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An Improved Procedure for the Synthesis of Allylic Spiro-γ-Lactones

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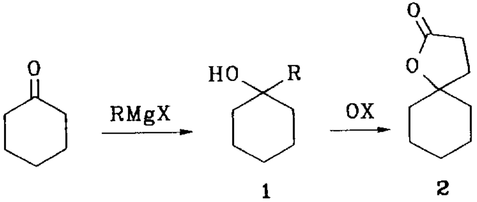
Abstract: Allylic spiro-γ-lactones of the type **4** have been synthesised in two steps starting from the carbonyl precursors using heterogeneous permanganate oxidation as the key step.

Numerous methods are available for the synthesis of spiro-γ-lactones of the type **2** from the carbonyl precursors.[1] In most of the cases the carbonyl compound is reacted with a Grignard reagent to give the alcohol **1** which is then oxidised to produce the spiro-γ-lactone **2** (Scheme 1).[1a,c] The same strategy cannot be easily extended to the preparation of allylic spiro-γ-lactones like **4** since the oxidation at the final step also attacks the internal double bond (Scheme 2). Moreover the precursor **3** has marked tendency for elimination because the alcohol is tertiary as well as allylic. In view of these difficulties, Constantino *et al*[2] developed a circuitous route for the synthesis of allylic spiro-γ-lactone **4** starting from dimedone in an overall yield of 9%.

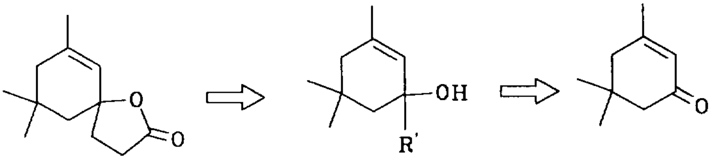
Earlier we showed[1c] that γ- and δ-hydroxy alkenes can be oxidatively cyclised to the corresponding γ- and δ-lactones using $KMnO_4$ as the oxidant and $CuSO_4.5H_2O$ as the solid support in the presence of catalytic amounts of water. We have also shown that the reagent system, $KMnO_4$-$CuSO_4.5H_2O$ in the presence of catalytic amounts of water and *tert*-butyl alcohol behaves differently from the classical permanganate oxidation.[3] It is believed that in these oxidations *tert*-butyl alcohol acts as a phase transfer catalyst and both water and *tert*-butyl alcohol form a third phase (omega phase)[3,4] over the inorganic solid and it is in or on the interface that the reaction takes place.

In this report, we demonstrate that the route based on retrosynthesis (Scheme 2) can in fact be applied to the synthesis of allylic spiro-γ-lactones with facility involving the use of permanganate oxidation under omega phase catalysis.

Scheme 1



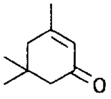
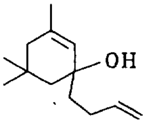
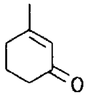
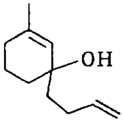
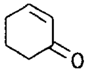
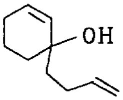
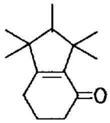
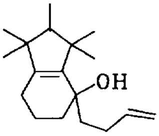
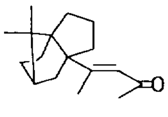
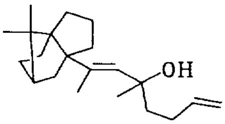
Scheme 2



4 3 5

Table 1

Ultrasound–Promoted Barbier–type Adddition of 4–Bromo–1–butene to α,β–Unsaturated Ketones

Substrate	Product	Time(h)	Yield(%)
 5	 6	1	93
 7	 8	1	91
 9	 10	0.25	60
 11	 12	1	63
 13	 14	1	80

