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 (I) 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-4 with carboxylic acids, thiophenols, 3-formyldindole and dibenzyl phosphate when the corresponding ω-hydroxyalkylated products were obtained in good yields. This method provides a convenient synthesis for monoacyl diols, arymercaptoalkanols, 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, arymercaptoalkanols, phosphate esters.

1. Introduction

Lactam acetals exist in equilibrium with immonium, enamine and alkoide species and can thus react with nucleophiles at position-2, electrophiles at position-3 and generate in situ a carbanion from a reactive methylene substrate. 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 (Scheme 1). In our continuing study of the chemistry and synthetic utility of lactam acetals it appeared of interest to prepare different types of lactam spirocyclic acetals through trans-acetalisation reaction of lactam acetals I with alkane diols, which appeared suitable reagents for providing ω-hydroxyalkyl equivalent for alkylation as

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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 recently6.

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.

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 I

Physical constants of the lactam spirocyclic acetals 5

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>A</th>
<th>R'</th>
<th>bp,°C/</th>
<th>% Yield</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>torr(mm of Hg)</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>CH₂</td>
<td>H</td>
<td>89–90/15</td>
<td>95</td>
</tr>
<tr>
<td>b</td>
<td>(CH₂)₃</td>
<td>H</td>
<td>39–43/0 6</td>
<td>98</td>
</tr>
<tr>
<td>c</td>
<td>(CH₂)₂OCH₂</td>
<td>H</td>
<td>98–100/0.6</td>
<td>85</td>
</tr>
<tr>
<td>d</td>
<td>(CH₂)₂N(Me)CH₂</td>
<td>H</td>
<td>a</td>
<td>85ᵇ</td>
</tr>
<tr>
<td>e</td>
<td>CH₂C₆H₅</td>
<td>C₆H₅</td>
<td>a</td>
<td>96ᵇ</td>
</tr>
<tr>
<td>f</td>
<td>(CH₂CH₂O)₂CH₂</td>
<td>H</td>
<td>a</td>
<td>97ᵇ</td>
</tr>
<tr>
<td>g</td>
<td>(CH₂OCH₂)₂CH₂O</td>
<td>H</td>
<td>a</td>
<td>94ᵃ</td>
</tr>
<tr>
<td>h</td>
<td>CH₂</td>
<td>CH₃</td>
<td>98–99/15</td>
<td>83ᶜ</td>
</tr>
<tr>
<td>i</td>
<td>CH₂</td>
<td>C₆H₅</td>
<td>102–103/0.6</td>
<td>82ᶜ</td>
</tr>
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</table>

