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Lactam acetals: Part XXIII. Synthesis of lactam spirocyclic acetals and their use in ω-hydroxyalkylation reactions†

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Abstract

Lactam spirocyclic acetals, prepared by *trans*-acetalisation of lactam 2,2-dimethoxy acetals (**1**) with diols, have proved to be useful reagents for ω-hydroxyalkylations under mild conditions and without the use of acid or base. The general applicability of this reaction for C-, N-, O- and S-ω-hydroxyalkylation reactions has been demonstrated by reacting acetals **5a–i** with carboxylic acids, thiophenols, 3-formylindole and dibenzyl phosphate when the corresponding ω-hydroxyalkylated products were obtained in good yields. This method provides a convenient synthesis for monoacyl diols, arylmercaptoalkanols, N-hydroxyalkylindoles and phosphate esters, which usually have to be prepared by multistep synthesis and using acid or base catalysis.

Key words: Lactam acetals, lactam spirocyclic acetals, diols, ω-hydroxyalkylation reaction, monoacyl diols, arylmercaptoalkanols, phosphate esters.

1. Introduction

Lactam acetals exist in equilibrium with immonium, enamine and alkoxide species[1] and can thus react with nucleophiles at position-2, electrophiles at position-3 and generate *in situ* a carbanion from a reactive methylene substrate.[2] Besides, the immonium species can undergo O-alkyl bond fission in the presence of appropriate anionic substrate resulting in the alkylation of the latter, thus providing a convenient method for C-, N-, O- and S-alkylations under mild and neutral conditions[3] (Scheme 1). In our continuing study of the chemistry and synthetic utility[4,5] of lactam acetals it appeared of interest to prepare different types of lactam spirocyclic acetals **5** through *trans*-acetalisation reaction of lactam acetals **1** with alkane diols, which appeared suitable reagents for providing ω-hydroxyalkyl equivalent for alkylation as

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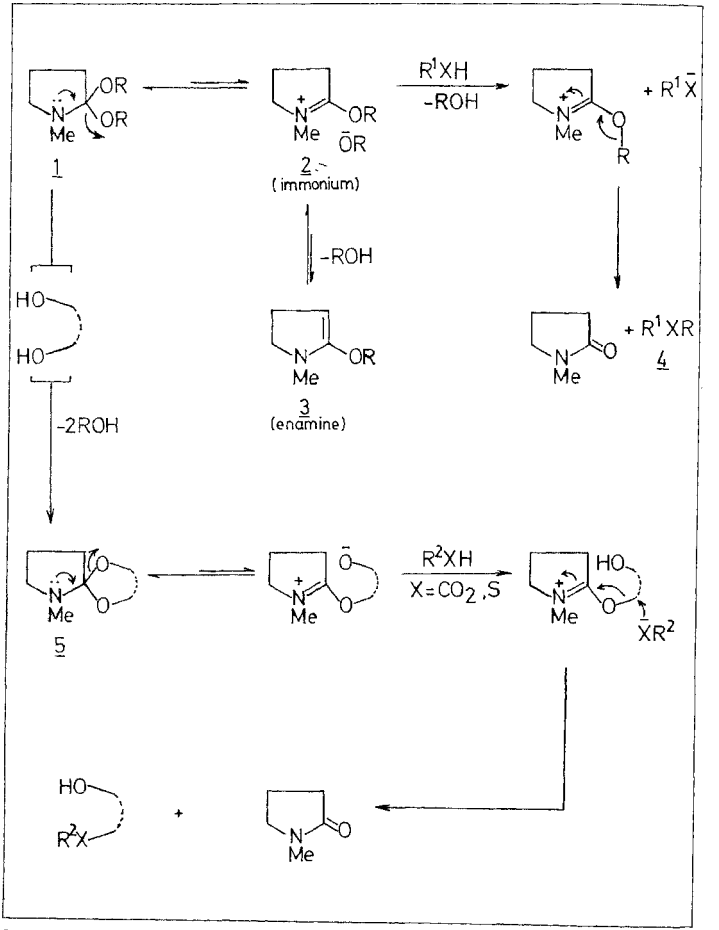

OR
OR
N
Me
1
OR
OR
N
Me
2
(immonium)
R¹XH
-ROH
+ R¹X⁻
R
-ROH
HO
HO
-2ROH
OR
N
Me
3
(enamine)
+ R¹XR
4
O
N
Me
5
R²XH
X=CO₂, S
HO
XR²
HO
R²X
+
O
N
Me

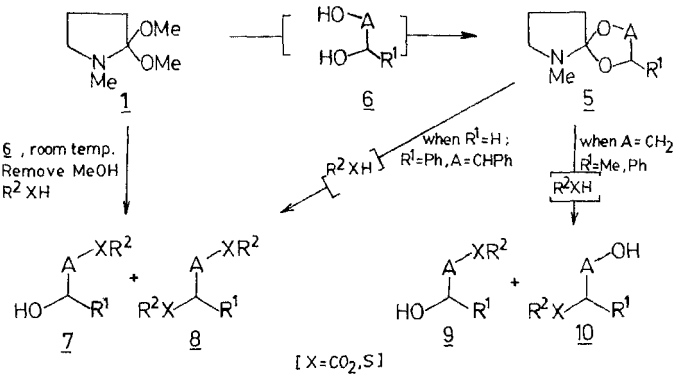
SCHEME 1.

shown in Scheme 1. The usefulness of this reaction has been demonstrated by reacting lactam spirocyclic acetals **5a–i** with carboxylic acids, thiophenols, indoles and phosphates to provide a convenient method for the preparation of monoacyl diols, arylmercaptoalkanols, N-hydroxyalkyl indoles and phosphate esters, which is described in this paper. The preparation of monoacyl diols and arylmercaptoalkanols involving reaction of lactam spirocyclic acetals **5a–d** of symmetrical diols with carboxylic acids and thiophenols was reported recently[6].

2. Chemistry

2.1. Lactam spirocyclic acetals

Stirring of lactam acetal **1** with equimolar amounts of different diols under low vacuum (15–20 mm) at room temperature for 2 h formed the lactam spirocyclic acetals **5a–i** (Table I). Of these, lactam spirocyclic acetals, **5a–c,h,i** were purified by vacuum distillation, while **5d–g** which partially decomposed during distillation were used in subsequent reactions without purification (Scheme 2). Lactam spirocyclic acetals **5h** and **5i** of unsymmetrical diols showed the presence of diastereomeric pairs in 1:1 ratio as evident from their ^{1}H NMR and ^{13}C NMR spectra.



