

# Water as catalyst and solvent: tetrahydropyranylation of alcohols in an aqueous medium

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## Abstract

Water is found to catalyze the tetrahydropyranylation of alcohols at elevated temperature. Interestingly, tetrahydropyranylation of alcohols works under a wide range of pH, 6.5 to 2, and does not work beyond pH 7.5 in an aqueous medium. Hydrophobic interactions between the substrate alcohol and dihydropyran ether (DHP) and favorable pKa's of water, alcohols, and protonated hydroxyl and protonated ethereal functions are the driving forces for the reaction. Thus the reaction, which is carried out in anhydrous aprotic solvents, can be carried out in aqueous medium in an environmentally benign way.

**Keywords:** Protection, aqueous medium, tetrahydropyranylation, chemoselectivity

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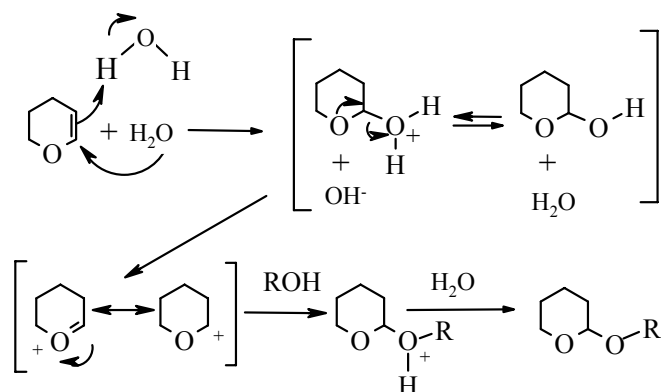
## Introduction

Aqueous mediated reactions have received considerable attention in organic synthesis due to environmental safety reasons. Water is the cheapest, most abundant and non-toxic chemical in Nature. It has unique physical and chemical properties such as a high dielectric constant and cohesive energy density compared to organic solvents. It has also special effects on reactions arising from inter and intramolecular non-covalent interactions leading to novel solvation and assembly processes. Large numbers of organic reactions have been performed successfully utilizing water as the reaction medium, and several books and reviews have been devoted to such a use.<sup>1</sup> Thus, development of an efficient and convenient synthetic methodology in water is an important subject in these environmentally conscious days. Recently, we have reported acylation of amines in an aqueous medium.<sup>2</sup>

## Results and Discussion

The tetrahydropyranyl ether is one of the most frequently used protecting groups for alcohols employed during multi-step organic synthesis.<sup>3</sup> Most of the reported methods use acidic reagents in an aprotic solvent such as CH<sub>2</sub>Cl<sub>2</sub>, THF, acetone and toluene.<sup>4</sup> At times their formation has

been carried out in ionic liquids.<sup>5</sup> Although these methods are suitable for many synthetic conditions, some of these methods suffer from use of excess amounts and/or toxic catalysts, volatile organic solvents and large amounts of solid supports which ultimately result in the generation of considerable amounts of toxic wastes. Tetrahydropyranylation is usually performed in anhydrous aprotic organic solvents because of the longer reaction time and poor yields of products obtained in the presence of water. Based on the pKa's of water (15.74), alcohols (~16.5), protonated hydroxyl of 2-hydroxytetrahydropyran (~-2) and protonated ethereal functions (~-6), we speculate that pyranylation of alcohols should occur in an aqueous medium and, due to an unfavorable pKa, phenol should not undergo pyranylation in water. 2-Hydroxytetrahydropyran is formed in all reactions involving dihydropyran (DHP) and water. The hydroxyl group of 2-hydroxytetrahydropyran is more likely to be protonated compared to the ethereal oxygen. An oxycarbenium species could be generated due to protonation of the hydroxyl group followed by water elimination, which should react with alcohol giving rise to the corresponding THP ether. The attack of water occurs but it is unproductive and regenerates the oxycarbenium species via a hemiacetal while the attack of the alcohol produces the acetal. The latter should be favored because the hydroxyl group having a lower pKa will leave preferentially over the alkoxide, driving the reaction in favor of product formation as shown in Scheme 1.