RESULTS & DISCUSSION

The synthesis of the key intermediates, γ-hydroxy alkenes, utilised a Barbier-type addition[5] promoted by ultrasound irradiation, to give the 1,2-addition products exclusively[6] in good yields (Table 1). Thus, when isophorone (**5**) was treated with 4-bromo-1-butene and lithium metal in dry THF and sonicated for 1 h under argon atmosphere, the alcohol **6** was obtained in 93% yield. Under similar reaction conditions 3-methylcyclohexenone (**7**) afforded the alcohol **8** in high yield (91%) whereas the reaction of 2-cyclohexenone (**9**) with 4-bromo-1-butene gave the alcohol **10** in 60% yield. Compounds **11** and **13** also produced the corresponding alcohols **12** and **14** in 73% and 80% yield, respectively (Table 1).[7] In contrast, the reaction of isophorone (**5**) with Grignard reagent derived from 4-bromo-1-butene failed to produce appreciable amount of alcohol **6**. The reaction was complicated by the formation of 1,2- and 1,4-addition products apart from products of elimination.

All the alcohols **6**, **8**, **12** and **14** underwent smooth oxidative cyclisation with $KMnO_4$-$CuSO_4.5H_2O$ under conditions of omega phase catalysis to afford the corresponding allylic spiro-γ-lactones **15**, **16**, **18** and **19** respectively in good yields (Table 2). The only substrate that gave poor yield of the lactone after oxidative cyclisation was the alcohol **10**. Competing reaction at the alkene allylic to the hydroxyl group leading to highly polar poly hydroxy compounds as byprodunts[8] is responsible for the lower yield in this case. Since the formation of the lactone from the hydroxy olefins is a hydroxyl directed oxidative cyclisation[9] it is the terminal olefin that preferentially reacts to form the products. This kind of selectivity is not usually observed in a classical permanganate oxidation, and we believe that the chemoselectivity observed is due to the non-classical phase transfer catalysis (omega phase catalysis) in the heterogeneous permanganate oxidation.

EXPERIMENTAL SECTION

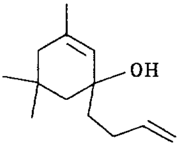
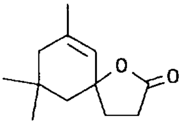
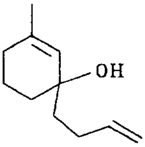
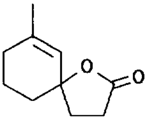
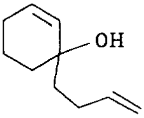
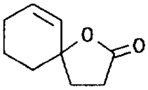
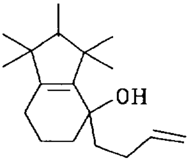
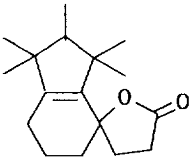
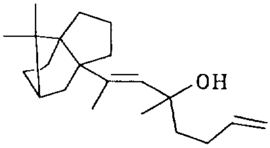
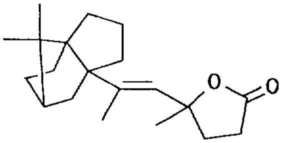
General Remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$. TLC were performed on 0.25 mm E. Merck precoated silica plates (60F-254). All the products were purified by flash chromatography on silica gel (230-400 mesh). Sonication experiments were carried out in an ultrasonic cleaning bath operating at 25 KHz.

Representative Procedure for the Ultrasound-Promoted Barbier-type Addition of 4-Bromo-1-Butene to α,β-Unsaturated Ketones

*Preparation of Alcohol **6** from Isophorone (**5**)*. In a 100 mL two necked round bottom flask was placed freshly cut lithium (0.210 g, 30 mg atom). Dry THF (25 mL) was added through a septum under argon atmosphere. To this suspension, isophorone (**5**) (0.69 g, 0.75 mL, 5 mmol) and 4-bromo-1-butene (1.0 g, 0.76 mL, 7.5 mmol) were added through syringes. The flask was partially submerged in an ice-cold water bath of ultrasonic cleaner and sonicated for 1h. Excess lithium was filtered off and THF was diluted with moist ether. The THF-ether extract was washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (99:1, EtOAc and petroleum ether 60-80) to afford the alcohol **6** (0.902 g, 93%), **IR** (neat/cm^{-1}) 3400, 3150, 1625,

Table 2

Oxidation of Allylic Alcohols with $KMnO_4-CuSO_4.5H_2O$

Substrate	Product	t(h)	Yield(%)
 **6**	 **15**	1	66
 **8**	 **16**	1	62
 10	 17	1	33
 12	 **18**	4	63
 14	 19	1	56

900; **^{1}H NMR** ($CDCl_3$, 90 MHz) 1.00-1.08 (m, 8H), 1.40-1.60 (m, 5H), 1.70 (s, 2H), 2.20 (s, 2H), 4.84-5.20 (m, 2H), 5.32 (br s, 1H), 5.60-6.00 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) 24.6, 28.0, 28.7, 30.7, 32.4, 43.9, 45.2, 48.4, 72.1, 114.8, 126.3, 136.5, 139.8; **MS** (*m/z*) 194 (M^+), 176, 139.