SCHEME 2.

2.2. Acyl diols and arylmercaptoalkanols

Lactam spirocyclic acetals **5a,b** when reacted with a variety of acids in THF yielded the monoacyldiols **7a–g** in 42–66% yields (Table II). Diacyl diols **8e–g** were also isolated as minor products in some of these reactions. The diacyl diols **8e–g** are very likely formed by *trans*-acetalisation of the acetals **5a,b** with the initially formed

Table 1

Physical constants of the lactam spirocyclic acetals 5

Entry no.	*A*	*R*[1]	*bp,°C/ torr(mm of Hg)*	*% Yield*
a	CH_2	H	89–90/15	95
b	$(CH_2)_3$	H	39–43/0 6	98
c	$(CH_2)_2OCH_2$	H	98–100/0.6	85
d	$(CH_2)_2N(Me)CH_2$	H	[a]	85[b]
e	CHC_6H_5	C_6H_5	[a]	96[b]
f	$(CH_2CH_2O)_2CH_2$	H	[a]	92[b]
g	$(CH_2OCH_2)_2CH_2O$	H	[a]	94[b]
h	CH_2	CH_3	98–99/15	83[c]
i	CH_2	C_6H_5	102–103/0.6	82[c]

[a]Thick oils; [b]Crude product yield; [c]These show the presence of diastereomeric pair from their ^1H NMR and ^{13}C NMR spectra recorded on Bruker WM-400 MHz spectrometer.

monosubstituted products followed by acylation of the new acetals thus generated. Similarly, reactions of lactam spirocyclic acetals **5a–g** with thiophenol and *p*-substituted thiophenols in dry THF under refluxing yielded the corresponding arylmercaptoalkanols **7h–q** in 47–60% yield along with a small amount (5–13%) of the disubstituted products **8h–l** (Scheme 2, Table II). The spectral and analytical data of chromatographically pure compounds **7a–l** and **8e,g–l** were consistent with the expected data[7-13].

The ω-hydroxyalkylation could also be carried out as one-pot synthesis by reacting the lactam spirocyclic acetals **5a–g**, generated *in situ*, with the carboxylic acids or thiophenols to yield the monosubstituted products **7** in 43–88% yields (Scheme 2, Table II). A typical procedure of the one-pot reaction is described in experimental section (Method D).

The lactam spirocyclic acetals **5h** & **i** of unsymmetrical diols (1,2-propanediol and 1-phenyl-1, 2-ethanediol), could, in principle, on reacting with carboxylic acids form a mixture of two regioisomers. With **5h** the reaction of benzoic acid, phenylacetic acid and isonicotinic acid gave a mixture of primary and secondary acylated products **9a–c** and **10a–c** in almost equal proportions as determined from their ^1H NMR spectra. However, lactam spirocyclic acetal **5i** on treatment with benzoic acid under similar conditions gave only the primary alcohol **9d** (2-hydroxy-2-phenylethyl benzoate)[14] as a single product (Scheme 2, Table III). With a view to explore if regioselectivity could be obtained by changing the reaction conditions, the condensations were carried out in different solvents and at different temperatures. It was found that reaction in dioxane led to some regioselectivity and formed primary and secondary acylated products in 1:3 ratio.

Reaction of lactam spirocyclic acetal **5h** & **i** with thiophenols under similar condition formed a mixture of monosubstituted products **9e–f** and **10e–f** in 1:2 ratio which

Table II

Physical constants of compounds 7 and 8*

Entry no.	$R^2\bar{X}H$	*A*	R^1	*Method used*†	**7**		**8**	
					mp,°C	*% yield*	*mp, °C*	*% yield*
a	$C_6H_5CO_2H$	CH_2	H	A,B,D,	oil	14, 59, 67	–	–
b	$C_6H_5CH_2CO_2H$	CH_2	H	B	oil	42	–	–
c	3-$(C_5H_4N)CO_2H$	CH_2	H	B,D	oil	61, 78	–	–
d	4-$(C_5H_4N)CO_2H$	CH_2	H	D	oil	58	–	–
e	4-$ClC_6H_4CO_2H$	CH_2	H	C,D	71–72	48, 59	135–136	13,7
f	4-$MeOC_6H_4CO_2H$	CH_2	H	C	oil	57	107–108	11
g	$C_6H_5CO_2H$	$(CH_2)_3$	H	B,D	oil	44, 52	75–76	7, 4
h	C_6H_5SH	CH_2	H	C,D	oil	58, 88	69–70	9,5
i	4-ClC_6H_4SH	CH_2	H	C	oil	60	93–93.5	13
j	4-BrC_6H_4SH	CH_2	H	C	oil	57	110–111	5
k	4-MeC_6H_4SH	CH_2	H	C	oil	67	72–73	16
l	C_6H_5SH	$(CH_2)_3$	H	C,D	oil	55, 72	85–86	15, 3
m	C_6H_5SH	$(CH_2)_2OCH_2$	H	D	oil	47	–	–
n	C_6H_5SH	$(CH_2CH_2O)_2CH_2$	H	D	oil	57	–	–
o	C_6H_5SH	$(CH_2OCH_2)_2CH_2O$	H	D	oil	54	–	–
p	C_6H_5SH	$(CH_2)_2N(CH_3)CH_2$	H	D	oil	46	–	–
q	C_6H_5SH	CHC_6H_5	C_6H_5	B	oil	64	–	–

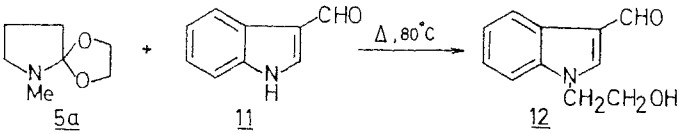
*Compounds were purified by chromatography using silica gel (230–400 mesh), and characterised by their IR, PMR, MS data and satisfactory elemental analysis.

†See experimental section.

could be separated in quantity by flash silica gel coulmn chromatography (Scheme 2, Table III).

2.3. N-ω-Hydroxyalkyl indoles

This study was extended to the N-ω-hydroxylalkylation reactions since lactam acetals have been shown to be useful reagents for N-alkylation[2] of imidazoles, indoles, etc. Since, N-(β-hydroxyethyl) group is an important pharmacophore of some important antiparasitic indoles and imidazoles[15], their preparation using lactam spirocyclic acetals was studied. Reaction of 3-formylindole **11** with the lactam spirocyclic acetal **5a** gave 1-hydroxyethyl-3-formylindole **12** (Scheme 3).