**Scheme 1.** Mechanism of formation of THP ether in water.

With this assumption, when 3-phenyl-1-propanol **2** (5 mmol) was treated with DHP (7.5 mmol) in water (5 ml), 60% of the product was formed after 24 h at room temperature. However, *ca.* 60% conversion was achieved in 7 h by performing the reaction at reflux temperature. Alcohol and DHP formed a heterogeneous reaction mixture in water. In order to make the reaction homogeneous with the hope of accelerating the reaction, phase transfer reagents such as tetrabutylammonium bromide (*ca.* 50 mg) were added to the medium. Unfortunately, the percentage conversion was a mere 50% after 10 h, even at reflux temperature. When the reaction was repeated in a saturated solution of sodium chloride under reflux conditions, the yield improved to *ca.* 80% within 7 h. Thus, hydrophobic interactions between the alcohol and the DHP unit are essential for the reaction leading to product formation. The pH of the medium progressively decreased from *ca.* 6.8 at the beginning of the reaction to *ca.* 4.3 after the completion of the reaction when 3-phenyl-1-propanol **2** was used as the substrate. This prompted

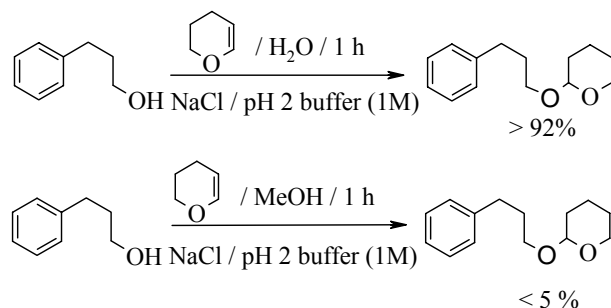
us to investigate the optimum pH conditions of the reaction medium required for the pyranylation of alcohol. Pyranylation was performed under reflux at different pH (1 M buffer), saturated with NaCl. The results are summarized in Table 1.

**Table 1.** Tetrahydropyranylation of 3-phenyl-1-propanol **2** in different buffers

pH of the Solution	Time (h)	Conversion (%) <sup>a</sup>	Types of Buffer Used
8	15	Nil	Na <sub>2</sub> HPO <sub>4</sub> + NaH <sub>2</sub> PO <sub>4</sub>
7.5	15	10%	Na <sub>2</sub> HPO <sub>4</sub> + NaH <sub>2</sub> PO <sub>4</sub>
7	15	20%	Na <sub>2</sub> HPO <sub>4</sub> + NaH <sub>2</sub> PO <sub>4</sub>
6.5	15	72%	Na <sub>2</sub> HPO <sub>4</sub> + NaH <sub>2</sub> PO <sub>4</sub>
6	15	80%	Na <sub>2</sub> HPO <sub>4</sub> + NaH <sub>2</sub> PO <sub>4</sub>
5.5	10	> 95%	Na <sub>2</sub> HPO <sub>4</sub> + NaH <sub>2</sub> PO <sub>4</sub>
5	8	> 95%	Na <sub>2</sub> HPO <sub>4</sub> + NaH <sub>2</sub> PO <sub>4</sub>
4.5	7	> 95%	Na <sub>2</sub> HPO <sub>4</sub> + NaH <sub>2</sub> PO <sub>4</sub>
4	5	> 95%	Sodium citrate + Citric acid
3.5	4.5	> 95%	Sodium citrate + Citric acid
3	3	> 95%	Sodium citrate + Citric acid
2	1	> 95%	Sodium citrate + Citric acid

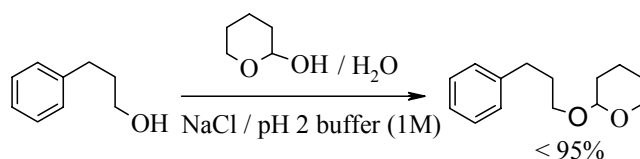
<sup>a</sup> GC yields.