Preparation of Alcohol 8 from 3-Methylcyclohexen-1-one (7). Yield 91%, **IR** (neat/cm^{-1}) 3380, 3060, 1630, 1440, 900; **^{1}H NMR** ($CDCl_3$, 90 MHz) 1.39-2.29 (m, 13H), 4.77-5.15 (m, 2H), 5.40 (br s, 1H), 5.56-6.16 (m, 1H); **^{13}C NMR** ($CDCl_3$, 22.5 MHz) 19.2, 23.5, 27.9, 30.1, 34.9, 41.5, 69.9, 113.9, 127.2, 137.3, 139.0; **MS** (*m/z*) 166 (M^+), 150, 148.

Preparation of Alcohol 10 from 2-Cyclohexenone (9). Yield 60%, **IR** (neat/cm^{-1}) 3400, 3060, 1640, 1450, 930; **^{1}H NMR** ($CDCl_3$, 90 MHz) 1.56-1.80(m, 6H), 1.88-2.32 (m, 4H), 4.84-5.16 (m, 2H), 5.60-6.08 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) 19.7, 25.9, 28.6, 36.2, 41.9, 70.2, 114.9, 130.5, 133.2, 139.7; **MS (m/z)** 153 ($M^+ + 1$), 152, 134, 97.

Preparation of Alcohol 12 from enone 11. Yield 63%, **IR** (neat/cm^{-1}) 3460, 3050, 1630; **^{1}H NMR** ($CDCl_3$, 90 MHz) 0.82 (d, 3H), 0.79, 0.90, 1.03, 1.15 (4s, $4CH_3$), 1.41-2.29 (m, 10H), 4.79-5.18 (m, 2H), 5.50-6.19 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) 8.5, 20.6, 22.1, 22.3, 25.4, 28.5, 29.1, 29.6, 37.9, 39.6, 46.3, 48.6, 54.4, 74.8, 114.8, 139.9, 144.5, 145.2; **MS** (*m/z*) 262 (M^+), 246, 245, 244, 207.

Preparation of Alcohol 14 from enone 13. Yield 80%, **IR** (neat/cm^{-1}) 3388, 3064, 1641; **^{1}H NMR** ($CDCl_3$, 90 MHz) 0.84 and 0.95 (2s, 6H), 1.40 (s, 3H), 1.44-1.79 (m, 15H), 1.84 (m, 3H), 2.03-2.32 (m, 2H), 4.95-5.16 (m, 2H), 5.23 (s, 1H), 5.70-6.15 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) 15.4, 16.0, 20.5, 21.5, 22.8, 29.7, 30.1, 33.3, 37.7, 37.8, 39.6, 43.7, 45.5, 47.3, 48.5, 51.8, 52.5, 74.2, 114.9, 130.9, 139.9; **MS** (*m/z*) 302 (M^+), 286, 285, 284, 247.

