Synthesis of *cis*-2,6-tetrahydropyran-4-one via diastereoselectively intramolecular cyclization of β-hydroxy allyl ketone

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A B S T R A C T

A series of *cis*-2,6-tetrahydropyran-4-ones was synthesized from the intramolecular cyclization reaction of β-hydroxy allyl ketones in the presence of Me₃SiOTf as catalyst. The β-hydroxy allyl ketone was prepared from allylation reaction with β-hydroxynitrile without protection of hydroxy functionality under the Barbier-type reaction condition.
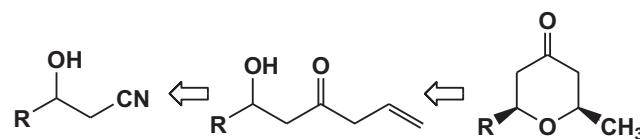
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1. Introduction

Tetrahydropyrans bearing substituents at the 2- and/or 6-positions on the ring are often observed in a large number of biologically important natural products, which exhibit interesting biological properties such as phorboxazole,[1] zampanolide,[2] lasonolide,[3] ratjadone,[4] leucascandrolide,[5] swinholides,[6] misakinolides,[7] sorangicin A,[8] scytophycins,[9] and laulimalide.[10] Tetrahydropyran-4-ones usually employed as important synthetic intermediates for natural product synthesis. Over the years much effort has been directed toward the development of new strategies for their synthesis.[11–17] Continuing interest in the development of synthetic methodology of tetrahydropyranone synthesis provided the impetus to initiate a project designed to develop a new and more expedient route to the formation of tetrahydropyranone rings. Our group reported a Barbier-type reaction of allyl bromide with nitrile could generate allyl ketone at room temperature[18] and an intramolecular cyclization of homoallyl alcohol to tetrahydrofuran was afforded in the presence of L-proline as a promoter.[19] Our attention was attracted to the formation of β-hydroxy allyl ketone, which may be achieved by reaction of β-hydroxynitrile with allyl bromide under the Barbier-type reaction condition and then this β-hydroxy allyl ketone undergo intramolecular cyclization (6-*endo-trig*)[20] would generate the desired tetrahydropyran-4-one (Scheme 1).[21,22]
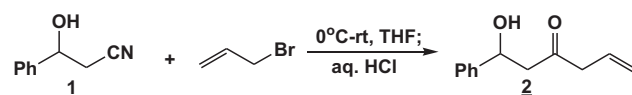
2. Results and discussion

3-Hydroxy-3-phenylpropanenitrile **1** was initially chosen as the investigating substrate. Treatment of **1** with allyl bromide in the presence of a Lewis acid AlCl₃ should generate β-hydroxy allyl ketone product **2**. To a reaction mixture of 3-hydroxy-3-phenylpropanenitrile **1** (1.0 equiv), zinc powder (4.0 equiv), and allyl bromide (2.0 equiv) in anhydrous THF was added AlCl₃ (0.6 equiv) at 0 °C and stirred at room temperature for 2 h and the expected product **2** (42%) was obtained with 35% recovery of starting material (Scheme 2). An exothermic phenomenon was observed when AlCl₃ was introduced to the reaction mixture. It should be noted that the slow addition of AlCl₃ decreased the formation yield of product **2**. We also observed that increment of allyl bromide to 2.5 equiv did improve the product yield. Thus, we rearranged the introducing amount of allyl bromide in consequent steps, 0.5 equiv of allyl bromide was added to the reaction mixture after 1 h stirring at room temperature, and the yield of **2** was dramatically increased to 80%. The less acidic quenching process

Scheme 1.

Scheme 2. Optimization of allylation to nitrile.

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also improved the yield of product **2**. It is interesting to note that protection of hydroxy group was not necessary under this Barbier-type reaction condition.

To understand the scope of this new reaction, various β-hydroxynitriles were studied as the substrates for prepration of β-hydroxy allyl ketones and the results are shown in Table 1.

Table 1
Synthesis of β-hydroxy allyl ketones

Entry	R	Yield
1		57%
2		59%
3		84%
4		67%
5		56%
6		67%
7		72%
8		72%
9		51%

As shown in Table 1, reactions using aliphatic β-hydroxynitriles (entries 1 and 2), electron-poor (entries 4–6) or electron-rich (entry 7) benzanitriles, or heteroaromatic nitriles (entries 8 and 9) gave the desired β-hydroxy allyl ketones in reasonable to good yields. Aliphatic β-hydroxynitrile (entry 2) having another β-hydrogen next to hydroxyl functionality also proceeded clean reaction under standard reaction condition.