It is interesting to note that the reaction worked from pH 7.5 down to pH 2. The process is more facile at lower pH and worked even in 10% aqueous HCl giving 90% yield of the product after 2.5 h. It seems that under acidic conditions the oxycarbenium species is more susceptible to attack by alcohol than water (Scheme 1). There are several reports of deprotection of THP ethers<sup>3</sup> in an acidic medium and in almost all of these cases methanol or ethanol is used as the co-solvent, possibly because a large excess of the alcohol shifts the equilibrium with concurrent formation of 2-methoxytetrahydropyran via a transacetalization process. When the THP ether of 3-phenyl-1-propanol **2a** (1 mmol) was treated with 10% aq. HCl (2 mL) and refluxed for 2 h, less than 5% of the product was deprotected. However, more than 90% deprotection could be achieved after 2 h under identical conditions when methanol (2 mL) was added to the medium. When pyranylation of 3-phenyl-1-propanol **2** (1 mmol) was performed under identical conditions at pH 2 (1M buffer) in the presence of methanol (2 mL), only a trace of pyranylated product (< 5 %) could be seen, further supporting the facile formation of 2-methoxytetrahydropyran and the role of methanol during the depyranylation process (Scheme 2).



**Scheme 2.** Pyranylation in different solvents.

Mechanistically, it is possible to suggest other reasonable pathways, as for instance the addition of the alcohol to the aldehyde group of the open-chain tautomer of 2-hydroxytetrahydropyran followed by protonation of the hemiacetal OH, loss of water, intramolecular acetalisation followed by deprotonation. This possibility can be ruled out because IR and  $^1\text{H}$  NMR analysis of 2-hydroxytetrahydropyran showed less than 1% of the open chain tautomer. Similar to reducing sugars it may contain < 0.01% of the aldehydic form, however unlike glucose, 2-hydroxytetrahydropyran failed to respond to both Tollen's and Fehling's tests. In another experiment, when 2-hydroxytetrahydropyran (5 mmol) and 3-phenyl-1-propanol **2a** (2 mmol) were reacted in a pH 2 buffer (1 M, 2 mL) saturated with NaCl and refluxed for 2 h, more than 95% of the pyranylated product could be obtained, further supporting the intermediacy of 2-hydroxytetrahydropyran (Scheme 3).



**Scheme 3.** Pyranylation of 3-phenyl-1-propanol **2** with 2-hydroxytetrahydropyran.

The reaction works even in pure water under non buffered conditions, giving a moderate yield of the product, but the pH of the medium changes depending on the nature of the substrate. Therefore, we decided to perform the reaction under buffered conditions. In spite of the shorter reaction time at lower pH we decided to perform the reaction at pH 5 since many acid sensitive groups are expected to survive at this pH. Thus, in a typical reaction, alcohol (5 mmol), DHP (7.5 mmol), in 1M phosphate buffer (5 mL) saturated with NaCl was refluxed for a specific period of time as shown in Table 2.

**Table 2.** Tetrahydropyranylation<sup>a</sup> of alcohol in phosphate buffer pH 5

Substrate	Product <sup>b</sup>	Time (h)	Yield (%) <sup>c</sup>
(1)	(1a)	6	82
(2)	(2a)	5	92
(3)	(3a)	7	85
(4)	(4a)	7	87
(5)	(5a)	10	72
(6)	(6a)	6	82
(7)	(7a)	8	72
(8)	(8a)	10	76
(9)	(9a)	7.5	79
(10)	(10a)	6	88
(11)	(11a)	7	84
(12)	(12a)	9	55
(13)	(13a)	9	81
(14)	(14a)	8.5	78
(15)	(15a)	7.5	72
(16)	(16a)	7	75
(17)	(17a)	7	78

<sup>a</sup> Reactions were monitored by TLC. <sup>b</sup> Confirmed by comparison with IR, <sup>1</sup>H NMR of the authentic sample. <sup>c</sup> Isolated yields.

