The 'Aqueous' Prins Cyclization: A Diastereoselective Synthesis of 4-Hydroxytetrahydropyran Derivatives

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Abstract: Phosphomolybdic acid ($H_3PMo_{12}O_{40}$, a heteropoly acid) is found to catalyze efficiently the Prins cyclization of homoallylic alcohols with aldehydes in water at room temperature to provide tetrahydropyran-4-ol derivatives in high yields with all *cis*-selectivity. Only cyclic ketones can give spirocyclic products. The use of phosphomolybdic acid in water makes this procedure simple, more convenient, cost-effective, and environmentally friendly.

Keywords: Prins cyclization, phosphomolybdic acid, heteropoly acid, homoallyl alcohol, tetrahydropyran-4-ols

The tetrahydropyrans are important building blocks for many biologically active natural products (Figure 1).[1,2] Thus, considerable efforts have been made to develop reliable synthetic procedures for the construction of these heterocycles. The reaction between homoallylic alcohols and aldehydes under strongly acidic conditions, known as the Prins cyclization, is a direct and one of the most widely used methods for the preparation of tetrahydropyran derivatives.[3] A number of methods have been developed using various Brønsted acids and Lewis acids as promoters to accomplish this transformation;[4,5] a few methods have been reported for the preparation of tetrahydropyran-4-ols under various reaction conditions.[6] However, many of these classical methods often involve the use of expensive reagents, high temperatures, extended reaction times, and strongly acidic conditions and they also produce mixtures of products. Furthermore, there have been no examples of the preparation of spirocyclic tetrahydropyran-4-ols from cyclic ketones and homoallylic alcohols via the Prins cyclization. This is due to the intrinsic low reactivity of the ketones compared to aldehydes. Therefore, there is still scope to develop more general and practical methods for this transformation.[7] Recently, much attention has been focused on the use of water as a 'green' solvent in various organic transformations. In addition to its abundance and also for economical and safety reasons, water has naturally become as a substitute and an alternative environmentally benign solvent in organic synthesis.[8] The use of aqueous media as the solvent also reduces the harmful effects of organic solvents on the environment. This becomes more sophisticated if these reactions can be performed using inexpensive and recyclable solid acids. A significant benefit of using water for this transformation is its ability to act as both nucleophile and solvent.