β-Hydroxy allyl ketones were successfully prepared by the Barbier-type reaction conditions. Therefore, the intramolecular cyclizations of β-hydroxy allyl ketones for generating the desired tetrahydropyran-4-one were further investigated. 1-Hydroxy-1-phenylhex-5-en-3-one (Table 1, entry 3) was chosen as the investigating substrate for intramolecular cyclization reaction (6-*endo-trig*). Treatment of 1-hydroxy-1-phenylhex-5-en-3-one with Lewis acid BF$_3$·OEt$_2$ in THF and the mixture was stirred at room temperature for 24 h generated the expected tetrahydropyran-4-one product in 48% yield with diastereoselectivity (*cis/trans*=71/29). Other Lewis acids also were investigated and Me$_3$SiOTf was observed as the best choice of catalyst for this intramolecular cyclization reaction (Scheme 3). A reaction mixture of 1-hydroxy-1-phenylhex-5-en-3-one (1.0 mmol) and Me$_3$SiOTf (0.1 mmol) in THF (20 mL) was stirred at room temperature for 18 h and the expected 2,6-disubstituted tetrahydropyran-4-one was obtained as the only cis-stereoisomer and the dehydration product also was obtained with 13% yield. Increasing the amount of Me$_3$SiOTf did not improved the yield of tetrahydropyran-4-one but the slightly increased the yield of dehydration product.

Reaction condition	Yield (*cis* / *trans*)		
* 0.5 BF$_3$·OEt$_2$, THF, rt, 120h	Low yield		
* 1.0 BF$_3$·OEt$_2$, THF, rt., 24h	48% (71 / 29)		
* 0.1 ZnCl$_2$, THF, rt., 33h	NR (SM)		
* 0.1 SnCl$_2$, THF, rt., 58h	NR (SM)		
* 0.1 MgBr$_2$, THF, rt., 58h	NR (SM)		
* 0.1 BCl$_3$, THF, rt., 42h	Complicate		
* 0.1 BBr$_3$, THF, rt., 11h	Complicate		
* 0.1 Me$_3$SiOTf, THF, rt., 18h	53% (100/ 0)	+	13%
* 0.2 Me$_3$SiOTf, THF, rt., 18h	53% (100/ 0)	+	21%
* 0.5 Me$_3$SiOTf, THF, rt., 18h	43% (100/ 0)	+	17%

Scheme 3.

Intramolecular cyclization reaction, in general, was reacted at low concentration circumstance. In order to decreasing the using amount of solvent, we investigated the higher reaction concentration for this intramolecular cyclization reaction and the results are shown in Scheme 4. The experimental results showed that 2.5% introducing amount of Me$_3$SiOTf to reacting substance 1-hydroxy-1-phenylhex-5-en-3-one afforded the nearly yield of tetrahydropyran-4-one at higher reaction concentration (0.1 M).

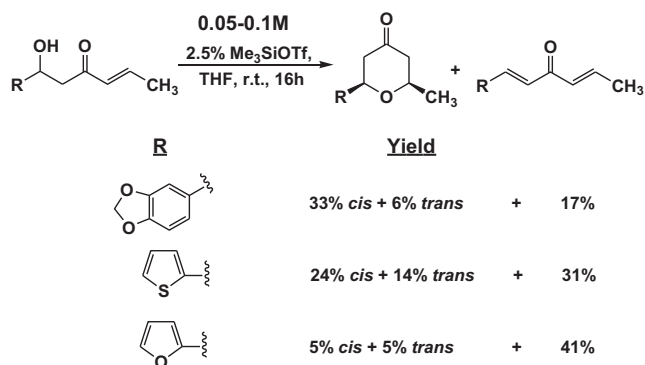|	Reaction condition	Yield (*cis* only)	+	Dehydration product
0.02M	* 0.1 Me$_3$SiOTf, THF, rt., 18h	51%	+	16%
0.05M	* 0.1 Me$_3$SiOTf, THF, rt., 18h	53%	+	13%
0.05M	* 0.05 Me$_3$SiOTf, THF, rt., 18h	48%	+	8%
0.1M	* 0.05 Me$_3$SiOTf, THF, rt., 18h	51%	+	18%
0.1M	* 0.025 Me$_3$SiOTf, THF, rt., 18h	52%	+	16%

Scheme 4.

A series of β-hydroxy allyl ketones was investigated under this Me$_3$SiOTf-catalyzed intramolecular cyclization and the results are shown in Table 2.

As shown in Table 2, reactions using aliphatic allyl ketones (entries 1 and 2) and electron-poor (entries 4–6) aromatic allyl ketones gave the desired cyclization products in reasonable to moderate yields. The product yield of using electron-rich (entry 7) aromatic allyl ketone was obtained much lower than those of using electron-poor aromatic allyl ketones. Only the dehydrated with isomerized product was obtained for heteroaromatic allyl ketones (entries 8 and 9) under the reaction condition. We propose the dehydration process may be faster than isomerization process that causes the unsuccessfully intramolecular cyclization process. Thus, we prepared the isomerized β-hydroxy-α,β-unsaturated ketone and then investigated this compound under the reaction condition.[23] The expected heteroaromatic substituted tetrahydropyran-4-ones were obtained under the reaction condition (Scheme 5).