Pyranylation of several alcohols such as primary, benzylic and secondary was achieved in good to excellent yields *via* this procedure as shown in Table 2. In all the cases examined the reactions were nearly complete, however isolated yields were 10-15% less. As evident from Table

2, acid sensitive protecting groups such as THP, TBS, TBDPS and isopropylidene survived these conditions. Thus, the present method is mild enough to tolerate a wide range of functional groups. As shown in Table 1, depending on the sensitivity of the other protecting group present in the substrate, this reaction can be performed from pH 6.5-2. Phenol, which has a lower pKa than water, is a better leaving group; hence the method was not successful for pyranylation of phenols in the entire range of pH tested. One important feature of this method is the chemoselective mono tetrahydropyranylation of symmetrical 1,n-diols **18** and **19** and unsymmetrical diol **20** (Table 3), a transformation that is difficult to accomplish via conventional methods. Only a few methods have been reported in the literature.<sup>4m-s,5a-b</sup> We assume that the selectivity of the mono tetrahydropyranylation arises because, after the monopyranylation, the other hydroxyl group points away from the hydrophobic pockets formed by the DHP and alcohol. A primary alcohol has been selectively pyranylated in the presence of a secondary alcohol **20** and a phenolic hydroxyl group **21**.

**Table 3.** Tetrahydropyranylation<sup>a</sup> of alcohol in water

Substrate	Product <sup>b</sup>	Time (h)	Yield (%) <sup>c</sup>
HO-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OH ( <b>18</b> )	HO-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OTHP ( <b>18a</b> )	8	78
	THPO-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OTHP ( <b>18b</b> )		09
HO-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OH ( <b>19</b> )	HO-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OTHP ( <b>16</b> )	8	76
	THPO-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OTHP ( <b>16a</b> )		08
HO-CH <sub>2</sub> -CH <sub>2</sub> -CH(OH)-CH <sub>3</sub> ( <b>20</b> )	HO-CH <sub>2</sub> -CH <sub>2</sub> -CH(OH)-CH <sub>3</sub> -OTHP ( <b>20a</b> )	8	72
	THPO-CH <sub>2</sub> -CH <sub>2</sub> -CH(OH)-CH <sub>3</sub> -OTHP ( <b>20b</b> )		10
HO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OH ( <b>21</b> )	HO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OTHP ( <b>21a</b> )	10	80
	THPO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OTHP ( <b>21b</b> )		00

<sup>a</sup> Reactions were monitored by TLC. <sup>b</sup> Confirmed by comparison with IR, <sup>1</sup>H NMR of the authentic sample. <sup>c</sup> Isolated yields.

## Conclusions

In conclusion, this manuscript describes a method for pyranylation in water that takes advantage of the pKa's of different functional groups and the reaction medium. Thus the reaction, which is typically carried out in an anhydrous aprotic solvent, can be carried out in water in an environmentally benign way. The procedure works over a broad pH range and even without an acid catalyst. Mild reaction conditions, simplicity of the procedure, general applicability for a wide range of alcohols and selective mono-tetrahydropyranylation of diols are other significant advantages over many existing procedures.

## Experimental Section

**General experimental procedure.** To a mixture of alcohol (5 mmol) and 3,4-dihydro-2H-pyran (7.5 mmol) was added 1M Na<sub>2</sub>HPO<sub>4</sub>+NaH<sub>2</sub>PO<sub>4</sub> buffer (5 mL) saturated with NaCl. The reaction was refluxed in a oil bath and the progress of the reaction was monitored by TLC. After the specific time, the reaction mixture was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed in a rotary evaporator under reduced pressure. The crude product was purified by passing through a short column of silica gel to yield the pure product, which was identified by its NMR<sup>6</sup> and IR spectra and GC pattern, and GC co-injection with authentic samples prepared by known methods.

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## [Supplementary Material Available](#)