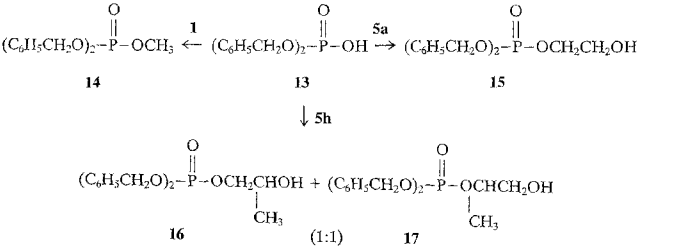


5a 11 12

SCHEME 3.

2.4. Phosphate esters

In view of the importance of mixed phosphate esters, the possibility of using lactam acetals and lactam spirocyclic acetals for their preparation has been investigated. It has been found that lactam acetal **1** on reacting with dibenzyl phosphate **13** yielded methyl dibenzyl phosphate **14** in excellent yield. Similarly, lactam spirocyclic acetal **5a** reacted with **13** in refluxing THF to furnish 2-hydroxyethyl dibenzyl phosphate **15** in good yield. **5h** on treatment with **13** under similar reaction conditions gave a mixture of **16** and **17** in 1:1 ratio determined by ^{1}H NMR spectrum of the chromatographically pure mixture (Scheme 4).



SCHEME 4.

3. Discussion

Lactam spirocyclic acetals appear useful reagents for ω-hydroxyalkylation under mild conditions and without the use of acid or base. The convenience to obtain monoacyl

diols[16,17] and arylmercaptoalkanols[18,19] is of significance since these are important classes of organic intermediates. Monoacyl diols are used as insoluble polymer supports in organic synthesis[16] and in the synthesis of sex pheromones[20], whereas arylmercaptoalkanols are used as protecting groups for oligonucleotide synthesis[21,22]. The known methods for their preparation, either by direct acylation of diols or from oxiranes or halohydrins are not satisfactory[20,23]. Direct acylation gives a mixture of products and low yields. The oxirane approach is useful only for 1,2-diols, whereas the preparation through halohydrin involves strong acidic conditions which are not suitable for diols containing acid-sensitive groups[24]. Furthermore, N-(β-hydroxyethyl)-group is an important pharmacophore of some important antiparasitic indoles and imidazoles[15] and the easy hydroxyethylation of indoles shows that lactam spirocyclic acetals provide an easy approach for the introduction of hydroxyalkyl group on acidic nitrogen.

Mixed phosphate esters are of importance in biological studies. Lactam spirocyclic acetals provide a convenient method for their preparation in good yield and under mild reaction conditions. Their extension to formation of phosphate esters in biological milieu is obvious.

4. Experimental

Melting points were taken in an electrically heated instrument and are uncorrected. Compounds were routinely checked for their purity on silica gel-G TLC plates and their spots were visualised by exposing them to iodine vapour by spraying with Dragendorff and $KMnO_4$ reagents. All compounds were purified by column chromatography over silica gel (230–400 mesh). IR spectra (λ_{max} in cm^{-1}) were recorded either on Perkin–Elmer 157 or Acculab-1 models and ^1H NMR and ^{13}C NMR spectra were recorded on Perkin–Elmer R32 or EM-360L or Bruker WM-400 MHz instruments using TMS as internal reference in $CDCl_3$, unless otherwise stated, and chemical shifts are in δ units. Mass spectra were run on Jeol JMS D300 instrument using direct inlet system.

General method for the preparation of lactam spirocyclic acetals **5a–i**

A mixture of 2,2-dimethoxy-1-methylpyrrolidine **1** (50 mmol) and freshly distilled diols **6** (60 mmol) was stirred at room temperature for 2 h under vacuum (15 mm) to remove methanol generated during the reaction to yield the products which on vacuum distillation gave the required lactam spirocyclic acetals **5a–c,h,i** (Table I). Their spectral data are given below.

6-Methyl-1,4-dioxa-6-azaspiro[4.4]nonane **(5a)**

IR($CHCl_3$): 3300, 2900, 1675, 1460, ^1H NMR: 1.50–2.20 (m, 4H, 8- & 9-CH_2), 2.25 (s, 3H, N-CH_3), 2.70–3.00 (m, 2H, N–CH_2), 3.60–4.10 (m, 4H, 2- & 3-CH_2). ^{13}C NMR: 20.01, 31.48, 35.94, 52.06, 64.56, 122.85. MS (*m/z*): 143 (M^+) at 23 eV and 100° C. UV λ_{max}: 241 nm.

8-Methyl-1,6-dioxa-8-azaspiro[4.6]undecane (**5b**)

IR($CHCl_3$): 2900, 1675, 1450. ^{1}H NMR: 1.30–2.00 (m, 8H, 3-, 4-, 10- & 11CH_2), 2.40 (s, 3H, N-CH_3), 2.55–2.95 (m, 2H, N-CH_2), 3.10–4.15 (m, 4H, 2- & 5-CH_2). MS (*m/z*): 171 (M^+) at 23 eV and 100°C.

9-Methyl-1,4,7-trioxa-9-azaspiro[4.7]dodecane (**5c**)

IR($CHCl_3$): 2910, 1660, 1430. ^{1}H NMR: 1.80–2.60 (m, 4H, 11- & 12-CH_2), 2.80 (s, 3H, N-CH_3), 3.40–4.00 (m, 10H, 2-, 3-, 5-, 6- & 10-CH_2). MS (*m/z*): 187 (M^+) at 23 eV and 100°C.

2,6-Dimethyl-1,4-dioxa-6-azaspiro[4.4]nonane (**5h**)

IR($CHCl_3$): 2900, 1670, 1450. ^{1}H NMR: 1.15 & 1.22 (2d, 3H, –CCH_3), 1.40–2.10 (m, 4H, 8- & 9-CH_2), 2.20 & 2.25 (2s, 3H, N-CH_3), 2.80 (t, 2H, *J*=4.0 Hz, N-CH_2), 3.10–3.50 (m, 1H, 2-C*H*), 3.70–4.30 (m, 2H,–OCH_2. ^{13}C NMR: 20.08, 31.45, 36.66, 51.90, 70.61, 71.06, 72.13, 122.80. MS (*M/z*): 157 (M^+) at 23 eV and 50°C. UV λ_{max}: 240 mm.