The reaction mechanism was proposed that β-hydroxy allyl ketone, which is firstly isomerized in situ to β-hydroxy-α,β-unsaturated ketone and then followed by the intramolecular Michael addition reaction to its corresponding tetrahydropyran-4-one. The

Table 2
Intramolecular cyclization reactions of β-hydroxy allyl ketones

Entry	R	Time (h)	Yield		
1	(pentenyl)	14	33%		
2	(cyclohexyl)	18	61%		
3	(phenyl)	16	52%	+	16%
4	(4-F-phenyl)	23	48%	+	9%
5	(4-Br-phenyl)	20	48%	+	12%
6	(Br-phenyl)	22	58%	+	12%
7	(methylenedioxyphenyl)	14	6%		
8	(thienyl)	23	Only 1,4-Dienyl-3-ketone		
9	(furyl)	21	Only 1,4-Dieny1-3-ketone		

Scheme 5.

Fig. 1. Proposed transition state of diastereoselectively intramolecular cyclization.

80% yield. Tetrahydro-3,6-dimethyl-2-phenylpyran-4-one **4a** and **4b** was not separated and theirs diastereomeric ratio was determined by comparison of ^{1}H NMR spectral analysis (**4a**:**4b**=81:19) of the authentic compounds.[24] It is interesting to note that α-methyl allyl ketone **5** was cyclized to 2-substituted tetrahydro-5,6-dimethylpyran-4-one with single stereoisomer and all-cis-2,5,6-diastereomer was observed.

Scheme 6.

The spiro-compound also may be generated by intramolecular cyclization of tertiary-hydroxy allyl ketone, which was prepared from allylation reaction of β-hydroxynitrile with ketone. Thus, compound **7** was synthesized and investigated under the intramolecular cyclization reaction condition and spiro-tetrahydropyran-4-one **8** was afforded with 60% yield (Scheme 7).

Scheme 7.

3. Conclusion

In conclusion, the β-hydroxy allyl ketone was prepared from allylation reaction of β-hydroxynitrile without protection of hydroxy functionality under the Barbier-type reaction condition. The cis-2,6-tetrahydropyran-4-one was synthesized from the intramolecular cyclization reaction of β-hydroxy allyl ketones in the presence of Me₃SiOTf as catalyst. The polysubstituted tetrahydropyran-4-one and spiro-compound also may be generated by this intramolecular cyclization reaction.

4. Experimental

4.1. General

All reagents were purchased from Aldrich and Riedel-deHaen and all were used directly without further purification. The [1]H

diastereoselectivity may be explained by the cyclization of β-hydroxy-α,β-unsaturated ketone to the corresponding tetrahydropyran-4-one via a chair-like transition state (Fig. 1). The possible stereochemical outcomes for the generation of cis-2,6-disubstituted tetrahydropyran-4-one by intramolecular cyclization of β-hydroxy-α,β-unsaturated ketone are proposed and explained for a thermodynamically control reaction whereas the bulky substituents (R and CH₃) occupy the equatorial positions to avoid the 1,3-diaxial repulsive interaction.[24]

In order to expand the scope of this intramolecular cyclization reaction, α-substituted allyl ketones were synthesized and investigated for synthesis of polysubstituted tetrahydropyran-4-one[16] (Scheme 6). 1-Hydroxy-2-methyl-1-phenylhex-5-en-3-one **3** was synthesized (anti/syn ratio was not determined) and it was cyclized under the reaction condition and a mixture of tetrahydro-3,6-dimethyl-2-phenylpyran-4-one **4a** and **4b** was obtained with
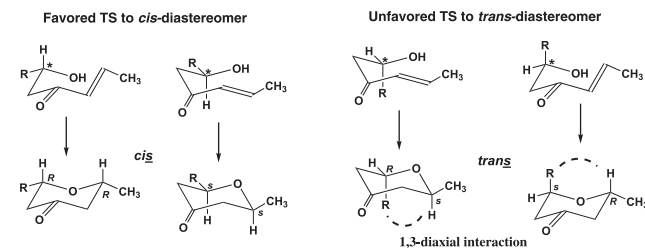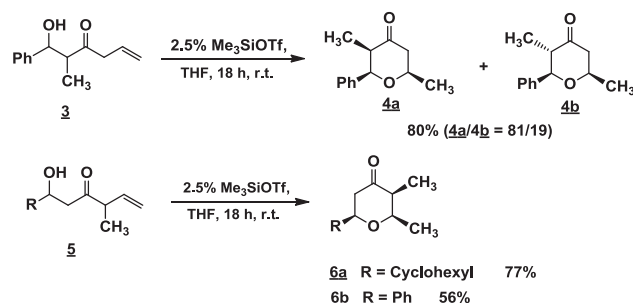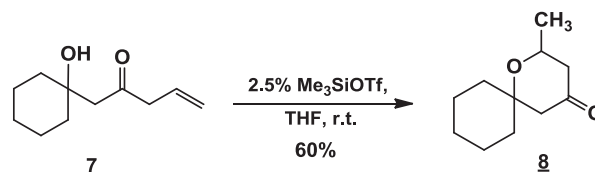
NMR (proton nuclear magnetic resonance) spectra were recorded at 300 MHz (Bruker-AC300P) with deuteriochloroform (CDCl$_3$, Aldrich 99.8 atom% D) as the solvent and the internal standard. The ^{13}C NMR (carbon nuclear magnetic resonance) spectra were recorded at 75.5 MHz (Bruker-AC300P) with CDCl$_3$ as the solvent and the internal standard. Chemical shifts are reported in parts per million and resonance patterns are reported with the notations of either s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constant (J) are reported in hertz (Hz).