Representative Procedure for the Preparation of Allylic Spiro-γ-Lactones

Preparation of Lactone 15 from Alcohol 6. $KMnO_4$ (4 g) and $CuSO_4.5H_2O$ (2 g) were ground to a fine powder, to which water (200 μL) was added and mixed thoroughly. The slightly wet mixture was transferred to a flask containing 10 mL of CH_2Cl_2. To a stirred suspension of the above mixture, was added the alcohol **6** (0.194 g, 1 mmol) in CH_2Cl_2 (1 mL) followed by the addition of *tert*-butyl alcohol (500 μL). It was filtered after 1 h through a pad of Celite and washed thoroughly with CH_2Cl_2. Removal of the solvent and purification by flash chromatography (96:4, EtOAc and petroleum ether 60-80) yielded the spiro-γ-lactone **15** (0.128 g, 66%) as an oil, **IR** (neat/cm^{-1}) 1755, 1660; **^{1}H NMR** ($CDCl_3$, 90 MHz) 1.00 and 1.04 (2s, 6H), 1.48-1.84 (m, 5H), 1.94-2.20 (m, 2H), 2.48-2.70 (m, 2H), 5.36 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 22.5 MHz) 23.8, 27.6, 28.6, 30.2, 35.6, 43.9, 47.4, 85.2, 121.4, 139.1, 176.9; **MS** (*m/z*) 194 (M^+), 150, 139; **HRMS** calcd for $C_{12}H_{18}O_2$ 194.1307, Found 194.1305.

Preparation of Lactone 16 from Alcohol 8. Yield 62%, **IR** (neat/cm^{-1}) 1760, 1660; **^{1}H NMR** ($CDCl_3$, 90 MHz) 1.76-2.20 (m, 11H), 2.52-2.76 (m, 2H), 5.35 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 22.5 MHz) 19.6, 23.4, 28.8, 29.6, 34.3, 84.5, 123.2, 141.0, 176.6; **MS** (*m/z*) 166 (M^+), 122, 111; **HRMS** calcd for $C_{10}H_{14}O_2$ 166.0994, Found 166.1004.

Preparation of Lactone 17 from Alcohol 10. Yield 33%, **IR** (neat/cm^{-1}) 1760; **^{1}H NMR** ($CDCl_3$, 90 MHz) 1.72-1.96 (m, 4H), 2.00-2.24 (m, 4H), 2.56-2.76 (m, 2H), 5.60-6.12 (m, 2H); **^{13}C NMR** ($CDCl_3$, 22.5 MHz) 15.2, 19.3, 24.6, 28.70, 33.9, 83.2, 128.5, 132.5, 176.8; **MS** (*m/z*) 152 (M^+), 124, 97; **HRMS** calcd for $C_9H_{12}O_2$ 152.0837, Found 152.0885.

Preparation of Lactone 18 from Alcohol 12. Yield 63%, m.p. 97-99°C; **IR** (nujol/cm^{-1}) 1755, 1450; **^{1}H NMR** ($CDCl_3$, 90 MHz) 0.84 (d, 3H), 0.89, 0.96, 1.06, 1.08 (4s, 4 CH_3), 1.40-2.02 (m, 8H), 2.60-3.16

(m, 2H); ^{13}**C NMR** ($CDCl_3$, 22.5 MHz) 8.0, 20.0, 21.0, 22.0, 24.0, 27.5, 28.0, 31.5, 36.5, 46.0, 47.0, 54.0, 87.0, 140.0, 146.5, 177.0; **MS** (*m/z*) 262 (M^+), 248, 247, 207; Anal calcd for $C_{17}H_{26}O_2$, C: 77.863, H: 9.924 Found C: 77.860, H: 10.209.

*Preparation of Lactone **19** from Alcohol **14**.* Yield 56%, **IR** (neat/cm^{-1}) 1760, 1640; ^{1}**H NMR** ($CDCl_3$, 90 MHz) 0.78, 0.88, (2s, 6H), 1.24-1.60 (m, 13H), 1.70 (d, 3H), 2.10-2.32 (m, 2H), 2.46-2.70 (m, 2H), 5.34 (s, 1H); ^{13}**C NMR** ($CDCl_3$, 22.5 MHz) 15.0, 19.5, 20.5, 22.0, 27.0, 29.0, 32.3, 35.5, 36.5, 38.8, 44.5, 46.3, 47.5, 51.0, 51.8, 86.5, 127.0, 146.0, 176.8; **MS** (*m/z*) 302 (M^+), 286, 229, 188; Anal calcd for $C_{20}H_{30}O_2$, C: 79.470, H: 9.934, Found C: 79.20, H: 10.150.

ACKNOWLEDGEMENT

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7. The same Barbier-type reaction when performed in the absence of sonication the reactions take much longer time to go to completion and the yields are inferior.
8. These poly hydroxy compounds (about 10-15%) were not characterised.
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