_{7-9})

Thionyl chloride (7.5 ml) taken in a two necked round bottomed flask (250 mL), equipped with a dropping funnel and a double surface reflux condenser, fitted with a gas absorption trap) was heated to boiling and to which of RPR_{4-6} (0.02 mol) was added at such a rate that the mixture refluxed gently, about 1 h. The mixture was refluxed for another 1 h to expell dissolved SO_2 and then allowed to cool. Pure red phosphorous (3.5 mg, 0.0001 mol) was added to it and then pure dry bromine (3.86 mL, 0.075 mol) was introduced into the gently boiling reaction mixture in a period of 5h.The crude 2-bromo-2-methyl-3-(4-substituted phenylpropanoyl chlorides thus obtained was taken in a dropping funnel and introduced into stirred absolute ethanol (40 mL) taken into a two necked round bottomed flask fitted with a reflux condenser during 1.5 h. The reaction mixture was refluxed for 4 h and the crude ester filtered into distilled water (100 mL). The oily mass thus separated was extracted with solvent ether (3 x 30 mL). The ethereal extract washed successively with distilled water, sodium bicarbonate (1%), distilled water, dried (Na_2SO_4), filtered and evaporated to yield RPR_{7-9} as a brown viscous mass.

Ethyl-2-bromo-2-methyl-3-phenylpropanoate (RPR_7): IR ν_{max} (Neat) 2981 and 2874, 2935 and 2855,1733,1450 and 1376,1177, 747 and 702, 526; ^1H NMR ($CDCl_3$) δ 7.410 -

7.490(m, 2H), 7.200 - 7.279(m, 3H), 4.237(q, 2H), 3.613 and 3.350 (two doublets, Jgem = 13.749 Hz and 13.800 Hz, 1H each), 1.818 (s, 3H), 1.320 (t, 3H).

Ethyl-2-bromo-3-(4-chlorophenyl)-2-methylpropanoate(RPR_8): IRν_{max} (Neat) 2982 and 2874, 2935 and 2855, 1734, 1450 and 1379, 1167, 807, 718, 533; ^{1}H NMR ($CDCl_3$) δ 7.309 (d, J = 8.928 Hz, 2H), 7.138(d, J = 8.337 Hz, 2H), 4.206(q, 2H), 3.530 and 3.285 (two doublets, Jgem = 13.776 Hz and 13.809 Hz,1H each), 1.780 (s, 3H), 1.296 (t, 3H); MS m/z (relative intensity) 304(M^+,0.36), 306 (M^++2,0.47%), 308 (M^++4,0.12),125(100).

Ethyl-2-bromo-3-(4-methoxyphenyl)-2-methylpropanoate (RPR_9): IR ν_{max} (Neat) 2981 and 2877, 2938 and 2855,1736,1452 and 1387, 1257 and 1059,1180, 811, 537; ^{1}H NMR ($CDCl_3$) δ 7.642 (d, J = 9.450 Hz, 2H), 7.331(d, J = 8.922 Hz, 2H), 4.284(q, 2H), 3.888(s, 3H), 3.471 and 3.271 (two doublets, Jgem = 13.938 Hz and 13.911 Hz, 1H each), 1.845(s, 3H), 1.336(t, 3H).

Ethyl-2-benzyloxy/2-(4-isopropylbenzyloxy)-2-methyl-3-phenyl propanoate (RSR_{10-12}/PKR_{10-12})

To a suspension of 60% NaH (0.4 g, 0.01 mol) in dry THF (50 mL) was added drop wise at 0°C, a solution of benzyl alcohol/4-isopropylbenzyl alcohol (0.01 mol) taken in dry THF (50 mL). The mixture was stirred at room temperature for 0.5 h. cooled to 0°C and treated drop wise with RPR_{7-9} (0.01 mol) in dry THF (10 mL). The reaction mixture allowed to cool to room temperature, stirred overnight and solvent removed *in vacuo*. The residue was treated with water and extracted with ether (3 x 75 ml). The ethereal extract washed with water, dried (Na_2SO_4), filtered and filtrate upon evaporation gave (RSR_{10-12}/PKR_{10-12}).