4.2. General procedure for synthesis of β-hydroxy allyl ketone from β-hydroxynitrile

Aluminum trichloride (0.6 mmol) was added at once to a solution of zinc powder (4.0 mmol), β-hydroxynitrile (1.0 mmol), and allylic bromide (1.5 mmol) in anhydrous THF (5 mL) at 0 °C (ice-water bath).[20] The reaction mixture was warmed to room temperature and then stirred at room temperature for an hour. Another 0.5 mmol of allylic bromide was added to the reaction mixture and stirred at room temperature for an hour. After the reaction was completed (monitored by TLC), aqueous HCl (2 M, 5 mL) was added to the reaction mixture and stirred at room temperature for 5 min. The reaction mixture was passed through a short silica gel column and the organic solvent was removed directly under reduced pressure. Further purification is achieved on a flash chromatograph with silica gel and ethyl acetate/hexane as eluant.

4.3. General procedure for synthesis of cis-2,6-disubstituted tetrahydropyran-4-one from β-hydroxy allyl ketone

Trimethylsilyl triflate (0.025 mmol) was added to a solution of β-hydroxy allyl ketone (1.0 mmol) in anhydrous THF (10 mL) at room temperature and the reaction mixture was stirred at room temperature for an appropriate time. After the reaction was completed (monitored by TLC), H$_2$O (2 M, 10 mL) ant extracted with ether (2×20 mL). The combined organic layer was washed with Brine (10 mL), and then dried with MgSO$_4$. The organic solvent was removed directly under reduced pressure and further purification is achieved on a flash chromatograph with silica gel and ethyl acetate/hexane as eluant.

4.3.1. (E)-6-Hydroxyundeca-1,7-dien-4-one (Table 1, entry 1). ^{1}H NMR: δ 0.89 (t, J=7.4 Hz, 3H), 1.32–1.42 (m, 2H), 1.90–2.03 (m, 2H), 2.38 (s, −OH, 1H), 2.66 (d, J=6.5 Hz, 2H), 3.20 (d, J=7.0 Hz, 2H), 4.52 (m, 1H), 5.12–5.22 (m, 2H), 5.46 (m, 1H), 5.69 (m, 1H), 5.90 (m, 1H); ^{13}C NMR: δ 13.6, 22.2, 34.2, 48.5, 48.9, 68.6, 119.3, 129.9, 130.8, 132.3, 208.9; HRMS m/z 182.1302 (calcd for C$_{11}$H$_{18}$O$_2$, 182.1307); MS m/z 109 (58), 124 (50), 136 (97), 154 (base).

4.3.2. 1-Cyclohexyl-1-hydroxyhex-5-en-3-one (Table 2, entry 2). ^{1}H NMR: δ 0.70–1.11 (m, 6H), 1.44–1.58 (m, 4H), 2.39 (d, J=6.7 Hz, 2H), 3.04 (dd, J=1.3, 7.1 Hz, 2H), 3.18 (s, OH, 1H), 3.61 (t, J=6.7 Hz, 1H), 4.96 (m, 1H), 5.78–5.69 (m, 2H); ^{13}C NMR: δ 25.7, 26.0, 27.7, 28.4, 31.1, 42.8, 45.7, 48.0, 71.2, 118.3, 130.0, 209.2; HRMS m/z 197.1542 (calcd for C$_{12}$H$_{21}$O$_2$, 197.1539 [M+H]$^+$); MS m/z 136 (57), 137 (62), 154 (base), 179 (93), 195 (22).