ᵃThick oils; ᵇCrude product yield; 'These show the presence of diastereomeric pair from their ¹H NMR and ¹³C 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 dissubstituted 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."\n
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 conditions formed a mixture of monosubstituted products 9e-f and 10e-f in 1:2 ratio which
<table>
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<tr>
<th>Entry no.</th>
<th>$R_2^\alpha H$</th>
<th>$A$</th>
<th>$R_1^j$</th>
<th>Method used$^1$</th>
<th>7 mp, °C</th>
<th>% yield</th>
<th>8 mp, °C</th>
<th>% yield</th>
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<tr>
<td>a</td>
<td>$C_4H_5CO_2H$</td>
<td>$CH_2$</td>
<td>$H$</td>
<td>A, B, D,</td>
<td>nd</td>
<td>14, 59, 67</td>
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<td>--</td>
</tr>
<tr>
<td>b</td>
<td>$C_6H_5CH_2CO_2H$</td>
<td>$CH_2$</td>
<td>$H$</td>
<td>B</td>
<td>oil</td>
<td>42</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>c</td>
<td>3-(C$_5H_5N)CO_2H$</td>
<td>$CH_2$</td>
<td>$H$</td>
<td>B, D</td>
<td>nd</td>
<td>61, 78</td>
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<td>--</td>
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<tr>
<td>d</td>
<td>4-(C$_5H_5N)CO_2H$</td>
<td>$CH_2$</td>
<td>$H$</td>
<td>D</td>
<td>oil</td>
<td>58</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>e</td>
<td>4-ClC$_6H_4CO_2H$</td>
<td>$CH_2$</td>
<td>$H$</td>
<td>C, D</td>
<td>71-72</td>
<td>48, 59</td>
<td>135-136</td>
<td>13, 7</td>
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<tr>
<td>f</td>
<td>4-MeOC$_6H_4CO_2H$</td>
<td>$CH_2$</td>
<td>$H$</td>
<td>C</td>
<td>oil</td>
<td>57</td>
<td>107-108</td>
<td>11</td>
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<tr>
<td>g</td>
<td>$C_4H_5CO_2H$</td>
<td>$(CH_2)_3$</td>
<td>$H$</td>
<td>B, D</td>
<td>oil</td>
<td>44, 52</td>
<td>75-76</td>
<td>7, 4</td>
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<tr>
<td>h</td>
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<td>$CH_2$</td>
<td>$H$</td>
<td>C, D</td>
<td>oil</td>
<td>58, 88</td>
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<td>9, 5</td>
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<tr>
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<td>$CH_2$</td>
<td>$H$</td>
<td>C</td>
<td>oil</td>
<td>60</td>
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<tr>
<td>j</td>
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<td>$CH_2$</td>
<td>$H$</td>
<td>C</td>
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<td>110-111</td>
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<tr>
<td>k</td>
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<td>$H$</td>
<td>C</td>
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<tr>
<td>l</td>
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<td>$H$</td>
<td>C, D</td>
<td>oil</td>
<td>55, 72</td>
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<td>D</td>
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<tr>
<td>n</td>
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<td>$(CH_2CH_2O)_2CH_2$</td>
<td>$H$</td>
<td>D</td>
<td>oil</td>
<td>57</td>
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<td>--</td>
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<tr>
<td>o</td>
<td>$C_6H_5SH$</td>
<td>$(CH_2OCH_2)_2CH_2$</td>
<td>$H$</td>
<td>D</td>
<td>oil</td>
<td>54</td>
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<tr>
<td>p</td>
<td>$C_6H_5SH$</td>
<td>$(CH_2)_2N(CH_2)CH_2$</td>
<td>$H$</td>
<td>D</td>
<td>oil</td>
<td>46</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>q</td>
<td>$C_6H_5SH$</td>
<td>$CHCH_2$</td>
<td>$C_6H_5$</td>
<td>B</td>
<td>oil</td>
<td>64</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*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 column 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\(^5\), their preparation using lactam spirocyclic acetals was studied. Reaction of 3-formylindole \(\text{11}\) with the lactam spirocyclic acetal \(\text{5a}\) gave 1-hydroxyethyl-3-formylindole \(\text{12}\) (Scheme 3).

\[\text{5a} \quad \begin{array}{c} \text{O} \\ \text{Me} \end{array} \quad + \quad \begin{array}{c} \text{CHO} \\ \text{N} \\ \text{H} \end{array} \quad \underset{\Delta, 80^\circC}{\longrightarrow} \quad \begin{array}{c} \text{CHO} \\ \text{CH}_2\text{CH}_2\text{OH} \end{array}\]

\text{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 \(\text{1}\) on reacting with dibenzyl phosphate \(\text{13}\) yielded methyl dibenzyl phosphate \(\text{14}\) in excellent yield. Similarly, lactam spirocyclic acetal \(\text{5a}\) reacted with \(\text{13}\) in refluxing THF to furnish 2-hydroxyethyl dibenzyl phosphate \(\text{15}\) in good yield. \(\text{5h}\) on treatment with \(\text{13}\) under similar reaction conditions gave a mixture of \(\text{16}\) and \(\text{17}\) in 1:1 ratio determined by \(^1\text{H}\) NMR spectrum of the chromatographically pure mixture (Scheme 4).

\[\begin{array}{c} \text{O} \\ \text{(C}_6\text{H}_5\text{CH}_2\text{O})_2\text{P}\text{--OCH}_3 \end{array} \leftarrow (\text{C}_6\text{H}_5\text{CH}_2\text{O})_2\text{P}--\text{OH} \rightarrow (\text{C}_6\text{H}_5\text{CH}_2\text{O})_2\text{P}--\text{OCH}_2\text{CH}_2\text{OH} \]

\[\text{14} \quad \text{13} \quad \text{15}\]

\[\text{5h}\]

\[\begin{array}{c} \text{O} \\ \text{(C}_6\text{H}_5\text{CH}_2\text{O})_2\text{P}--\text{OCH}_2\text{CH}_2\text{OH} + (\text{C}_6\text{H}_5\text{CH}_2\text{O})_2\text{P}--\text{OCH}_2\text{CH}_2\text{OH} \end{array} \]

\[\text{16} \quad (1:1) \quad \text{17} \]