6-Methyl-2-phenyl-1,4-dioxa-6-azaspiro[4.4]nonane (**5i**)

IR($CHCl_3$): 1670, 1460. ^{1}H NMR: 1.30–2.20 (m, 4H, 8- & 9-CH_2), 2.30 & 2.35 (2s, 3H, N-CH_3), 2.60–3.00 (m, 2H, N-CH_2), 3.20–3.70 (m, 1H, 2-C*H*), 3.80–4.40 (m, 1H, 3-C*H*), 4.60–5.10 (m, 1H, 3′-C*H*), 7.00–7.50 (m, 5H, Ar*H*). ^{13}C NMR: 20.03, 32.01, 36.69, 52.07, 71.03, 77.78, 123.39, 126.65, 128.12. MS (*m/z*): 219 (M^+) at 23 eV and 100°C.

Compounds 4,9-dimethyl-1,7-dioxa-4,9-diazaspiro[4.7]dodecane (**5d**), 12-methyl-1,4,7,10-tetraoxa-12-azaspiro[4.10]pentadecane (**5f**) and 15-methyl-1,4,7,10,13-pentaoxa-15-azaspiro[4.13]octadecane (**5g**) were also prepared according to the procedure described above, but they decomposed during attempted purification by vacuum distillation and thus **5d,f** & **g** were used in further reactions without purification.

6-Methyl-2,3-diphenyl-1,4-dioxa-6-azaspiro[4.4]nonane (**5e**)

A mixture of 2,2-dimethoxy-1-methylpyrrolidine **1** (2.90 g, 20 mmol) and hydrobenzoin (3.40 g, 16 mmol) was stirred at room temperature for 30 min. Methanol generated during the reaction was removed *in vacuo* and the residue was triturated with dry hexane. The combined hexane fraction was concentrated to give **5e** as thick oil, yield 4.50 g (96%). IR(Neat): 2910, 1660, 1350. ^{1}H NMR: 1.50–2.50 (m, 4H, 8- & 9-CH_2) 2.70 (s, 3H, N-CH_3), 2.90–3.20 (m, 2H, 7-CH_2), 5.30 & 5.60 (2s, 2H, 2- & 3-C*H*), 6.85–7.30 (m, 10H, Ar*H*). MS (*m/z*): 295 (M^+).

General methods for the preparation of monoacyl diols (**7**) *and arylmercaptoalkanols* (**8**)

Method A: A mixture of **5** (7 mmol) and the carboxylic acid/thiophenol (6 mmol) was heated under stirring at 70–80°C. Aftert 3 h ethyl acetate (25 ml) was added to

the reaction mixture and the organic layer was washed with saturated $NaHCO_3$ solution (2×10 ml), 10% aqueous HCl (1×5 ml) and finally with brine (2×20 ml). The organic layer was dried (Na_2SO_4) and concentrated to yield **7** and/or **8.**

Method B: A solution of **5** (20 mmol) and carboxylic acid/thiophenol (20 mmol) in dry THF (10 ml) was refluxed for 4–6 h. Solvent was removed *in vacuo* and the residue was dissolved in 50 ml ethyl acetate and washed successively with aqueous $NaHCO_3$ solution (2×10 ml), water (2×10 ml) and finally with brine (2×20 ml), dried (Na_2SO_4) and concentrated to give **7** and/or **8.**

Method C: To a solution of **5** (38 mmol) in dry THF (30 ml), carboxylic acid/thiophenol (32 mmol) in 20 ml dry THF was added under stirring in a dropwise manner; the stirring was continued for 1 h and then refluxed for 1 h. THF was removed *in vacuo* and the residue was subjected to column chromatography to give **7** and/or **8.**

Method D: A mixture of 2,2-dimethoxy-1-methylpyrrolidine **1** (18 mmol) and alkanediol **6** (18 mmol) was stirred at room temperature for 1 h and then kept under reduced pressure (15 mm of Hg) at room temperature for 30 min to remove methanol generated in *trans*-acetalization reaction to yield **5.** To this lactam spirocyclic acetal **5,** generated *in situ,* 15 ml dry THF was added followed by carboxylic acid/thiophenol (13 mmol) and the solution was heated under reflux for 2–5 h. Solvent was removed under reduced pressure and the residue was subjected to column chromatography to give **7** and/or **8.**

Compounds **7a–q** and **8e–l** were prepared by either of the above four methods (Table II) and their spectral and analytical data are given below.

2-Hydroxyethyl benzoate **(7a)**

Oil. IR(Neat): 3400, 2950, 1710, 1610, 1455. ^{1}H NMR: 2.30–2.90 (br s, 1H, -O*H*, D_2O exchangeable), 3.60–4.20 (m, 2H, $-OCH_2$), 4.25–4.80 (m, 2H, $-CO_2CH_2$), 7.10–7.70 (m, 3H, 2-, 3- & 4-Ar*H*), 7.80–8.40 (m, 2H, 1- & 5-Ar*H*). MS(*m/z*): 166 (M^+). Analysis Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.97; H, 6.15%.

2-Hydroxyethyl phenylacetate **(7b)**

Oil. IR(Neat): 3440, 2980, 1720, 1610. ^{1}H NMR: 1.75–2.40 (br s, 1H, –O*H*, D_2O exchangeable), 3.45–3.90 (m, 4H, $PhCH_2$ & $-OCH_2$), 4.00–4.40 (m, 2H, $-CO_2CH_2$), 7.30–7.50 (m, 5H, Ar*H*). MS(*m/z*): 180 (M^+). Analysis Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.71. Found: C, 66.67; H, 6.37%.

2-Hydroxyethyl nicotinate **(7c)**

Oil. IR(Neat): 3450, 1740, 1610. ^{1}H NMR: 3.80–4.40 (m, 3H, $-CH_2OH$), 4.50–5.00 (m, 2H, $-CO_2CH_2$), 7.50–7.90 (m, 1H, 4-Ar*H*), 8.50–8.90 (m, 1H, 3-Ar*H*). 8.95–9.35 (m, 1H, 5-Ar*H*), 9.50–9.90 (m, 1H, 1-Ar*H*). MS(*m/z*): 167 (M^+). Analysis Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.31; H, 5.21; N, 8.02%.