Ethyl-2-benzyloxy)-2-methyl-3-phenyl propanoate (RSR_{10}): IR ν_{max} (Neat) 2980 and 2871, 2930, 1736, 1452 and 1375, 1205,1102, 743 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.184-7.507 (m, 10H), 4.615(s, 2H),,4.236(q, 2H), 3.600 and 3.341(two doublets, Jgem = 13.860 Hz and 13.794Hz, 1H each), 1.825(s, 3H),1.284 (t,3H).

Ethyl-2-benzyloxy)- 3-(4-chlorophenyl)-2-methyl propanoate (RSR_{11}):IR ν_{max} (Neat) 2981 and 2872, 2930, 1733, 1453 and 1379, 1206, 1095, 807, 737 and 699, 722; ^{1}H NMR ($CDCl_3$) δ 7.152 - 7.450 (m, 9H), 4.694(s, 2H), 4.244(q, 2H), 3.542 and 3.337(two doublets, Jgem = 13.884 Hz and 13.845 Hz, 1H each), 1.812 (s, 3H), 1.310(t, 3H). MS m/z (relative intensity) 332(M^+, 0.64), 334 (M^+ + 2, 0.23), 91(100).

Ethyl-2-benzyloxy)-3-(4-methoxyphenyl)-2-methylpropanoate (RSR_{12}): IR ν_{max} (Neat), 2968 and 2872, 2929, 1735, 1469 and 1376, 1259 and 1048, 1205, 1115, 811, 742 and 699; ^{1}H NMR ($CDCl_3$) δ 7.261 -7.528 (m, 9H), 4.704(s, 2H), 4.267 (q, 2H), 3.888 (s, 3H), 3.470 and 3.270(two doublets, Jgem = 13.827 Hz and 13.926Hz, 1H each), 1.844(s, 3H), 1.345 (t, 3H).

Ethyl-2-(4-isopropylbenzyloxy)-2-methyl-3-phenyl propanoate (PKR_{10}):IR ν_{max} (Neat) 2960 and 2870, 2925, 1732, 1462 and 1365, 1382 and 1365, 1205, 1112, 921, 752 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.234 - 7.539(m, 9H), 4.661(s, 2H), 4.284(q, 2H), 3.574 and 3.362(two doublets, Jgem = 13.850 Hz and 13.832Hz, 1H each), 2.947(quintet, 1H), 1.855(s, 3H), 1.399 (t, 3H),1.289(d, J = 6.940 Hz, 6H) MS m/z (relative intensity) 340(M^++, 0.04), 133(100).

Ethyl-3-(4-chlorophenyl)-2-(4-isopropylbenzyloxy)-2-methyl propanoate (PKR_{11}):IR ν_{max} (Neat) 2975 and 2872, 2925, 1736, 1460 and 1365, 1380 and 1365, 1203, 1094, 920, 816, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.140 - 7.388 (m, 8H), 4.626(s, 2H), 4.255(q, 2H), 3.550 and 3.318 (two doublets, Jgem = 13.869 Hz and 13.828 Hz, 1H each), 2.899(quintet, 1H), 1.816(s, 3H), 1.380(t, 3H),1.264(d, J= 6.919 Hz, 6H).

Ethyl-2-(4-isopropylbenzyloxy)-3-(4-methoxyphenyl)-2-methylpropanoate(PKR_{12}):IR ν_{max} (Neat) 2970 and 2872, 2930, 1732, 1470 and 1370, 1383 and 1370, 1262 and 1056, 1206, 1113, 921, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.222 -7.442 (m, 8H), 4.651(s, 2H), 4.300

(q, 2H), 3.892(s, 3H), 3.508 and 3.301(two doublets, Jgem = 13.892 Hz and13.888 Hz, 1H each), 2.937(quintet, 1H), 1.880(s, 3H),1.379 (t, 3H),1.281(d, J= 6.940 Hz, 6H).

2-Benzyloxy/4-(isopropylbenzyloxy)-2-methyl-3-(4-substitutedphenylpropanoic acid (RSR_{13-15}/PKR_{13-15})

To a solution of (RSR_{10-12}/PKR_{10-12}) (0.0075 mol) in ethanol (20 mL) was added 4N-NaOH (5mL) and the mixture warmed to 60°C for 6 h. After cooling to room temperature, ethanol was removed *in vacuo* and the residue was partitioned between water and ether. The aqueous phase was acidified with 5N-HCl to pH 1.0 and extracted with $CHCl_3$ (3 x 75 ml). The $CHCl_3$ extracts were dried ($MgSO_4$), filtered and the filtrate upon evaporation gave solid mass which upon recrystallisation from ethylacetate gave (RSR_{13-15}/PKR_{13-15}).