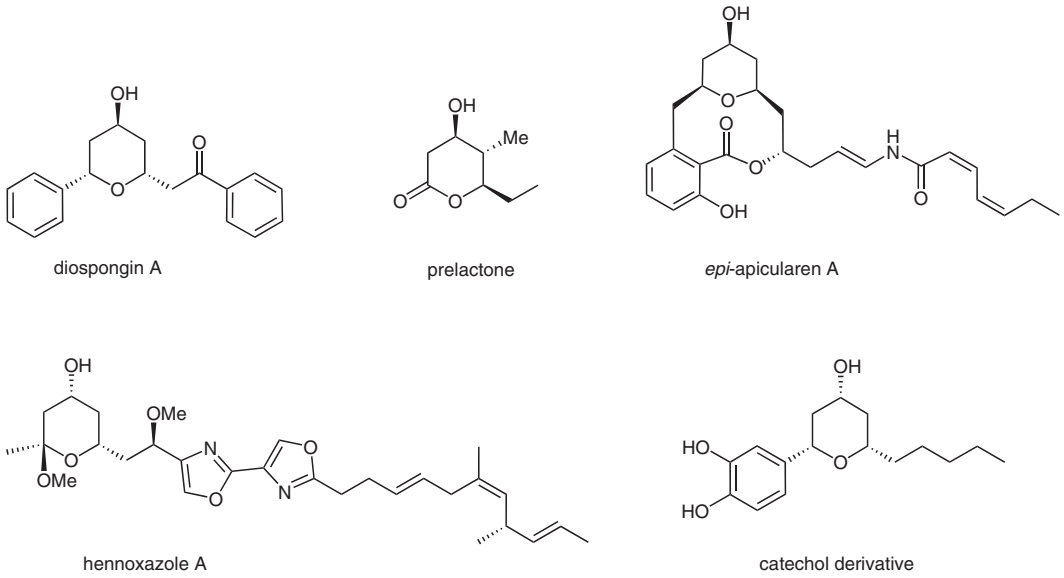

Figure 1

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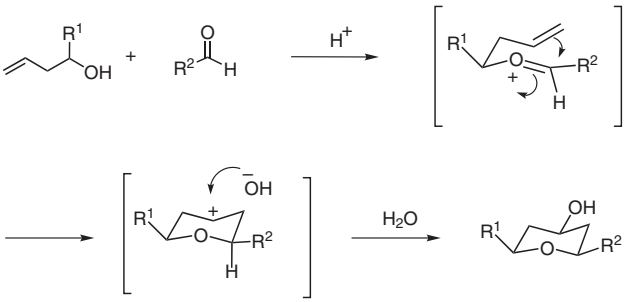
Recently, the use of heteropoly acids (HPAs) as environmentally friendly and economically viable solid acids has continuously increased because of their ease of handling and high catalytic activity and reactivity.[9] These compounds possess unique properties, such as well-defined structures, Brønsted acidity, the possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), the ability to accept and release electrons, high proton mobility, etc. In addition to their abundance, HPAs have naturally become a substitute or alternative solid acids for economical and safety reasons.[10] HPAs are very strong acids, approaching the super acid region, with a Brønsted acidity greatly exceeding that of ordinary mineral acids and solid acid catalysts. This makes it possible to carry out a catalytic process at low concentrations and at lower temperatures.[11] Among various heteropoly acids, phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) is one of the less expensive and commercially available solid acid catalysts.[12,13] However, there have been no reports on the use of phosphomolybdic acid for the synthesis of tetrahydropyran-4-ols via the Prins cyclization.

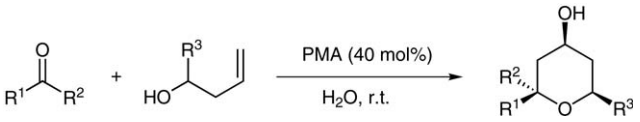
In the ever-increasing quest for exploration of newer reactions in water, we report herein the phosphomolybdic acid catalyzed Prins cyclization of aldehydes or ketones with homoallylic alcohols in water at room temperature producing tetrahydropyran-4-ol derivatives. Accordingly, treatment of benzaldehyde with but-3-en-1-ol in the presence of phosphomolybdic acid (PMA) for eight hours gave 2-phenyltetrahydropyran-4-ol (**1a**) in 92% yield with *cis*-selectivity (Table 1, entry 1).

A single diastereomer was obtained from each reaction, the structure of which was confirmed by ^{1}H NMR and also by comparison with authentic samples.[6] The formation of the products may be realized by assuming a chair-like transition state to give the all-*cis*-configured products (Scheme 1).



Scheme 1

Table 1 Phosphomolybdic Acid Catalyzed Preparation of Tetrahydropyran-4-ol Derivatives[a]



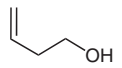
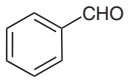
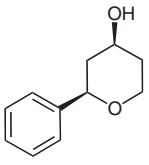
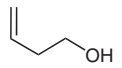
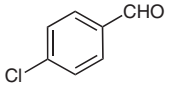
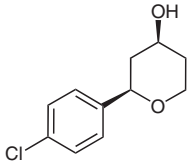
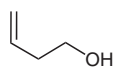
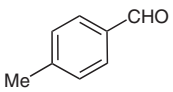
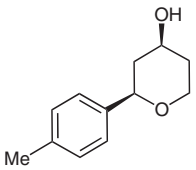
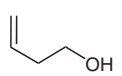
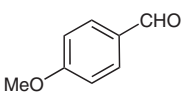
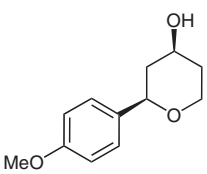
Entry	Alcohol	Carbonyl compound	Product pyran-4-ol[b]		Time (h)	Yield[c] (%)
1				**1a**	8.0	92
2				**1b**	8.5	90
3				**1c**	8.5	89
4				**1d**	9.5	82