4.3.3. 1-Hydroxy-1-phenylhex-5-en-3-one (Table 1, entry 2 and 3). ^{1}H NMR: δ 2.73–2.92 (m, 2H), 3.17 (d, J=6.9 Hz, 2H), 5.09–5.20 (m, 3H), 5.87 (m, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR: δ 48.2, 50.6, 69.6, 119.1, 125.5, 127.4, 128.3, 129.7, 142.8, 208.5; HRMS m/z 190.0998 (calcd for C$_{12}$H$_{14}$O$_2$, 190.0994); MS m/z 105 (81), 107 (base), 120 (25), 149 (26), 162 (12).

4.3.4. 1-(4-Fluorophenyl)-1-hydroxyhex-5-en-3-one (Table 1, entry 4). ^{1}H NMR: δ 2.73–2.90 (m, 2H), 3.18 (d, J=6.4 Hz, 2H), 3.41 (s, −OH, 1H), 5.10–5.21 (m, 3H), 5.92 (m, 1H), 6.98–7.04 (m, 2H), 7.26–7.32 (m, 2H); ^{13}C NMR: δ 48.3, 50.6, 69.1, 115.1, 115.4, 119.4, 127.2, 127.3, 129.7, 138.5, 138.6, 208.7; HRMS m/z 208.0897 (calcd for C$_{12}$H$_{13}$FO$_2$, 208.0900); MS m/z 123 (33), 125 (base), 149 (5), 167 (28).

4.3.5. 1-(4-Bromophenyl)-1-hydroxyhex-5-en-3-one (Table 1, entry 5). ^{1}H NMR: δ 2.82–2.84 (m, 2H), 3.20 (d, J=7.1 Hz, 2H), 5.12–5.24 (m, 3H), 5.75 (m, 1H), 7.24 (dd, J=1.7, 6.7 Hz, 2H), 7.48 (dd, J=1.9, 6.6 Hz, 2H); ^{13}C NMR: δ 48.1, 50.4, 68.9, 119.3, 121.1, 127.2, 129.5, 131.3, 141.8, 208.3; HRMS m/z 268.0099 (calcd for C$_{12}$H$_{13}$BrO$_2$, 268.0099); MS m/z 157 (13), 185 (base), 187 (83), 227 (23), 229 (21).

4.3.6. 1-(3-Bromophenyl)-1-hydroxyhex-5-en-3-one (Table 1, entry 6). ^{1}H NMR: δ 2.76–2.85 (m, H$_2$, 2H), 3.20 (d, J=6.9 Hz, 2H), 5.11–5.24 (m, 3H), 5.90 (m, 1H), 7.18–7.28 (m, 2H), 7.41 (d, J=7.5 Hz, 1H), 7.54 (d, J=6.8 Hz, 1H); ^{13}C NMR: δ 48.1, 50.4, 68.8, 119.3, 122.4, 124.1, 128.6, 129.5, 129.6, 130.4, 145.1, 208.3; HRMS m/z 268.0103 (calcd for C$_{12}$H$_{13}$BrO$_2$, 268.0099); MS m/z 155 (10), 157 (21), 183 (48), 185 (base), 225 (7), 227 (20), 251 (12), 253 (11), 270 (15).

4.3.7. 1-(Benzo[d][1,3]dioxol-6-yl)-1-hydroxyhex-5-en-3-one (Table 1, entry 7). ^{1}H NMR: δ 2.80–2.85 (m, 2H), 3.20 (dd, J=1.2, 7.3 Hz, 2H), 5.12–5.18 (m, 3H), 5.89–5.94 (m, 2H), 6.75–6.80 (m, 2H), 6.87 (d, J=1.1 Hz, 1H); ^{13}C NMR: δ 48.2, 50.7, 69.5, 100.9, 106.2, 108.0, 118.9, 119.2, 129.8, 136.9, 146.8, 147.6, 208.6; HRMS m/z 234.0889 (calcd for C$_{13}$H$_{14}$O$_4$, 234.0892); MS m/z 121 (16), 149 (base), 150 (50), 151 (85), 175 (8), 193 (80), 216 (5).

4.3.8. 1-Hydroxy-1-(thiophen-2-yl)hex-5-en-3-one (Table 1, entry 8). ^{1}H NMR: δ 2.91–3.08 (m, 2H), 3.22 (d, J=6.8 Hz, 2H), 5.14–5.24 (m, 2H), 5.41 (m, 1H), 5.91 (m, 1H), 6.94–6.97 (m, 2H), 7.24 (d, J=3.3 Hz, 1H); ^{13}C NMR: δ 48.0, 50.4, 66.0, 119.1, 123.3, 124.4, 126.4, 129.7, 144.6, 207.9; HRMS m/z 196.0560 (calcd for C$_{10}$H$_{12}$O$_2$S, 196.0558); MS m/z 112 (33), 113 (55), 126 (base), 137 (8), 163 (10), 168 (12).