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6. **Spectroscopic data of compounds**  
**1a.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.90 (t, 3H, *J* = 7.2 Hz), 1.20-1.40 (brs, 14H), 1.50-1.69 (m, 6H), 1.7 (m, 1H), 1.80 (m, 1H), 3.35 (m, 1H), 3.50 (m, 1H), 3.75 (m, 1H), 3.85 (m, 1H), 4.60 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.5, 20.1, 23.1, 25.9, 26.6, 29.7, 29.9, 29.98, 30.0, 30.2, 31.1, 32.3, 62.6, 68.0, 99.0.  
**2a.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.48-1.96 (m, 8H), 2.69 (m, 2H), 3.35-3.49 (m, 2H), 3.72-3.85 (m, 2H), 4.56 (m, 1H), 7.23 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.5, 25.4, 30.6, 31.2, 32.4, 62.1, 66.7, 98.7, 125.6, 128.1, 128.3, 141.9.  
**3a.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.48-1.90 (m, 6H), 3.52 (m, 1H), 3.89 (m, 1H), 4.42 (d, 1H, *J* = 11.6 Hz), 4.70 (m, 1H), 4.80 (d, 1H, *J* = 12.0 Hz) 7.25 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.8, 25.9, 31.0, 62.4, 69.1, 97.9, 127.7, 128.0, 128.5, 138.5.  
**4a.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.40-1.91 (m, 6H), 3.50 (m, 1H), 3.76 (s, 3H), 3.90 (m, 1H), 4.42 (d, 1H, *J* = 11.6 Hz), 4.69 (m, 2H), 6.87 (d, 2H, *J* = 8.8 Hz) 7.28 (d, 2H, *J* = 8.8 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.8, 25.9, 31.0, 55.6, 62.4, 68.8, 97.7, 113.9, 129.6, 130.5, 159.2.



**5a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.43-1.99 (m, 6H), 3.52 (m, 1H), 3.89 (m, 1H), 4.75 (m, 1H), 4.89 (d, 1H,  $J = 15.6$  Hz), 5.15 (d, 1H,  $J = 14.8$  Hz), 7.40 (t, 1H,  $J = 7.2$  Hz), 7.63 (t, 1H,  $J = 7.2$  Hz), 7.80 (d, 1H,  $J = 7.6$  Hz), 8.05 (d, 1H,  $J = 8.0$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.7, 25.7, 30.8, 62.6, 66.1, 98.9, 124.7, 128.0, 128.9, 133.6, 135.2, 147.4. Peaks from other enantiomers (20.1, 25.8, 31.6, 63.1, 94.7). Anal. calcd for  $\text{C}_{12}\text{H}_{15}\text{NO}_4$ : C, 60.75; H 6.37; N 5.90. Found C, 61.04, H, 6.31, N, 5.82.

**6a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.48-2.0 (m, 6H), 3.55 (m, 1H), 3.88 (m, 1H), 4.50 (d, 1H,  $J = 13.2$  Hz), 4.79 (m, 2H), 4.80 (d, 1H,  $J = 13.2$  Hz), 7.23 (m, 1H), 7.35 (d, 1H,  $J = 1.6$  Hz), 7.44 (d, 1H,  $J = 8.4$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.7, 25.8, 30.8, 62.5, 66.0, 98.6, 127.1, 129.1, 129.8, 133.5, 133.6, 135.0.

**7a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.40-1.98 (m, 9H), 3.50 (m, 1H), 3.98 (m, 1H), 4.40 (m, 1H), 4.90 (m, 1H), 7.30 (m, 5H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.2, 24.8, 25.98, 31.2, 63.0, 73.5, 96.3, 126.6, 127.1, 128.3, 143.8. Peaks from other diastereomers (19.7, 22.4, 25.95, 31.3, 62.2, 73.3, 96.4, 126.1, 127.5, 128.5, 143.9). Anal. calcd for  $\text{C}_{13}\text{H}_{18}\text{O}_2$ : C, 75.69; H 8.80. Found C, 75.78, H, 8.92.

**8a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) Obtained as a mixture of diastereomers.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) (Peaks from both diastereomers)  $\delta$  16.0, 16.7, 20.1, 20.7, 21.6, 21.7, 22.7, 22.8, 23.4, 23.7, 25.6, 25.9, 26.00, 26.04, 31.6, 31.7, 31.8, 32.2, 34.8, 34.9, 40.5, 43.9, 48.5, 49.2, 62.7, 63.3, 74.4, 80.2, 94.6, 101.5. Anal. calcd for  $\text{C}_{15}\text{H}_{28}\text{O}_2$ : C, 74.95; H 11.74. Found C, 74.58, H, 12.02.