2-Benzyloxy-2-methyl-3-phenylpropanoic acid (RSR_{13}): IR ν_{max} (KBr) 3350 - 2550, 2979 and 2874, 2927 and 2852, 1693,1451 and 1371, 1101,738 and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.050 – 7.650 (m, 10H), 4.702(s, 2H), 3.162 and 2.942(two doublets, Jgem = 13.449 Hz and 13.437 Hz, 1H each), 2.133(s, 3H) MS m/z (relative intensity) 270(M^+, 0.07), 91(100).

2-Benzyloxy-3-(4-chlorophenyl)-2-methylpropanoic acid (RSR_{14}):IR ν_{max} (KBr) 3300 – 2550, 2981, 2929 and 2855, 1704, 1449 and 1359, 1092, 831, 757 and 668, 713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.950–7.550 (m, 9H), 4.665(s, 2H), 3.056 and 2.901(two doublets, Jgem = 13.620 Hz and 13.677 Hz, 1H each), 2.095(s, 3H). MS m/z (relative intensity)304 (M^+, 0.43), 306(M^+ + 2, 0.14), 196 (100).

2-Benzyloxy-3-(4-methoxyphenyl)-2-methyl propanoic acid (RSR_{15}):IR ν_{max} (KBr) 3200-2600, 2974, 2919 and 2846, 1703, 1451 and 1358, 1254 and 1065, 1119, 818,744 and 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.150 - 7.700(m, 9H), 4.714(s, 2H), 3.893(s, 3H), 3.023 and 2.865(two doublets, Jgem = 13.773 Hz and 13.695 Hz,1H each), 2.124(s, 3H).

2-(4-Isopropylbenzyloxy)-2-methyl-3-phenylpropanoic acid (PKR_{13}): IR ν_{max} (KBr), 3300 - 2550, 2979 and 2874, 2927 and 2852, 1701, 1455 and 1365, 1380 and 1365, 1117, 920, 753 and 700 cm^{1}; ^{1}H NMR ($CDCl_3$) δ 7.129 – 7.458 (m, 9H), 4.694(s, 2H), 3.623 and 3.556(two overlapping doublets, Jgem = 12.804 Hz and 14.080 Hz, 1H each), 3.012(quintet, 1H), 2.023(s, 3H), 1.301(d, J = 6.820 Hz, 6H); MS m/z (relative intensity) 312(M^+, 0.40), 133(100).

3-(4-Chlorophenyl)-2-(4-isopropylbenzyloxy)-2-methylpropanoic acid (PKR_{14}): IR ν_{max} (KBr), 3300 – 2500, 2980 and 2870, 2930 and 2855, 1706, 1448 and 1360, 1385 and 1360, 1092, 918, 835, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.100–7.422 (m, 8H), 4.680(s, 2H), 3.621 and 3.554(two overlapping doublets, Jgem = 12.551 Hz and 13.002 Hz, 1H each), 3.046(quintet, 1H), 1.921(s, 3H), 1.276(d, J = 6.930 Hz, 6H), MS m/z (relative intensity) 346($M^{+\cdot}$ 1.01), 348(M^+ + 2, 0.36), 125(100).

2-(4-Isopropylbenzyloxy)-3-(4-methoxyphenyl)-2-methyl propanoic acid (PKR_{15}): IR ν_{max} (KBr) 3250-2550, 2975 and 2872, 2930 and 2850, 1702, 1451 and 1357, 1380 and 1357, 1254 and 1065, 1125, 923, 818 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.212 - 7.628(m, 8H), 4.675(s, 2H), 3.904(s, 3H), 3.682 and 3.556(two overlapping doublets, Jgem = 13.200 Hz and 13.000 Hz, 1H each), 2.943(quintet, 1H), 1.989(s, 3H), 1.265(d, J = 6.960 Hz, 6H).

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