4.3.9. 1-(Furan-2-yl)-1-hydroxyhex-5-en-3-one (Table 1, entry 9). ^{1}H NMR: δ 2.87–3.13 (m, 2H), 3.23 (d, J=7.2 Hz, 2H), 5.13–5.24 (m, 3H), 5.91 (m, 1H), 6.26 (d, J=3.4 Hz, 1H), 6.33 (m, 1H), 7.36 (d, J=2.1 Hz, 1H); ^{13}C NMR: δ 46.8, 48.1, 63.3, 106.0, 110.1, 119.2, 129.6, 141.8, 154.9, 207.9; HRMS m/z 180.0786 (calcd for C$_{10}$H$_{12}$O$_3$, 180.0786); MS m/z 110 (base), 111 (16), 137 (10), 139 (42), 155 (10).

4.3.10. Tetrahydro-2-methyl-6-(pent-1-enyl)pyran-4-one (Table 2, entry 1). ^{1}H NMR: δ 0.87 (t, J=7.4 Hz, 3H), 1.32 (d, J=6.1 Hz, 3H), 1.35–1.42 (m, 2H), 1.97–2.04 (m, 2H), 2.17–2.36 (m, 4H), 3.75 (m, 1H), 4.03 (m, 1H), 5.51 (m, 1H), 5.70 (m, 1H); ^{13}C NMR: δ 13.9, 22.0, 22.1, 34.2, 47.6, 49.2, 73.0, 77.5, 129.2, 133.5, 206.9; HRMS m/z 182.1311 (calcd for C$_{11}$H$_{18}$O$_2$, 182.1307); MS m/z 110 (7), 111 (18), 126 (91), 139 (base), 180 (30), 181 (58); IR: (neat) 2961 (w), 2932 (w), 2872 (w) 2361 (w), 1721 (C=O, s), 1050 (m), 967 (m).

4.3.11. 2-Cyclohexyl-tetrahydro-6-methylpyran-4-one (Table 2, entry 2). ^{1}H NMR: δ 0.95–1.15 (m, 2H), 1.19–1.27 (m, 3H), 1.30 (d, J=6.1 Hz, 3H), 1.50 (m, 1H), 1.64–1.77 (m, 4H), 1.96 (m, 1H), 2.20–2.26 (m, 2H), 2.32–2.39 (m, 2H), 3.30 (m, 1H), 3.70 (m, 1H); ^{13}C NMR: δ 22.0, 25.9, 26.0, 26.4, 28.2, 28.9, 43.1, 44.9, 49.6, 73.2, 81.2, 208.3; HRMS m/z 196.1468 (calcd for C$_{12}$H$_{20}$O$_2$, 196.1463); MS m/z 112 (36), 113 (base), 137 (3), 152 (5), 178 (4); IR: (neat) 2925 (s), 2852 (m), 1720 (C=O, s), 1272 (m), 1063 (w).

4.3.12. Tetrahydro-2-methyl-6-phenylpyran-4-one (Table 2, entry 3). ^{1}H NMR: δ 1.42 (d, J=6.2 Hz, 3H), 2.33–2.64 (m, 4H), 3.93 (m, 1H), 4.65 (dd, J=3.9, 10.5 Hz, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR: δ 21.9, 46.0, 48.1, 73.3, 76.6, 78.4, 125.5, 126.5, 127.8, 128.4, 140.7, 206.3; HRMS: m/z 190.0993 (base)(calcd for C$_{12}$H$_{14}$O$_2$, 190.0994);

MS m/z 105 (60), 107 (33), 171 (3), 172 (4), 190 (base); IR (neat) 2975 (w), 2865 (w), 2360 (w), 1716 (C=O, s), 1056 (m), 697 (s).

4.3.13. 2-(4-Fluorophenyl)-tetrahydro-6-methylpyran-4-one (Table 2, entry 4).
^{1}H NMR: δ 1.41 (d, J=6.0 Hz, 3H), 2.31–2.62 (m, 4H), 3.91 (m, 1H), 4.63 (dd, J=3.4, 10.9 Hz, 1H), 7.02–7.10 (m, 2H), 7.32–7.38 (m, 2H); ^{13}C NMR: δ 22.1, 49.2, 49.3, 73.7, 78.1, 115.4, 115.6, 127.4, 127.5, 136.6, 164.1, 206.4; HRMS m/z 208.0903 (calcd for $C_{12}H_{13}FO_2$, 208.0900); MS m/z 122 (65), 123 (base), 124 (32), 125 (44), 149 (18), 190 (10); IR (neat) 2976 (w), 1715 (C=O, s), 1607 (w), 1510 (s), 1221 (s), 825 (s).