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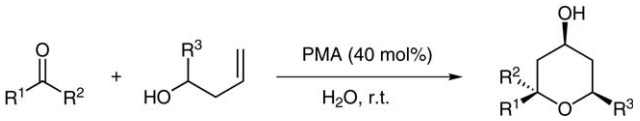
Table 1 Phosphomolybdic Acid Catalyzed Preparation of Tetrahydropyran-4-ol Derivatives[a] (continued)



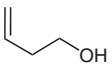
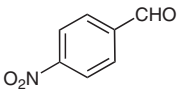
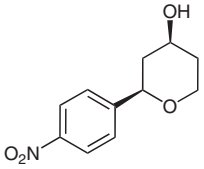
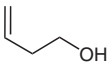
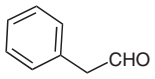
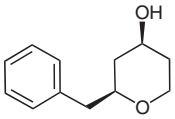
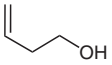
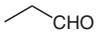
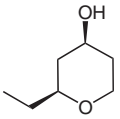
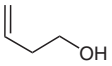
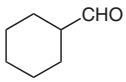
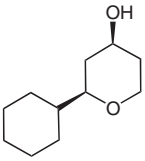
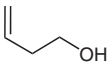
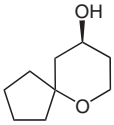
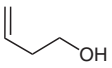
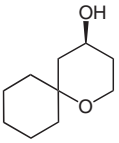
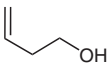
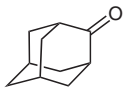
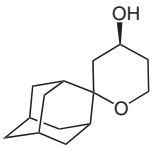
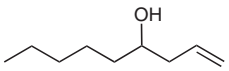
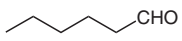
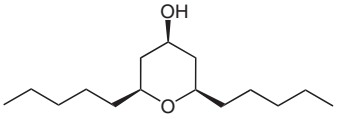
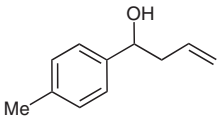
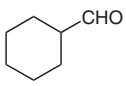
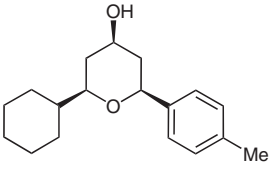
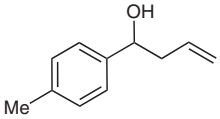
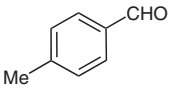
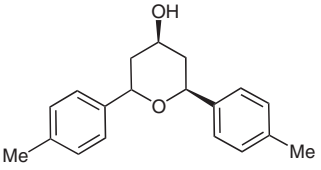
Entry	Alcohol	Carbonyl compound	Product pyran-4-ol[b]		Time (h)	Yield[c] (%)
5				**1e**	9.5	80
6				**1f**	7.5	90
7				**1g**	7.0	92
8				**1h**	7.5	90
9				**1i**	9.0	84
10				**1j**	9.5	88
11				**1k**	9.0	86
12				**1l**	8.0	90
13				**1m**	8.0	84
14				**1n**	8.5	88

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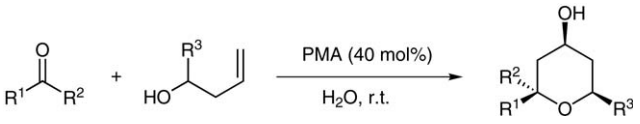
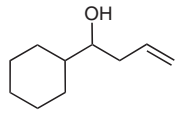
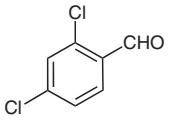
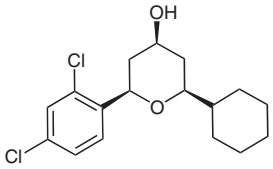
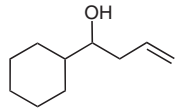
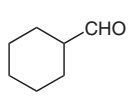
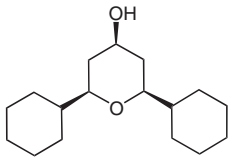
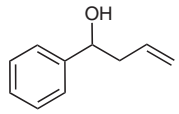
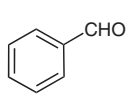
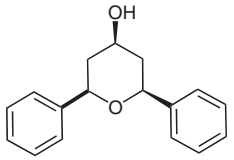
Table 1 Phosphomolybdic Acid Catalyzed Preparation of Tetrahydropyran-4-ol Derivatives[a] (continued)