2-Hydroxyethyl isonicotinate (**7d**)

Oil. IR(Neat): 3420, 1720, 1605. ^{1}H NMR: 2.90–3.50 (br s, 1H, –O*H*, D_2O exchangeable), 3.55–4.20 (m, 2H. –OCH_2), 4.30–4.70 (m, 2H, –CO_2CH_2), 7.85 (d, 2H, *J*=8.0 Hz, 3- & 5-Ar*H*), 8.75 (d, 2H, *J*=8.0 Hz, 2- & 6-Ar*H*). MS (m/z): 167 (M^+). Analysis Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.55; H, 5.60; N, 8.15%.

2-Hydroxyethyl p-chlorobenzoate (**7e**)

mp 71–72°C [lit.[8], mp 72°C]. IR(KBr): 3420, 1710, 1690. ^{1}H NMR: 2.00–2.60 (br s, 1H, –O*H*, D_2O exchangeable), 3.70–4.20 (m, 2H, –OCH_2), 4.30–4.70 (m, 2H, –CO_2CH_2), 7.45 (d, 2H, *J*=8.0 Hz, 3- & 5-Ar*H*), 8.05 (d, 2H, *J*=8.0 Hz, 2- & 4-Ar*H*). MS (*m/z*): 200 (M^+) & 202 (M+2). Analysis Calcd for $C_9H_9ClO_3$: C, 53.87; H, 4.52. Found: C, 53.25; H, 4.60%.

2-Hydroxyethyl p-methoxybenzoate (**7f**)

Oil. IR(Neat): 3420, 1710, 1600. ^{1}H NMR: 2.60 (s, 1H, –O*H*, D_2O exchangeable), 3.90–4.15 (m, 5H. –OCH_3 & –OCH_2), 4.30–4.75 (m, 2H, -CO_2CH_2), 7.00 (d, 2H, *J*=8.0 Hz, 3- & 5-Ar*H*), 8.15 (d, 2H, *J*=8.0 Hz, 2- & 6-Ar*H*). MS (*m/z*): 196 (M^+). Analysis Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.16. Found: C, 60.73; H, 6.37%.

4-Hydroxybutyl benzoate (**7g**)

Oil. IR(Neat): 3395, 1700, 1600. ^{1}H NMR: 1.30–2.10 (m, 4H, 2x-CCH_2), 2.80 (s, 1H, –O*H*, D_2O exchangeable), 3.30–3.80 (m, 2H, –OCH_2, 4.20 (t, 2H, *J*=4.0 Hz, –CO_2CH_2), 7.00–7.60 (m, 3H, 3-, 4- & 5-Ar*H*), 7.70–8.20 (m, 2H, 2- & 6-Ar*H*). MS (*m/z*): 194 (M^+). Analysis Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.98; H, 7.13%.

2-(Phenylthio)ethanol (**7h**)

Oil. IR(Neat): 3360, 2920, 1580. ^{1}H NMR: 2.10–2.70 (br s, 1H, –O*H*, D_2O exchangeable), 3.05 (t, 2H, *J*=4.0 Hz, –SCH_2), 3.45–3.95 (m, 2H, –OCH_2), 7.00–7.60 (m, 5H, Ar*H*). MS (*m/z*): 154 (M^+). Analysis Calcd for $C_8H_{10}OS$: C, 62.29; H, 6.53. Found: C, 62.56; H, 6.76%.

2-(p-Chlorophenylthio)ethanol (**7i**)

Oil. IR(Neat): 3360, 2930, 1470. ^{1}H NMR: 2.30 (t, 1H, *J*=4.0 Hz, –O*H*, D_2O exchangeable), 3.10 (t, 2H, *J*=4.0 Hz, –SCH_2), 3.50–3.90 (m, 2H, –OCH_2), 7.00–7.60 (m, 4H, Ar*H*), MS (*m/z*): 188 (M^+) & 190 (M+2). Analysis Calcd for C_8H_9ClOS: C, 50.92; H, 4.80. Found: C, 51.03; H, 4.87%.

2-(p-Bromophenylthio)ethanol (**7j**)

Oil. IR(Neat): 3380, 2940, 1470. ^{1}H NMR: 2.10 (s, 1H, –O*H*, D_2O exchangeable), 3.10 (t, 2H, *J*=4.0 Hz, –SCH_2), 3.80 (t, 2H, *J*=4.0 Hz, –OCH_2), 7.40 (d, 2H, *J*=8.0 Hz, 3- & 5-Ar*H*), 7.60 (d, 2H, *J*=8.0 Hz, 2- & 6-Ar*H*). MS (*m/z*): 233 (M^+). Analysis Calcd for C_8H_9BrOS: C, 41.21; H, 3.89. Found: C, 41.53; H, 3.73%.

2-(p-Methylphenylthio)ethanol (**7k**)

Oil. IR(Neat): 3200, 1660, 1220. ^{1}H NMR: 2.30 (s, 3H, –CC*H*$_3$), 2.40–2.70 (br s, 1H, –O*H*, D_2O exchangeable), 2.90–3.20 (m, 2H, –SC*H*$_2$), 3.50–3.90 (m, 2H, –OC*H*$_2$), 7.09 (d, 2H, *J*=8.0 Hz, 3- & 5-Ar*H*), 7.28 (d, 2H, *J*=8.0 Hz, 2- & 6-Ar*H*). MS (*m/z*): 168 (M^+). Analysis Calcd. for $C_9H_{12}OS$: C, 64.24; H, 7.19. Found: C, 64.78; H, 6.91%.

4-(Phenylthio)butanol (**7l**)

Oil. IR(Neat): 3380, 2960, 1590, 1490. ^{1}H NMR: 1.30–2.00 (m, 5H, 2×C-C*H*$_2$ & –O*H*), 2.60–3.10 (m, 2H, –SC*H*$_2$), 3.30–3.80 (m, 2H, –OC*H*$_2$), 7.00–7.60 (m, 5H, Ar*H*). MS (*m/z*): 182 (M^+). Analysis Calcd for $C_{10}H_{14}OS$: C, 65.88; H, 7.74. Found: C, 65.76; H, 7.79%.

2-(β-Phenylthioethoxy)ethanol (**7m**)

Oil. IR(Neat): 3220, 1660. ^{1}H NMR: 2.30–2.80 (br s, 1H, –O*H*, D_2O exchangeable), 3.10 (t, 2H, *J*=4.0 Hz, –SC*H*$_2$), 3.40–3.90 (m, 6H, 3x-OC*H*$_2$), 7.00–7.60 (m, 5H, Ar*H*). MS (*m/z*): 198 (M^+). Analysis Calcd for $C_{10}H_{14}O_2S$: C, 60.57; H, 7.11. Found: C, 60.93; H, 7.35%.