4.3.14. 2-(4-Bromophenyl)-tetrahydro-6-methylpyran-4-one (Table 2, entry 5).
^{1}H NMR: δ 1.41 (d, J=6.1 Hz, 3H), 2.62–2.31 (m, 4H), 3.97–3.86 (m, 1H), 4.61 (dd, J=3.1, 11.1 Hz, 1H), 7.23–7.27 (m, 2H), 7.50 (dd, J=6.7, 1.8 Hz, 2H); ^{13}C NMR: δ 21.9, 48.9, 49.0, 73.4, 77.7, 127.2, 128.3, 131.5, 139.7, 205.9; HRMS m/z 268.0103 (calcd for $C_{12}H_{13}BrO_2$, 268.0099); MS m/z 155 (13), 157 (15), 183 (73), 184 (85), 185 (base), 270 (78); IR (neat) 2974 (w), 1716 (C=O, s), 1488 (m), 1066 (s), 1010 (s), 814 (s).

4.3.15. 2-(3-Bromophenyl)-tetrahydro-6-methylpyran-4-one (Table 2, entry 6).
^{1}H NMR: δ 1.42 (d, J=6.3 Hz, 3H), 2.31–2.62 (m, 4H), 3.91 (m, 1H), 4.62 (dd, J=3.0, 11.3 Hz, 1H), 7.25 (m, 1H), 7.44 (m, 1H), 7.57 (d, J=1.7 Hz, 1H); ^{13}C NMR: 22.1, 49.1, 49.2, 73.7, 77.8, 122.8, 124.2, 128.8, 130.2, 131.1, 143.1, 206.0; HRMS m/z 268.0103 (calcd for $C_{12}H_{13}BrO_2$, 268.0099); MS m/z 103 (25), 155 (14), 157 (16), 182 (68), 184 (base), 270 (80); IR: (neat) 2975 (w), 2861 (w), 1715 (C=O, s), 1061 (m), 781 (m), 691 (m).

4.3.16. 2-(Benzo[d][1,3]dioxol-5-yl)-tetrahydro-6-methylpyran-4-one (Table 2, entry 7).
^{1}H NMR: δ 1.40 (d, J=6.1 Hz, 3H), 2.30–2.55 (m, 4H), 3.90 (m, 1H), 4.56 (dd, J=5.2, 9.1 Hz, 1H), 5.95 (s, 2H), 6.77–6.84 (m, 2H), 6.91 (d, J=1.3 Hz, 1H); ^{13}C NMR: δ 22.2, 49.3, 49.4, 73.6, 78.6, 101.1, 106.5, 108.3, 119.3, 134.8, 147.4, 148.0, 206.7; HRMS m/z 234.0888 (calcd for $C_{13}H_{14}O_4$, 234.0892); MS m/z 121 (7), 149 (56), 150 (98), 234 (base); IR (neat) 2974 (w), 2899 (w), 2361 (w), 1716 (C=O, s), 1239 (s), 1036 (s), 810 (m).

4.3.17. Tetrahydro-2-methyl-6-(thiophen-2-yl)pyran-4-one (cis/trans=1/1) (Table 2, entry 8).
^{1}H NMR: δ 1.27 (d, J=6.0 Hz, 3H), 1.40 (d, J=6.0 Hz, 3H), 2.27–2.48 (m, 4H), 2.69–2.72 (m, 2H), 2.89–2.91 (m, 2H), 3.90–4.03 (m, 2H), 4.89 (dd, J=5.3, 9.1 Hz, 1H), 5.54 (t, J=4.9 Hz, 1H), 6.91–6.99 (m, 4H), 7.29–7.33 (m, 2H); ^{13}C NMR: δ 21.2, 22.0, 45.2, 48.9, 49.1, 67.6, 70.9, 73.5, 74.5, 124.1, 125.4, 126.3, 126.4, 126.6, 143.7, 205.9, 206.3; HRMS m/z 196.0560 (calcd for $C_{10}H_{12}O_2S$, 196.0558); MS m/z 112 (32), 113 (54), 126 (base), 137 (5), 163 (10), 168 (14); IR: (neat) 2974 (w), 1717 (C=O, s), 1585 (s), 1442 (w), 1043 (m), 700 (s).