\text{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...
LACTAM ACETALS

Diols\textsuperscript{16,17} and arylmercaptoalkanols\textsuperscript{18,19} is of significance since these are important classes of organic intermediates. Monoacyl diols are used as insoluble polymer supports in organic synthesis\textsuperscript{10} and in the synthesis of sex pheromones\textsuperscript{20}, whereas arylmercaptoalkanols are used as protecting groups for oligonucleotide synthesis\textsuperscript{21,22}. The known methods for their preparation, either by direct acylation of diols or from oxiranes or halohydrins are not satisfactory\textsuperscript{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 halohydrins involves strong acidic conditions which are not suitable for diols containing acid-sensitive groups\textsuperscript{24}. Furthermore, N-(β-hydroxyethyl)-group is an important pharmacophore of some important antiparasitic indoles and imidazoles\textsuperscript{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 KMnO₄ reagents. All compounds were purified by column chromatography over silica gel (230–400 mesh). IR spectra ($\lambda_{\text{max}}$ in cm\textsuperscript{-1}) were recorded either on Perkin–Elmer 157 or Acculab-I models and \textsuperscript{1}H NMR and \textsuperscript{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 CDCl₃, unless otherwise stated, and chemical shifts are in $\delta$ 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.

\textbf{6-Methyl-1,4-dioxo-6-azaspiro[4.4]nonane (5a)}

IR(CHCl₃): 3300, 2900, 1675, 1460, \textsuperscript{1}H NMR: 1.50-2.20 (m, 4H, 8- & 9-CH₂), 2.25 (s, 3H, N-CH₃), 2.70-3.00 (m, 2H, N-CH₂), 3.60-4.10 (m, 4H, 2- & 3-CH₂). \textsuperscript{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 $\lambda_{\text{max}}$: 241 nm.
8-Methyl-1,6-dioxa-8-azaspiro[4.6]undecane (5b)
IR(CHCl₃): 2900, 1675, 1450. ¹H NMR: 1.30–2.00 (m, 8H, 3-, 4-, 10- & 11-CH₂), 2.40 (s, 3H, N-CH₃), 2.55–2.95 (m, 2H, N-CH₂), 3.10–4.15 (m, 4H, 2- & 5-CH₂). MS (m/z): 171 (M⁺) at 23 eV and 100°C.

9-Methyl-1,4,7-trioxa-9-azaspiro[4.7]dodecane (5c)
IR(CHCl₃): 2910, 1660, 1430. ¹H NMR: 1.80–2.60 (m, 4H, 11- & 12-CH₂), 2.80 (s, 3H, N-CH₃), 3.40–4.00 (m, 10H, 2-, 3-, 5-, 6- & 10-CH₂). MS (m/z): 187 (M⁺) at 23 eV and 100°C.

2,6-Dimethyl-1,4-dioxa-6-azaspiro[4.4]nonane (5b)
IR(CHCl₃): 2900, 1670, 1450. ¹H NMR: 1.15 & 1.22 (2d, 3H, -CCH₃), 1.40–2.10 (m, 4H, 8- & 9-CH₂), 2.20 & 2.25 (2s, 3H, N-CH₃), 2.80 (t, 2H, J=4.0 Hz, N-CH₂), 3.10–3.50 (m, 1H, 2-CH), 3.70–4.30 (m, 2H, -OCH₂). ¹³C 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 50°C. UV λ_max: 240 mm.

6-Methyl-2-phenyl-1,4-dioxa-6-azaspiro[4.4]nonane (5i)
IR(CHCl₃): 1670, 1460. ¹H NMR: 1.30–2.20 (m, 4H, 8- & 9-CH₂), 2.30 & 2.35 (2s, 3H, N-CH₃), 2.60–3.00 (m, 2H, N-CH₂), 3.30–3.70 (m, 1H, 2-CH), 3.90–4.40 (m, 1H, 3-CH), 4.60–5.10 (m, 1H, 3’-CH), 7.00–7.50 (m, 5H, ArH). ¹³C NMR: 20.03, 32.01, 36.69, 52.07, 71.03, 77.78, 123.39, 126.65, 128.12. MS (m/z): 295 (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-penta-oxa-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. ¹H NMR: 1.50–2.50 (m, 4H, 8- & 9-CH₂), 2.70 (s, 3H, N-CH₃), 2.90–3.20 (m, 2H, 7-CH₂), 5.30 & 5.60 (2s, 2H, 2- & 3-CH₂), 6.85–7.30 (m, 10H, ArH). MS (m/z): 295 (M⁺).