**9a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) Obtained as a mixture of diastereomers  $\delta$  0.93 (t, 3H,  $J = 7.6$  Hz), 1.41-1.88 (m, 8H), 3.48 (m, 1H), 3.95 (m, 1H), 4.40 (t, 1H,  $J = 4$  Hz), 4.59 (t, 1H,  $J = 6$  Hz), 7.2-7.4 (m, 5H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.0, 20.0, 26.0, 31.2, 31.6, 62.7, 78.8, 95.5, 126.7, 127.2, 128.2, 142.5, Peaks from other diastereomers (10.2, 19.6, 25.9, 30.1, 31.1, 62.2, 80.1, 98.1, 127.0, 127.5, 128.4, 143.5). Anal. calcd for  $\text{C}_{14}\text{H}_{20}\text{O}_2$ : C, 76.33; H 9.15. Found C, 76.59, H, 9.04.

**10a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.50-1.86 (m, 6H), 3.50 (m, 1H), 3.90 (m, 1H), 4.15 (m, 1H), 4.38 (m, 1H), 4.69 (m, 1H), 6.30 (m, 1H), 6.60 (d, 1H,  $J = 16$  Hz), 7.15-7.40 (m, 5H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.9, 25.9, 31.0, 62.5, 67.9, 98.1, 126.2, 126.7, 127.8, 128.7, 132.5, 136.9.

**11a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.50-2.0 (brm, 6H), 3.45 (m, 1H), 3.54 (t, 1H,  $J = 8.8$  Hz), 3.83 (m, 1H), 4.05 (t, 1H,  $J = 8.0$  Hz), 4.18 (t, 1H,  $J = 8.0$  Hz), 4.67 (t, 1H,  $J = 3.2$  Hz), 7.26 (d, 2H,  $J = 7.6$  Hz), 7.34 (t, 2H,  $J = 7.2$  Hz), 7.63 (d, 2H,  $J = 7.6$  Hz), 7.72 (d, 2H,  $J = 7.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.0, 24.1, 29.2, 46.4, 60.5, 68.6, 97.4, 118.17, 118.18, 123.6, 123.7, 125.2, 125.2, 125.7, 139.5, 143.0, 143.5.

**12a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) Obtained as a mixture of diastereomers  $\delta$  1.30-1.84 (brm, 12H), 3.49 (m, 2H), 3.75 (m, 3H), 4.06 (m, 1H), 4.29 (m, 1H), 4.62 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) Peaks from both diastereomers  $\delta$  19.6, 19.8, 25.7, 25.8, 25.9, 27.0, 27.1, 30.7, 62.3, 62.5, 67.0, 67.2, 68.2, 68.8, 74.9, 75.1, 99.1, 99.3, 109.4, 109.6; Anal. calcd for  $\text{C}_{11}\text{H}_{20}\text{O}_4$ : C, 61.09; H 9.32. Found C, 61.23, H, 8.43.

**13a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.50-1.86 (m, 6H), 3.54 (m, 1H), 3.90 (m, 1H), 4.42 (d, 1H,  $J = 11.2$  Hz), 4.52 (m, 2H), 4.70 (m, 2H), 5.30 (dd, 2H,  $J = 10.8$  Hz,  $J = 17.2$  Hz), 6.02

(m, 1H), 6.87 (d, 2H,  $J=8.0$  Hz), 7.27 (d, 2H,  $J=8.4$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.8, 25.8, 30.9, 62.4, 68.8, 69.1, 97.7, 114.8, 117.8, 129.6, 130.6, 133.4, 158.2.

**14a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.45-1.90 (brm, 6H), 3.51 (m, 1H), 3.80 (m, 1H), 3.88 (m, 1H), 4.05 (m, 1H), 4.51 (m, 2H), 4.71 (m, 1H), 7.44 (m, 2H), 7.55 (m, 1H), 8.06 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.6, 25.8, 30.8, 62.3, 64.5, 65.5, 99.0, 128.5, 129.8, 130.3, 133.0, 166.6.