8-Phenylmercapto-3,6-dioxaoctane-1-ol (**7n**)

Oil. IR(Neat): 3380, 2900, 1650. ^{1}H NMR: 1.80–2.60 (m, 3H, –SC*H*$_2$ & –O*H*), 3.50–4.00 (m, 10H, 5x-OC*H*$_2$), 7.10–7.60 (m, 5H, Ar*H*). MS (m/z): 242 (M^+). Analysis Calcd for $C_{12}H_{18}O_3S$: C, 59.42; H, 7.46. Found: C, 59.63; H, 7.75%.

11-Phenylmercapto-3,6,9-trioxaundecane-1-ol (**7o**)

Oil. IR(Neat): 3380, 2840, 1650. ^{1}H NMR: 1.90–2.50 (m, 3H, –SC*H*$_2$ & –O*H*), 3.20–4.00 (m, 14H, 7x-OC*H*$_2$, 7.10–7.60 (*m*, 5H, Ar*H*). MS (*m/z*): 286 (M^+). Analysis Calcd for $C_{14}H_{22}O_4S$: C, 58.77; H, 7.75. Found: C, 58.30; H, 7.43%.

N-Methyl-N-(β-phenylthioethyl)ethanolamine (**7p**)

Oil. IR(Neat): 3440, 3040, 1660. ^{1}H NMR: 1.60–2.10 (m, 1H, –O*H*, D_2O exchangeable), 2.40–2.70 (m, 2H, –SC*H*$_2$), 2.75 (s, 3H, NC*H*$_3$), 2.80–3.20 (m, 4H, 2x-NC*H*$_2$), 3.30–4.60 (m, 2H, –OC*H*$_2$), 7.00–7.40 (m, 5H, Ar*H*). MS (*m/z*): 211 (M^+). Analysis Calcd for $C_{11}H_{17}NOS$: C, 62.51; H, 8.11; N, 6.62. Found: C, 62.13; H, 8.35; N, 6.43%.

1,2-Diphenyl-2-(phenylthio) ethanol (**7q**)

Oil. IR(Neat): 3430, 3060, 1580, 1450. ^{1}H NMR: 3.00–3.50 (br s, 1H, –O*H*, D_2O exchangeable), 4.30 (d, 1H, *J*=8.0 Hz, –SC*H*), 4.85 (d, 1H, *J*=6.0 Hz, –OC*H*), 6.70–7.50 (m, 15H, Ar*H*). MS (*m/z*): 306 (M^+). Analysis Calcd for $C_{20}H_{18}OS$: C, 78.39; H, 5.92. Found: C, 78.15; H, 6.13%.

Ethylene glycol di-p-chlorobenzoate **(8e)**

mp 135–136°C [lit[8], mp 141°C]. IR(KBr): 1710, 1590. ^{1}H NMR: 4.70 (s, 4H, 2x OCH_2), 7.45 (d, 4H, J=8.0 Hz, 3- & 5-Ar*H*), 8.05 (d, 4H, J=8.0 Hz, 2- & 6-Ar*H*) MS (*m/z*): 338 (M^+) & 342 (M+4). Analysis Calcd for $C_{16}H_{12}Cl_2O_4$: C, 56.65; H 3.56. Found: C, 56.87; H, 3.64%.

Ethylene glycol di-p-methoxybenzoate **(8f)**

mp 107–108°C. IR(KBr): 1680, 1575. ^{1}H NMR: 3.90 (s, 6H, 2x-OCH_3), 4.65 (s, 4H, 2x-OCH_2), 7.00 (d, 4H, J=10.0 Hz, 3- & 5-Ar*H*), 8.10 (d, 4H, J=10.0 Hz, 2- & 6 -Ar*H*). MS (*m/z*): 330 (M^+). Analysis Calcd for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.63; H, 5.37%.

1,4-Butanediol dibenzoate **(8g)**

mp 75–76°C [lit[9]. mp 80°C]. IR(KBr): 1695, 1600. ^{1}H NMR: 1.60–2.20 (m, 4H, 2x-CH_2), 4.00–4.70 (m, 4H, 2x-OCH_2), 7.10–7.70 (m, 6H, 3-, 4- & 5-Ar*H*), 7.80–8.30 (m, 4H, 2- & 6-Ar*H*). MS (*m/z*): 298 (M^+). Analysis Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.13; H, 6.27%.

1,2-bis(Phenylthio)ethane **(8h)**

mp 69–70°C [lit[10] mp 69°C]. IR(KBr): 1570, 1470. ^{1}H NMR: 3.00 (s, 4H, 2x-SCH_2), 7.00–7.40 (m, 10H, Ar*H*). MS (*m/z*): 246 (M^+). Analysis Calcd for $C_{14}H_{14}S_2$: C, 68.24; H, 5.72. Found: C, 67.87; H, 5.69%.

1,2-bis(p-Chlorophenylthio)ethane **(8i)**

mp 93–93.5°C [lit[11], mp 94°C]. IR(KBr): 1470, 1380. ^{1}H NMR; 3.05 (s, 4H, 2x-SCH_2), 7.00–7.50 (m, 8H, Ar*H*). MS (*m/z*): 314 (M^+), 318 (M+4). Analysis Calcd for $C_{14}H_{12}Cl_2S_2$: C, 53.31; H, 3.83. Found: C, 53.45; H, 3.93%.

1,2-bis(p-Bromophenylthio)ethane **(8j)**

mp 110–111°C [lit[12], mp 109°C]. IR(KBr): 1470, 1425. ^{1}H NMR: 3.05 (s, 4H, 2x-SCH_2), 7.20 (d, 4H, J=8.0 Hz, 3- & 5-Ar*H*), 7.50 (d, 4H, J=8.0 Hz, 2- & 6-Ar*H*). MS (*m/z*): 402 (M^+). Analysis Calcd for $C_{14}H_{12}Br_2S_2$: C, 41.60: H, 2.99. Found: C, 41.90; H, 3.17%.

1,2-bis(p-Methylphenylthio)ethane **(8k)**

mp 72–73°C. IR(KBr): 1580, 1490. ^{1}H NMR: 2.34 (s, 6H, 2x-CCH_3), 3.01 (s, 4H, 2x-SCH_2), 6.80–7.30 (m, 8H, Ar*H*). MS (*m/z*): 274 (M^+). Analysis Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61. Found: C, 70.77; H, 6.64%.