Entry	Alcohol	Carbonyl compound	Product pyran-4-ol[b]		Time (h)	Yield[c] (%)
15				**1o**	9.0	86
16				**1p**	7.5	90
17				**1q**	8.0	88

[a] Reaction conditions: PMA (40 mol%), H_2O, r.t.
[b] All products were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy, and mass spectrometry.
[c] Yield refers to pure products after chromatography.

A rationale for the *cis*-selectivity could be explained by assuming the formation of an (*E*)-oxocarbenium ion via a chairlike transition state, which has increased stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudoaxial position, which favors equatorial attack of the nucleophile.[14] This result provided the incentive for further study of reactions with various aldehydes. Interestingly, a wide range of aldehydes such as 4-chlorobenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, phenylacetaldehyde, propanal, and cyclohexanecarbaldehyde reacted well with but-3-en-1-ol to produce the corresponding tetrahydropyranols **1b–h** in high yields (Table 1, entries 2–8). This reaction was also successful with cyclic ketones such as cyclopentanone, cyclohexanone, and adamantan-2-one to give spirocyclic tetrahydropyran-4-ols **1i–k** comparably in good yields (Table 1, entries 9–11).

In addition, substituted homoallylic alcohols like non-1-en-4-ol, 1-(4-methylphenyl)but-3-en-1-ol, 1-cyclohexylbut-3-en-1-ol, and 1-phenylbut-3-en-1-ol also participated well in this transformation to give **1l–q** (Table 1, entries 12–17) under similar conditions.

In the absence of phosphomolybdic acid, no reaction was observed between the aldehyde and homoallylic alcohol even under reflux conditions with a long reaction time (12 h). In all cases, the reactions proceeded readily at room temperature under mild conditions and the products were obtained in excellent yields and with high diastereoselectivity as determined from the NMR spectrum of the crude product. No intrusion of HPA anion was observed in the Prins cyclization because the nucleophilicity of ^-OH is higher than that of the HPA anion ($PMo_{12}O_{40}^{3-}$). The nature of the substituents on the aromatic ring shows some effect on this conversion. It should be noted that aliphatic, simple aromatic, and moderately activated aldehydes such as methyl-, chloro- or bromo-substituted benzaldehydes gave higher yields of products compared to strongly activated or deactivated aldehydes. The scope of this process is illustrated with respect to various aldehydes and ketones and homoallylic alcohols and the results are presented in Table 1.

In summary, the combination of phosphomolybdic acid with water has been shown to be a useful and novel catalytic medium to accomplish the Prins cyclization under mild conditions. The use of phosphomolybdic acid in water makes this process convenient, cost-effective, and environmentally benign. This method provides an easy access to tetrahydropyran-4-ols with diverse chemical structures.

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. TLC was monitored on 0.25 mm pre-coated silica gel plates (60F-254).

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Tetrahydropyran-4-ols 1; General Procedure

A mixture of homoallylic alcohol (1 mmol), aldehyde (1 mmol), and phosphomolybdic acid (0.4 mmol) in H_2O (5 mL) was stirred at 23 °C for the specified time (Table 1). When the reaction was complete (TLC), the mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried (anhyd Na_2SO_4). Removal of the solvent followed by purification on silica gel (Merck, 60–120 mesh, EtOAc–hexane, 2:8) gave the pure tetrahydropyran-4-ol. The products thus obtained were characterized by IR, NMR, and mass spectroscopy. The products **1a–c**,**e**,**n**,**q** are known and the spectral data were found to be consistent with authentic samples.[6]

2-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-ol (1d)

Light yellow liquid.