**15a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.03 (s, 6H), 0.88 (s, 9H), 1.28-1.90 (m, 14H), 3.37 (m, 1H), 3.48 (m, 1H), 3.59 (t, 2H,  $J=6.8$  Hz), 3.70 (m, 1H), 3.84 (m, 1H), 4.56 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  -4.7, 18.7, 20.0, 25.9, 26.1, 26.3, 26.4, 30.1, 31.1, 33.2, 62.5, 63.5, 67.8, 99.0.

**16a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.40-1.88 (m, 20H), 3.38 (m, 2H), 3.48 (m, 2H), 3.73 (m, 2H), 3.85 (m, 2H), 4.57 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.1, 25.9, 26.5, 30.1, 31.1, 62.6, 67.8, 99.0.

**17a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.22-1.83 (m, 14H), 2.45 (s, 3H), 3.34 (m, 1H), 3.49 (m, 1H), 3.68 (m, 1H), 3.83 (m, 1H), 4.02 (t, 2H,  $J=6.4$  Hz), 4.54 (m, 1H), 7.33 (d, 2H,  $J=8.4$  Hz), 7.77 (d, 2H,  $J=8.4$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.1, 22.0, 25.6, 25.8, 26.0, 29.1, 29.8, 31.1, 62.7, 67.6, 70.8, 99.1, 128.0, 129.9, 133.3, 144.7.

**18a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.40-1.84 (brm, 13H), 3.43 (m, 1H), 3.50 (m, 1H), 3.65 (t, 2H,  $J=6.4$  Hz), 3.75 (m, 1H), 3.84 (m, 1H), 4.57 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.0, 22.8, 25.8, 29.8, 31.1, 32.9, 62.7, 63.1, 67.8, 99.1.

**18b.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.44-1.86 (m, 18H), 3.39 (m, 2H), 3.49 (m, 2H), 3.72 (m, 2H), 3.86 (m, 2H), 4.57 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.1, 23.3, 25.9, 30.0, 31.1, 62.6, 67.8, 99.0.

**16.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.39 (m, 4H), 1.50-1.80 (m, 11H), 3.38 (m, 1H), 3.49 (m, 1H), 3.63 (t, 2H,  $J=6.4$  Hz), 3.74 (m, 1H), 3.85 (m, 1H), 4.57 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.0, 25.8, 25.9, 26.4, 30.0, 31.1, 33.0, 62.6, 62.9, 67.8, 99.0.

**20a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.23 (d, 3H,  $J=6.4$  Hz), 1.40-1.68 (m, 9H), 2.09 (brs, 1H), 3.62 (t, 2H,  $J=6.4$  Hz), 3.73 (m, 2H), 4.07 (m, 1H), 4.53 (t, 1H,  $J=5.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.6, 22.0, 32.6, 33.3, 34.9, 62.4, 66.7, 73.0, 102.0.

**20b.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) Obtained as a mixture of diastereomers  $\delta$  1.23 (d, 3H,  $J=6.4$  Hz), 1.40-1.84 (m, 14H), 3.37 (m, 1H), 3.49 (m, 1H), 3.71 (m, 3H), 3.85 (m, 1H), 4.06 (m, 1H), 4.52 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) Peaks from both diastereomers  $\delta$  19.8, 20.0, 21.1, 21.2, 21.9, 22.1, 25.7, 25.8, 29.8, 29.9, 30.95, 31.09, 33.2, 33.4, 35.1, 35.3, 62.2, 62.5, 66.6, 66.8, 67.4, 67.6, 72.7, 72.9, 98.7, 98.9, 101.8, 102.0. Anal. calcd for  $\text{C}_{14}\text{H}_{26}\text{O}_4$ : C, 65.09; H 10.14. Found C, 65.26, H, 9.87.

**21a.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.48-1.84 (m, 6H), 2.82 (t, 2H,  $J=12$  Hz), 3.48-3.62 (m, 2H), 3.79-3.92 (m, 2H), 4.61 (m, 1H), 6.07 (brs, 1H), 6.73 (d, 2H,  $J=8.4$  Hz), 7.05 (d, 2H,  $J=8.4$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.4, 25.4, 26.4, 30.6, 35.4, 62.2, 68.6, 98.7, 115.1, 130.0, 130.7, 154.3.