1,4-bis(Phenylthio)butane **(8l)**

mp 85–86°C [lit[13], mp 84°C]. IR(KBr): 1580, 1480. ^{1}H NMR(CCl_4): 1.40–2.00 (m,

4H, 2x-CH_2), 2.60–3.10 (m, 4H, 2x-SCH_2), 6.80–7.50 (m, 10H, Ar*H*). MS (*m/z*): 274 (M^+). Analysis Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61. Found: C, 70.38; H, 6.75%.

Reaction of **5h** *with benzoic acid*

Method E: A mixture of **5h** (1.0 g, 6.37 mmol) and benzoic acid (0.77 g, 6.37 mmol) was heated at 80°C under stirring for 3 h. To this reaction mixture, ethyl acetate (30 ml) was added and washed successively with saturated $NaHCO_3$ solution (1×10 ml), 10% HCl (1×10 ml), water and then with brine (2×20 ml), dried (Na_2SO_4) and concentrated to give an oil. The oily product obtained (278 mg, 24.5%) contained primary benzoate **9a** and secondary benzoate **10a** in the ratio of 1:2 as shown by ^1H NMR analysis of the chromatographically pure mixture.

Method F: Benzoic acid (1.22 g, 10 mmol) was added to a solution of the lactam spirocyclic acetal **5h** (1.57 g, 10 mmol) in 15 ml dry THF and refluxed for 4 h. The THF was removed *in vacuo* and the crude product was subjected to column chromatography. The oily product obtained (1.12 g, 62.2%) contained the primary benzoate **9a** and the secondary benzoate **10a** in the ratio of 2:5 as shown by ^1H NMR analysis of the mixture. IR(Neat): 3400, 3000, 1720, 1620. ^1H NMR: 1.29 and 1.38 (2d, 3H, J=8.0 Hz, $-CCH_3$), 2.30–2.70 (br s, 1H, $-OH$, D_2O exchangeable), 3.70–3.90 (m, 2H, $-CH_2$), 4.14–4.24 (m, 0.71H, $-CH_2$), 4.30–4.38 (m, 0.29H, $-CH$), 5.18–5.30 (m, 1H, $-CH$), 7.36–7.64 (m, 3H, Ar*H*), 7.98–8.18 (m, 2H, Ar*H*). MS (*m/z*): 180 (M^+) 162 (M-18). Analysis Calcd for $C_{10}H_{12}O_3$: C, 66.68; H, 6.71. Found: C, 66.82; H, 6.59%.

Reaction of **5h** *with phenyl acetic acid*

Method F: Yield 50%, ratio of **9b** and **10b** is 1:1. Oil. IR(Neat): 3430, 1710. ^1H NMR: 1.15 & 1.30 (2d, 3H, J=8.0 Hz, $-CCH_3$), 3.40–3.80 (m, 4H, PhCH_2 & $-OCH_2$), 3.90–4.50 (m, 3.31H, $-CO_2CH_2$, $-CH$ & $-OH$), 4.80–5.30 (m, 0.70H, $-CO_2CH$), 7.40 (s, 5H, Ar*H*). MS (*m/z*): 194 (M^+), 176 (M-18), 91 (M-103). Analysis Calcd for $C_{11}H_{14}O_3$: C, 68.03; H, 7.27. Found: C, 67.92; H, 7.50%.

Reaction of **5h** *with isonicotinic acid*

Method F: Yield 44%, ratio of **9c** and **10c** is 1:2. Oil. IR(Neat): 3360, 1710, 1650. ^1H NMR: 1.25 & 1.40 (2d, 3H, J=8.0 Hz, $-CCH_3$), 2.20–2.80 (br s, 1H, $-OH$, D_2O exchangeable), 3.72–3.90 (m, 2H, $-OCH_2$), 4.15–4.46 (m, 3.35H, $-CO_2CH_2$ & $-OCH$), 5.24–5.38 (m, 0.64H, $-CO_2CH$), 7.75–8.10 (m, 2H, Ar*H*), 8.80–9.10 (m, 3H, Ar*H*). MS (*m/z*): 181 (M^+), 163 (M-18), 136 (M-45), 106 (M-75). Analysis Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 60.04; H, 6.10; N, 7.95%.

Reaction of **5i** *with benzoic acid*

A solution of **5i** (4.80 g, 22 mmol) and benzoic acid (2.44 g, 20 mmol) in 20 ml dry THF was refluxed for 4 h. Solvent was removed *in vacuo* and the residue was subjected to column chromatography using chloroform–methanol linear gradient (0–5) to give 2-benzyloxy-1-phenyl ethanol **9d** as white crystalline solid, yield 1.83 g (38%),

mp 58°C [lit.[1] mp 63–64°C]. IR(KBr): 3280, 1700, 1590. ^{1}H NMR: 2.40–2.90 : (br s, 1*H*, –O*H*. D_2O exchangeable), 4.20–4.70 (m, 2H, $-CO_2CH_2$) 4.85–5.30 (m, 1H, –OC*H*), 7.00–7.60 (m, 8H, Ar*H*), 7.70–8.20 (m, 2H, Ar*H*). MS (*m/z*): 244 (M^+). Analysis Calcd for $C_{15}H_{14}O_3$: C, 74.36, H, 5.82. Found: C, 74.55; H, 6.03%.

Reaction of **5h** *with thiophenol*

A solution of **5h** (1.57 g, 10 mmol) and thiophenol (1.10 g, 10 mmol) in 15 ml dry THF was heated at reflux for 2 h. Solvent was removed *in vacuo* and the residue was subjected to column chromatography using hexane–chloroform linear gradient to give **9e** and **10e** in the ratio of 1:2 as a colourless oil (1.06 g, 63%). IR(Neat): 3420, 1580. ^{1}H NMR: 1.18 & 1.25 (2d, 3H, J=8.0 Hz, $-CCH_3$), 2.42 (s, 1H, –O*H*, D_2O exchangeable), 2.70–2.84 (m, 1.3H, $-SCH_2$), 3.00–3.10 (m, 1.3H, $-OCH_2$), 3.18–3.29 (m, 0.69H, –SC*H*), 3.40–3.58 (m, 0.68 H, –OC*H*), 7.18–7.48 (m, 5H, Ar*H*). MS (*m/z*): 168 (M^+), 150 (M-18). Analysis Calcd for $C_9H_{12}OS$: C, 64.16; H, 8.18. Found: C, 64.11; H, 7.41%.