General methods for the preparation of monoacyl diols (T) and arylmercaptopoalkanols (8)

Method A: A mixture of 5 (7 mmol) and the carboxylic acid/thiophenol (6 mmol) was heated under stirring at 70–80°C. After 3 h ethyl acetate (25 ml) was added to
the reaction mixture and the organic layer was washed with saturated NaHCO₃ solution (2×10 ml), 10% aqueous HCl (1×5 ml) and finally with brine (2×20 ml). The organic layer was dried (Na₂SO₄) 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 NaHCO₃ solution (2×10 ml), water (2×10 ml) and finally with brine (2×20 ml), dried (Na₂SO₄) 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 8, 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. ¹H NMR: 2.30–2.90 (br s, 1H, -OH, D₂O exchangeable), 3.60–4.20 (m, 2H, -OCH₂), 4.25–4.80 (m, 2H, -CO₂CH₂), 7.10–7.70 (m, 3H, 2-, 3- & 4-ArH), 7.80–8.40 (s, 2H, 1- & 5-ArH). MS(m/z): 166 (M⁺). Analysis Calcd for C₉H₁₀O₃: C, 65.05; H, 6.07. Found: C, 64.97; H, 6.15%.

2-Hydroxyethyl phenylacetate (7b)

Oil, IR(Neat): 3440, 2980, 1720, 1610. ¹H NMR: 1.75–2.40 (br s, 1H, -OH, D₂O exchangeable), 3.45–3.90 (m, 4H, PhCH₂ & -OCH₂), 4.00–4.40 (m, 2H, -CO₂CH₂), 7.30–7.50 (m, 5H, ArH). MS(m/z): 180 (M⁺). Analysis Calcd for C₁₀H₁₀O₅: C, 66.64; H, 6.71. Found: C, 66.67; H, 6.37%.

2-Hydroxyethyl nicotinate (7c)

Oil, IR(Neat): 3450, 1740, 1610. ¹H NMR: 3.80–4.40 (m, 3H, -CH₂OH), 4.50–5.00 (m, 2H, -CO₂CH₂), 7.50–7.90 (m, 1H, 4-ArH), 8.50–8.90 (m, 1H, 3-ArH). 8.95–9.35 (m, 1H, 5-ArH), 9.50–9.90 (m, 1H, 1-ArH). MS(m/z): 167 (M⁺). Analysis Calcd for C₈H₇NO₃: 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, -OH, D$_2$O exchangeable), 3.35-4.20 (m, 2H, -OCH$_2$), 4.30-4.70 (m, 2H, -CO$_2$CH$_2$), 7.85 (d, 2H, J=8.0 Hz, 3- & 5-ArH). 8.75 (d, 2H, J=8.0 Hz, 2- & 6-ArH). MS (m/z): 167 (M$^+$). Analysis Calcd for CsH$_9$NO$_3$: 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, 1600. $^1$H NMR: 2.00-2.60 (br s, 1H, -OH, D$_2$O exchangeable), 3.70-4.20 (m, 2H, -OCH$_2$), 4.30-4.70 (m, 2H, -CO$_2$CH$_2$), 7.45 (d, 2H, J=8.0 Hz, 3- & 5-ArH). 8.05 (d, 2H, J=8.0 Hz, 2- & 6-ArH). MS (m/z): 200 (M$^+$) & 202 (M+2). Analysis Calcd for C$_{12}$H$_9$ClO$_3$: 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, -OH, D$_2$O exchangeable), 3.90-4.15 (m, 5H, -OCH$_2$ & -OCH$_3$), 4.30-4.75 (m, 2H, -CO$_2$CH$_2$), 7.00 (d, 2H, J=8.0 Hz, 3- & 5-ArH). 8.15 (d, 2H, J=8.0 Hz, 2- & 6-ArH). MS (m/z): 196 (M$^+$). Analysis Calcd for C$_{16}$H$_{14}$O$_3$: 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, -OH, D$_2$O exchangeable), 3.30-3.80 (m, 2H, -OCH$_2$), 4.20 (t, 2H, J=4.0 Hz, -CO$_2$CH$_2$), 7.00-7.60 (m, 5H, ArH). MS (m/z): 194 (M$^+$). Analysis Calcd for C$_{16}$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, -OH, D$_2$O 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, ArH). MS (m/z): 154 (M$^+$). Analysis Calcd for C$_{11}$H$_{15}$O$_2$: 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, -OH, D$_2$O 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, ArH). MS (m/z): 188 (M$^+$) & 190 (M+2). Analysis Calcd for C$_{15}$H$_{14}$ClO$_2$: 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, -OH, D$_2$O 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-ArH), 7.60 (d, 2H, J=8.0 Hz, 2- & 6-ArH). MS (m/z): 233 (M$^+$). Analysis Calcd for C$_{15}$H$_{14}$BrO$_2$: C, 41.21; H, 3.89. Found: C, 41.53; H, 3.73%.
2-(p-Methylphenylthio)ethanol (7k)