4.3.18. 2-(Furan-2-yl)-tetrahydro-6-methylpyran-4-one (cis/trans=6/4) (Table 2, entry 9).
^{1}H NMR: δ 1.27 (d, J=6.4 Hz, 3H), 1.38 (d, J=5.9 Hz, 3H), 2.30–2.89 (m, 8H), 3.87–3.92 (m, 2H), 4.70 (dd, J=2.5, 12.1 Hz, 1H), 5.35 (dd, J=6.9, 2.6 Hz, 1H), 6.27–6.37 (m, 4H), 7.40–7.42 (m, 2H); ^{13}C NMR: δ 21.6, 22.0, 43.1, 45.1, 49.1, 49.2, 67.8, 68.9, 71.9, 73.4, 107.7, 109.9, 110.2, 110.3, 142.9, 143.0, 206.0; HRMS m/z 180.0785 (calcd for $C_{10}H_{12}O_3$, 180.0786); MS m/z 110 (27), 121 (13), 122 (23), 136 (8), 138 (11), 152 (18), 180 (base); IR (neat) 2975 (w), 2360 (w), 1715 (C=O, s), 1344 (m), 1015 (m), 741 (s).

4.3.19. Tetrahydro-3,6-dimethyl-2-phenylpyran-4-one (Scheme 6, 4a+4b).
^{1}H NMR: (CDCl₃) δ 0.80 (d, J=6.6 Hz, 3H), 0.89 (d, J=7.3 Hz, 3H), 1.37 (d, J=6.0 Hz, 3H), 1.43 (d, J=6.3 Hz, 3H), 2.32 (dt, J=15.0,

1.5 Hz, 1H), 2.51 (d, J=6.2 Hz, 1H), 2.54 (d, J=3.3 Hz, 1H), 2.58–2.65 (m, 2H), 3.40 (d, J=5.8 Hz, 1H), 2.86–3.93 (m, 2H), 4.17 (d, J=10.3 Hz, 1H), 4.81 (d, J=2.8 Hz, 1H), 7.24–7.42 (m, 10H); HRMS m/z 204.1153 (calcd for $C_{13}H_{16}O_2$, 204.1150); MS m/z 107 (42), 115 (15), 117 (28), 118 (17), 162 (70), 203 (5), 204 (base); IR (neat) 2974 (w), 2933 (w), 2879 (w), 1712 (C=O, s), 1022 (m), 699 (s).

4.3.20. 2-Cyclohexyl-tetrahydro-5,6-dimethylpyran-4-one (Scheme 6, 6a).
^{1}H NMR: δ 0.95 (d, J=6.7 Hz, 3H), 0.98–1.25 (m, 6H), 1.31 (d, J=6.0 Hz, 3H), 1.48 (m, 1H), 1.71–1.74 (m, 4H), 1.94 (m, 1H), 2.15–2.41 (m, 3H), 3.26 (m, 1H); ^{13}C NMR: 9.3, 20.4, 25.9, 26.0, 26.4, 28.2, 28.9, 43.1, 45.2, 51.9, 79.0, 81.5, 209.5; HRMS m/z 210.1616 (calcd for $C_{13}H_{22}O_2$, 210.1620); MS m/z 109 (39), 127 (56), 137 (15), 166 (base), 167 (15); IR (neat) 2925 (m), 2853 (w), 1714 (C=O, s), 14,450 (w), 1160 (w), 1092 (w), 891 (w).

4.3.21. Tetrahydro-5,6-dimethyl-2-phenylpyran-4-one (Scheme 6, 6b).
^{1}H NMR: δ 1.07 (d, J=6.7 Hz, 3H), 1.45 (d, J=6.2 Hz, 3H), 2.37 (m, 1H), 2.63–2.69 (m, 2H), 3.7 (m, 1H), 4.66 (dd, J=6.3, 8.0 Hz, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR: δ 9.3, 20.5, 49.6, 51.6, 78.9, 79.3, 125.6, 127.9, 128.5, 140.9, 207.9; HRMS m/z 204.1150 (calcd for $C_{13}H_{16}O_2$, 204.1150); MS m/z 104 (base), 107 (54), 118 (25), 160 (32), 186 (3); IR (neat) 2975 (w), 1714 (C=O, s), 1453 (w), 1069 (m), 756 (m), 698 (s).

4.3.22. Spiro-tetrahydropyran-4-one (Scheme 7, 8).
^{1}H NMR: δ 1.28 (d, J=5.9 Hz, 3H), 1.38–1.51 (m, 6H), 1.68–1.76 (m, 4H), 2.15–2.32 (m, 4H), 3.95–2.89 (m, 1H); ^{13}C NMR: δ 21.2, 21.7, 22.5, 25.4, 31.9, 39.5, 49.3, 52.2, 65.7, 75.9, 208.3; HRMS m/z 182.1304 (calcd for $C_{11}H_{18}O_2$, 182.1307); MS m/z 105 (12), 126 (63), 139 (73), 142 (22), 141 (17), 149 (100), 182 (base). IR: (neat) 2930 (m), 2859 (w), 1717 (C=O, s), 1274 (m), 999 (m), 850 (w).

Acknowledgements

References and notes

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