Reaction of **5i** *with thiophenol*

A mixture of **5i** (4.80 g, 22 mmol), thiophenol (2.20 g, 20 mmol) in 20 ml dry THF was heated under refluxing for 6 h. Usual workup and column chromatography gave **9f** and **10f** in 20 & 24% yield, respectively, as an oil.

*1-Phenyl-2-phenylthio ethanol (***9f***)*

IR(Neat): 3420, 1470. ^{1}H NMR (CCl_4): 2.50–2.80 (br s, 1H, –O*H*, D_2O exchangeable), 2.85–3.30 (m, 2H, $-SCH_2$), 4.40–4.80 (m, 1H, –OC*H*), 7.00–7.60 (m, 10H, Ar*H*). MS (*m/z*): 230 (M^+), 124 (M-106). Analysis Calcd for $C_{14}H_{14}OS$: C, 73.00; H, 6.12. Found: C, 72.85; H, 5.99%.

*2-Phenyl-2-phenylthio ethanol (***10f***)*

IR(Neat): 3400, 3060, 1580. ^{1}H NMR(CCl_4): 1.90–2.40 (br s, 1H, –O*H*, D_2O exchangeable), 3.50–3.95 (m, 1H, –SC*H*), 4.00–4.40 (m, 2H, $-OCH_2$), 7.00–7.50 (m, 5H, Ar*H*). MS (*m/z*): 230 (M^+), 199 (M-31), 121 (M-109). Analysis Calcd for $C_{14}H_{14}OS$: C, 73.00; H, 6.12. Found: C, 73.13; H, 6.23%.

*1-Hydroxyethyl-3-formylindole (***12***)*

A mixture of **5a** (860 mg, 6 mmol) and 3-formylindole (730 mg, 5 mmol) was heated under stirring at 80°C for 6 h. The crude product was subjected to column chromatography using chloroform–methanol (98:2) as eluant to give **12** as a colourless crystalline solid, yield 460 mg (41%), mp 121–125°C. IR(KBr): 3400, 2850, 1660. ^{1}H NMR: 1.85 (br s, 1H, –O*H*, D_2O exchangeable), 3.80–4.05 (m, 2H, $-NCH_2$), 4.10–4.40 (m, 2H, $-OCH_2$), 7.10–7.50 (m, 4H, Ar*H*), 8.10–8.35 (m, 1H, 2-C*H*). MS (*m/z*): 189 (M^+). Analysis Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.85; N, 7.40. Found: C, 70.09; H, 5.73; N, 7.41%.

Table III

Physical constants of compounds 9 & 10

Entry no.	R^2×H	A	R^1		9 & 10 % Yield	Ratio*
a	C_6H_5COOH	CH_2	CH_3		62	1:2.5
b	$C_6H_5CH_2CO_2H$	CH_2	CH_3		50	1:1
c	4-(C_5H_4N)CO_2H	CH_2	CH_3		44	1:2
d	$C_6H_5CO_2H$	CH_2	C_6H_5	9	38**	-
e	C_6H_5SH	CH_2	CH_3		63	1:2
f	C_6H_5SH	CH_2	C_6H_5	9	20	1:1:2
				10	24	

* Ratio of the products was determined from the ^1H NMR spectrum of the chromatographically pure mixture, recorded on Bruker WM-400MHz spectrometer

** mp 61–62°C [lit[25] 63–64°C]

*Methyl dibenzyl phosphate (**14**)*

To a solution of 2,2-dimethoxy-1-methylpyrrolidine **1** (290 mg, 2 mmol) in 10 ml dry THF dibenzyl phosphate (556 mg, 2 mmol) was added and the resulting mixture was heated under reflux for 4 h. The solvent was removed *in vacuo* and the crude product was subjected to column chromatography using chloroform–methanol as eluant to give **14** as an oil, yield 540 mg (92.4%). ^1H NMR: 3.65 (d, 3H, J=12.0 Hz, $-OCH_3$), 4.98 (d, 4H, J=8.0 Hz, 2×PhCH_2), 7.35 (s, 10H, ArH). MS (*m/z*): 292 (M^+), 201 (M-91). Analysis Calcd for $C_{15}H_{17}O_4P$: C, 61.64; H, 5.86. Found: C, 61.67; H, 5.69%.

*2-Hydroxyethyl dibenzyl phosphate (**15**)*

A mixture of **5a** (280 mg, 2 mmol), dibenzyl phosphate (556 mg, 2 mmol) in 10 ml dry THF was heated under refluxing for 4–5 h. The THF was removed *in vacuo* and the residue was subjected to column chromatography using chloroform to give **15** as an oil, yield 370 mg (54%). ^1H NMR: 2.40–2.90 (br s, 1H, $-OH$, D_2O exchangeable), 3.50–3.75 (m, 2H, $-OCH_2$), 3.85–4.15 (m, 2H, $-PO_2CH_2$), 4.98 (d, 4H, J=8.0 Hz, 2×PhCH_2), 7.27 (s, 10H, ArH). MS (*m/z*): 322 (M^+), 251 (M-91), 125 (M-197). Analysis Calcd for $C_{16}H_{19}O_5P$: C, 59.63; H, 5.94. Found: C, 59.81; H, 6.05%.

*(2-Hydroxy-2-methyl)ethyl dibenzyl phosphate (**16**), and (2-Hydroxy-1-methyl)ethyl dibenzyl phosphate (**17**)*

To a solution of **5h** (314 mg, 2 mmol) in 10 ml dry THF, dibenzyl phosphate (566 mg, 2 mmol) was added and the resulting reaction mixture was heated under refluxing for 5 h. Solvent was removed *in vacuo* and the residue was purified by column chromatography using chloroform as eluant to give a mixture of **16** and **17** in 1:1 ratio determined with the help of ^1H NMR spectra of mixture in 420 mg (63%) yield. ^1H

NMR: 1.09 & 1.25 (2d, 3H, $-CCH_3$), 2.20–2.45 (br s, 1H, $-OH$, D_2O exchangeable), 3.50–3.65 (m, 1H, $-CH$), 3.75–4.00 (m, 2H, $-CH_2$), 5.05 (d, 4H, J=8.0 Hz, $2\times PhCH_2$), 7.40 (s, 10H, ArH). MS (m/z): 336 (M^+), 277 (M-59), 245 (M-91), 227 (M-109). Analysis Calcd for $C_{17}H_{21}O_5P$: C, 60.70; H, 6.29. Found: C, 60.77; H, 6.50%.

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