IR (KBr): 3387, 2923, 2851, 1595, 1493, 1365, 1250, 1139, 1083, 1014, 987, 825 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.35–1.65 (m, 2 H), 1.94 (m, 1 H), 2.10 (m, 1 H), 3.52 (m, 1 H), 3.78 (s, 3 H), 3.87 (m, 1 H), 4.13 (dd, *J* = 4.5, 12.0 Hz, 1 H), 4.21 (d, *J* = 11.2 Hz, 1 H), 6.77–6.83 (m, 2 H), 7.17–7.26 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4, 133.2, 128.5, 127.2, 77.6, 68.2, 66.3, 43.2, 35.3, 29.7.

LC-MS: *m*/*z* = 231 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{12}H_{16}NaO_3$: 231.0997; found: 231.0992.

2-Benzyltetrahydro-2*H*-pyran-4-ol (1f)

Colorless liquid.

IR (KBr): 3445, 2923, 2854, 1458, 1084, 770 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.34–1.64 (m, 2 H), 1.72–1.88 (m, 2 H), 2.77 (m, 1 H), 3.17–3.39 (m, 2 H), 3.64 (m, 1 H), 3.93–4.13 (m, 2 H), 7.06–7.30 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 129.4, 128.3, 126.3, 77.1, 67.9, 66.0, 42.6, 40.8, 35.4.

LC-MS: *m*/*z* = 215 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{12}H_{16}NaO_2$: 215.1047; found: 215.1049.

2-Ethyltetrahydro-2*H*-pyran-4-ol (1g)

Colorless liquid.

IR (KBr): 3388, 2938, 2848, 1458, 1372, 1251, 1147, 1083, 1045, 980, 874 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H), 1.02–1.96 (m, 7 H), 3.13 (m, 1 H), 3.33 (dt, *J* = 1.6, 11.6 Hz, 1 H), 3.71 (m, 1 H), 3.97 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.5, 67.6, 65.6, 40.7, 35.4, 28.7, 9.5.

LC-MS: *m*/*z* = 153 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_7H_{14}NaO_2$: 153.0891; found: 153.0899.

2-Cyclohexyltetrahydro-2*H*-pyran-4-ol (1h)

Colorless liquid.

IR (KBr): 3310, 2927, 2851, 1148, 1320, 1040, 996 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.76–1.45 (m, 10 H), 1.53–1.87 (m, 5 H), 2.22 (br s, OH), 2.88 (m, 1 H), 3.23 (m, 1 H), 3.61 (m, 1 H), 3.90 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 73.6, 64.4, 58.8, 44.7, 39.5, 35.7, 31.0, 25.8, 21.2.

LC-MS: *m*/*z* = 207 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{11}H_{20}NaO_2$: 207.1360; found: 207.1366.

6-Oxaspiro[4.5]decan-9-ol (1i)

Colorless liquid.

IR (KBr): 3390, 2955, 2850, 1463, 1369, 1251, 1152, 1084, 1052, 1000, 876, 724 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.26–2.03 (m, 12 H), 3.53 (dt, *J* = 3.0, 12.0 Hz, 1 H), 3.75 (m, 1 H), 3.84 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.9, 68.1, 62.4, 46.6, 41.6, 33.1, 23.1.

LC-MS: *m*/*z* = 179 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_9H_{16}NaO_2$: 179.1047; found: 179.1056.

1-Oxaspiro[5.5]undecan-4-ol (1j)

Colorless liquid.

IR (KBr): 3386, 2932, 2856, 1447, 1366, 1073, 970, 728 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.19–1.91 (m, 14 H), 3.50 (dt, *J* = 2.3, 11.7 Hz, 1 H), 3.71–3.90 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.5, 66.9, 61.6, 46.4, 40.6, 32.8, 23.4, 21.0.

LC-MS: *m*/*z* = 193 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{10}H_{18}NaO_2$: 193.1204; found: 193.1210.

Spiro[adamantane-2,2′-tetrahydropyran]-4′-ol (1k)

Colorless solid; mp 116–118 °C.