Oil. IR(Neal): 3200, 1660, 1220. H NMR: 2.30 (s, 3H, =CH2), 2.40–2.70 (br s, 1H, =OH, D2O exchangeable), 2.90–3.20 (m, 2H, =CH2), 3.50–3.90 (m, 2H, =OCH2), 7.09 (d, 2H, J=8.0 Hz, 3- & 5-ArH). MS (m/z): 168 (M+). Analysis Calcd. for C9H12O2S: C, 64.24; H, 7.19. Found: C, 64.78; H, 6.91%.

4-(Phenylthio)butanol (7l)

Oil. IR(Neal): 3380, 2960, 1590, 1490. H NMR: 1.30–2.00 (m, 5H, 2xC-CH2 & =OH), 2.60–3.10 (m, 2H, =SCH2), 3.30–3.80 (m, 2H, =OCH2). 7.00–7.60 (m, 5H, ArH). MS (m/z): 182 (M+). Analysis Calcd for C10H14O2S: C, 65.88; H, 7.74. Found: C, 65.76; H, 7.79%.

2-(p-Pheny1thioethoxy)ethanol (7m)

Oil. IR(Neal): 3220, 1660. H NMR: 2.30–2.80 (br s, 1H, =OH, D2O exchangeable), 3.10 (t, 2H, J=4.0 Hz, =SCH2), 3.40–3.90 (m, 6H, 3x-OCH2), 7.00–7.60 (m, 5H, ArH). MS (m/z): 198 (M+). Analysis Calcd for C16H24O2S: C, 60.57; H, 7.11. Found: C, 60.93; H, 7.35%.

8-Phenylmercaptopo-3,6-dioxoaoctane-1-ol (7n)

Oil. IR(Neal): 3380, 2900, 1650. H NMR: 1.80–2.60 (m, 3H, =SCH2 & =OH), 3.50–4.00 (m, 10H, 5x-OCH2), 7.10–7.60 (m, 5H, ArH). MS (m/z): 242 (M+). Analysis Calcd for C12H18O3S: C, 59.42; H, 7.46. Found: C, 59.63; H, 7.75%.

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

Oil. IR(Neal): 3380, 2840, 1650. H NMR: 1.90–2.50 (m, 3H, =SCH2 & =OH), 3.20–4.00 (m, 14H, 7x-OCH2), 7.10–7.60 (m, 5H, ArH). MS (m/z): 286 (M+). Analysis Calcd for C16H22O4S: C, 58.77; H, 7.75. Found: C, 58.30; H, 7.43%.

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

Oil. IR(Neal): 3440, 3040, 1660. H NMR: 1.60–2.10 (m, 1H, =OH, D2O exchangeable), 2.40–2.70 (m, 2H, =SCH2), 2.75 (s, 3H, NCH3), 2.80–3.20 (m, 4H, 2x-NCH2), 3.30–4.60 (m, 2H, =OCH2), 7.00–7.40 (m, 5H, ArH). MS (m/z): 211 (M+). Analysis Calcd for C23H17NOS: 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(Neal): 3430, 3060, 1580, 1450. H NMR: 3.00–3.50 (br s, 1H, =OH, D2O exchangeable), 4.30 (d, 1H, J=8.0 Hz, =SCH2), 4.85 (d, 1H, J=6.0 Hz, =OCH), 6.70–7.50 (m, 15H, ArH). MS (m/z): 306 (M+). Analysis Calcd for C20H19OS: C, 78.39; H, 5.92. Found: C, 78.15; H, 6.13%.
Ethylene glycol diperchlorobenzoate (8e)
mp 135–136°C [lit2, mp 141°C]. IR(KBr): 1710, 1590. 1H NMR: 4.70 (s, 4H, 2x OCH2), 7.45 (d, 4H, J=8.0 Hz, 3- & 5-ArH), 8.05 (d, 4H, J=8.0 Hz, 2- & 6-ArH) MS (m/z): 338 (M+) & 342 (M+4). Analysis Calcd for C18H12Cl2O4: C, 56.65; H, 3.56. Found: C, 56.87; H, 3.64%.