IR (KBr): 3304, 2922, 2853, 1447, 1358, 1246, 1173, 1081, 1036, 955, 720 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.02–1.50 (m, 4 H), 1.62–1.94 (m, 10 H), 1.97–2.14 (m, 2 H), 2.27 (m, 1 H), 2.46 (m, 1 H), 3.56 (dt, *J* = 3.0, 12.0 Hz, 1 H), 3.76 (m, 1 H), 3.87 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.6, 64.8, 58.0, 41.4, 39.5, 38.2, 35.9, 34.1, 33.8, 32.7, 31.7, 30.3, 29.7, 27.7, 27.4.

LC-MS: *m*/*z* = 245 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{14}H_{22}NaO_2$: 245.1517; found: 245.1527.

2,6-Dipentyltetrahydro-2*H*-pyran-4-ol (1l)

Colorless solid; mp 42–44 °C.

IR (KBr): 3409, 2921, 2852, 1512, 1450, 1357, 1152, 1080, 1037, 988, 803 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.80–1.17 (m, 7 H), 1.22–1.66 (m, 15 H), 1.75–1.99 (m, 4 H), 3.19 (m, 2 H), 3.70 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.5, 68.4, 41.4, 36.0, 31.7, 25.3, 22.6, 14.0.

LC-MS: *m*/*z* = 265 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{15}H_{30}NaO_2$: 265.2143; found: 265.2150.

2-Cyclohexyl-6-(4-methylphenyl)tetrahydro-2*H*-pyran-4-ol (1m)

Light brown solid; mp 141–143 °C.

IR (KBr): 3411, 2922, 2853, 1703, 1514, 1449, 1359, 1268, 1152, 1080, 1037, 988, 888, 802 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.96–1.82 (m, 11 H), 1.87–2.00 (m, 3 H), 2.13 (m, 1 H), 2.33 (s, 3 H), 3.19 (m, 1 H), 3.87 (m, 1 H), 4.24 (dd, *J* = 1.5, 11.3 Hz, 1 H), 7.05–7.21 (m, 4 H).

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^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5, 136.9, 128.9, 125.7, 80.1, 77.0, 69.1, 43.1, 42.7, 37.7, 29.1, 28.7, 26.6, 26.2, 21.1.

LC-MS: *m*/*z* = 297 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{18}H_{26}NaO_2$: 297.1830; found: 297.1839.

2-Cyclohexyl-6-(2,4-dichlorophenyl)tetrahydro-2*H*-pyran-4-ol (1o)

Pale yellow solid; mp 103–105 °C.

IR (KBr): 3344, 2925, 2852, 1472, 1448, 1364, 1073, 1047, 900, 865, 821 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92–1.72 (m, 11 H), 1.87–2.20 (m, 3 H), 2.27 (m, 1 H), 3.26 (m, 1 H), 3.91 (m, 1 H), 4.56 (dd, *J* = 1.8, 11.1 Hz, 1 H), 7.25 (d, *J* = 2.0 Hz, 1 H), 7.31 (d, *J* = 2.0 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5, 136.9, 128.9, 125.7, 80.1, 77.0, 69.1, 43.1, 42.7, 37.7, 29.1, 28.7, 26.6, 26.2, 21.1.

LC-MS: *m*/*z* = 352 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{17}H_{22}Cl_2NaO_2$: 351.0894; found: 351.0906.

2,6-Dicyclohexyltetrahydro-2*H*-pyran-4-ol (1p)

Colorless solid; mp 111–113 °C.

IR (KBr): 3275, 2927, 2851, 1448, 1364, 1320, 1270, 1123, 1071, 1040, 996, 895, 859 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.70–2.12 (m, 27 H), 2.79–3.02 (m, 2 H), 3.69 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 79.8, 69.2, 42.8, 38.5, 29.3, 28.9, 26.6, 26.2.

LC-MS: *m*/*z* = 289 (M + Na).

HRMS: *m*/*z* [M + Na] calcd for $C_{17}H_{30}NaO_2$: 289.2143; found: 289.2146.

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