Ethylene glycol dipropoxybenzoate (8f)
mp 107–108°C. IR(KBr): 1680, 1575. 1H NMR: 3.90 (s, 6H, 2x-OC2H5), 4.65 (s, 4H, 2x-OC2H5), 7.00 (d, 4H, J=10.0 Hz, 3- & 5-ArH), 8.10 (d, 4H, J=10.0 Hz, 2- & 6-ArH). MS (m/z): 328 (M+). Analysis Calcd for C18H18O2: C, 65.44; H, 5.49. Found: C, 65.63; H, 5.37%.

1,4-Butanediol dibenzoate (8g)
mp 75–76°C [lit6, mp 80°C]. IR(KBr): 1695, 1600. 1H NMR: 1.60–2.20 (m, 4H, 2x-CH2), 3.00–4.70 (m, 4H, 2x-OCH2), 7.10–7.70 (m, 6H, ArH). MS (m/z): 298 (M+). Analysis Calcd for C18H16O2: C, 72.46; H, 6.08. Found: C, 72.13; H, 6.27%.

1,2-bis(Phenylthio)ethane (8h)
mp 69–70°C [lit8, mp 69°C]. IR(KBr): 1570, 1470. 1H NMR: 3.00 (s, 4H, 2x-SCH2), 7.00–7.40 (m, 10H, ArH). MS (m/z): 246 (M+). Analysis Calcd for C14H14S2: 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 [lit9, mp 94°C]. IR(KBr): 1470, 1380. 1H NMR: 3.05 (s, 4H, 2x-SCH2), 7.00–7.50 (m, 8H, ArH). MS (m/z): 314 (M+), 318 (M+4). Analysis Calcd for C14H13Cl2S2: C, 53.31; H, 5.83. Found: C, 53.45; H, 3.93%.

1,2-bis(p-Bromophenylthio)ethane (8j)
mp 110–111°C [lit10, mp 109°C]. IR(KBr): 1470, 1425. 1H NMR: 3.05 (s, 4H, 2x-SCH2), 7.20 (d, 4H, J=8.0 Hz, 3- & 5-ArH), 7.50 (d, 4H, J=8.0 Hz, 2- & 6-ArH). MS (m/z): 402 (M+). Analysis Calcd for C14H12Br2S2: 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. 1H NMR: 2.34 (s, 6H, 2x-CCH3), 3.01 (s, 4H, 2x-SCH2), 6.80–7.30 (m, 8H, ArH). MS (m/z): 274 (M+). Analysis Calcd for C18H18S2: C, 70.02; H, 6.61. Found: C, 70.77; H, 6.64%.

1,4-bis(Phenylthio)butane (8l)
mp 85–86°C [lit12, mp 84°C]. IR(KBr): 1580, 1480. 1H NMR(CCl4): 1.40–2.00 (m,
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 NaHCO₃ solution (1×10 ml), 10% HCl (1×10 ml), water and then with brine (2×20 ml), dried (Na₂SO₄) 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, -CCH₂), 2.30-2.70 (br s, 1H, -OH, D₂O exchangeable), 3.70-3.90 (m, 2H, -CH₂), 4.14-1.24 (m, 0.71H, -CH₇), 4.30-1.38 (m, 0.29H, -CH₂), 5.18-5.30 (m, 1H, -CH), 7.36-7.64 (m, 3H, ArH), 7.98-8.18 (1H, 1H, ArH). MS (m/z): 180 (M⁺) 162 (M-18). Analysis Calcd for C₁₀H₁₂O₃: 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, -CCH₂), 3.40-3.80 (m, 4H, PhCH₂ & -OCH₂), 3.90-4.50 (m, 3.31H, -CO₂CH₂, -CH₂ & -OH), 4.80-5.50 (m, 0.70H, -CO₂CH), 7.40 (s, 5H, ArH). MS (m/z): 194 (M⁺), 176 (M-18), 91 (M-103). Analysis Calcd for C₁₁H₁₄O₃: 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, -CCH₂), 2.20-2.80 (br s, 1H, -OH, D₂O exchangeable), 3.72-3.90 (m, 2H, -OCH₂), 4.15-4.46 (m, 3.35H, -CO₂CH₂ & -OCH₂), 5.24-5.38 (m, 0.64H, -CO₂CH), 7.75-8.10 (m, 2H, ArH), 8.80-9.10 (m, 3H, ArH). MS (m/z): 181 (M⁺), 163 (M-18), 136 (M-45), 106 (M-75). Analysis Calcd for C₉H₁₁NO₃: 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. 1H NMR: 2.40–2.90 (br s, 1H, –OH, D$_2$O exchangeable), 4.20–4.70 (m, 2H, –CO$_2$CH$_2$), 4.85–5.30 (m, 1H, –OCH). 7.00–7.60 (m, 8H, ArH), 7.70–8.20 (m, 2H, ArH). MS (m/z): 244 (M$^+\text{).}$

Analysis Calcd for C$_{13}$H$_{10}$O$_2$: 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. 1H NMR: 1.18 & 1.25 (2d, 3H, J=8.0 Hz, –CCH$_3$), 2.42 (s, 1H, –OH, D$_2$O exchangeable), 2.70–2.84 (m, 1.3H, –SCH$_2$), 3.00–3.10 (m, 1.3H, –OCH), 3.75–3.95 (m, 0.68H, –OCH$_2$), 3.40–3.58 (m, 0.69H, –SCN), 3.40–3.58 (m, 0.68H, –SCN). 7.10–7.60 (m, 5H, ArH). MS (m/z): 168 (M$^+$), 150 (M-18). Analysis Calcd for C$_9$H$_{12}$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) and 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. 1H NMR (CCl$_3$): 2.50–2.80 (br s, 1H, –OH, D$_2$O exchangeable), 2.85–3.30 (m, 2H, –SCH$_2$), 4.40–4.80 (m, 1H, –OCH), 7.00–7.60 (m, 10H, ArH). 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. 1H NMR (CCl$_3$): 1.90–2.40 (br s, 1H, –OH, D$_2$O exchangeable), 3.50–3.95 (m, 1H, –SCF), 4.00–4.40 (m, 2H, –OCH$_2$), 7.00–7.50 (m, 10H, ArH). 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. 1H NMR: 1.85 (br s, 1H, –OH, D$_2$O exchangeable), 3.80–4.05 (m, 2H, –NCH$_2$), 4.10–4.40 (m, 2H, –OCH$_2$), 7.10–7.50 (m, 4H, ArH), 8.10–8.35 (m, 1H, 2-CH). MS (m/z): 189 (M$^+$). Analysis Calcd for C$_{14}$H$_{13}$NO$_2$: C, 69.82; H, 5.85; N, 7.40. Found: C, 70.09; H, 5.73; N, 7.41%. 

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### Table III

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

$^*$ mp 61–62°C [lit. 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%). $^1$H NMR: 3.65 (d, 3H, $J=12.0$ Hz, -OCH₃), 4.98 (d, 4H, $J=8.0$ Hz, 2×PhCH₂), 7.35 (s, 10H, ArH). MS (m/z): 292 (M⁺), 201 (M-91). Analysis Calcd for C₁₅H₁₉O₅P: 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%). $^1$H NMR: 2.40–2.90 (br s, 1H, -OH, D₂O exchangeable), 3.50–3.75 (m, 2H, -OCH₂), 3.85–4.15 (m, 2H, -PO₂CH₂), 4.98 (d, 4H, $J=8.0$ Hz, 2×PhCH₂), 7.27 (s, 10H, ArH). MS (m/z): 322 (M⁺), 251 (M-91), 125 (M-197). Analysis Calcd for C₁₆H₁₉O₅P: 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 $^1$H NMR spectra of mixture in 420 mg (63%) yield. $^1$H
NMR: 1.09 & 1.25 (2d, 3H, -CCH3), 2.20–2.45 (br s, 1H, -OH, D2O exchangeable),
3.50–3.65 (m, 1H, -CH), 3.75–4.00 (m, 2H, -CH2), 5.05 (d, 4H, J=8.0 Hz,
2xPhCH2), 7.40 (s, 10H, ArH). MS (m/z): 336 (M'), 277 (M-59), 245 (M-91), 227
(M-109). Analysis Calcd for C17H22O2P: C, 60.70; H, 6.29. Found: C, 60.77; H,
6.50%.

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