Facile Synthesis of Unsaturated Lactones *via* Intramolecular Wittig Reaction

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Abstract : The phosphoranes **3** formed from the reaction of a variety of keto alcohols **1** and (triphenylphosphoranylidene)ethenone **2** undergo intramolecular Wittig cyclization to afford the unsaturated lactones in moderate yields. © 1998 Elsevier Science Ltd. All rights reserved.

As part of our ongoing program for developing methodologies employing phosphacumulene[1] and their subsequent application to biologically useful compounds, the (triphenylphosphoranylidene)ethenone **2** is envisaged as a versatile reagent offering considerable opportunities for synthetic manipulations.[2] The intramolecular Wittig reaction has been extensively employed as an excellent method for the C-C bond forming process in the synthesis of natural products.[3] In this connection the phosphacumulene ylides, one of the recent arrivals in the series of organophosphorous reagents, are of special interest.

The presence of a lactone functionality fused to a carbocyclic framework is commonly encountered as an important structural feature in a variety of biologically active natural products[4] *e.g* iridoid lactones, iridomyrmecin, isoiridomyrmecin, teucriumlactone and boschnialactone etc.[5] While a variety of synthetic methodologies for unsaturated lactones have been developed,[6] the literature describing a novel one-pot cyclization method based on consecutive process is rather scarce. However, a few reports of syntheses of five- and six-membered cyclic compounds[7] including the macrocyclic lactones such as musk scent ambrettolide[2c] from H-acidic compounds and phosphacumulene ylides are known in the literature. As a part of our continuous interest in the chemistry of these phosphacumulene ylides, we report here, an efficient methodology for the conversion of hydroxy ketones into the corresponding lactones employing intramolecular Wittig reaction as the key step. The generality of this concept has been established with several models. The annulation protocol is depicted in Scheme-1.

Scheme-1
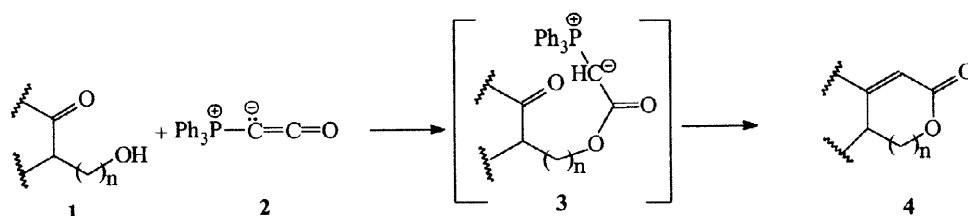
The various hydroxy ketones utilized in our studies e.g 1a[8a], 1d[8b], 1e[8c], 1i[8d] were prepared as per literature precedences, whereas the preparation of the remaining starting materials are reported in the experimental sections of this publication.

The synthesis of 1b was achieved from 2-carbethoxy cyclopentanone 5 by following a sequence of reactions. The protection of the keto group of 5 with ethylene glycol using a catalytic amount of pTSA gave compound 6 which on subsequent reduction of the ester group with lithium aluminium hydride furnished 1b. The deprotection of the ketal group from 1b was performed using 10% aq. oxalic acid and silica gel to afford the corresponding β-hydroxy ketone 1c.
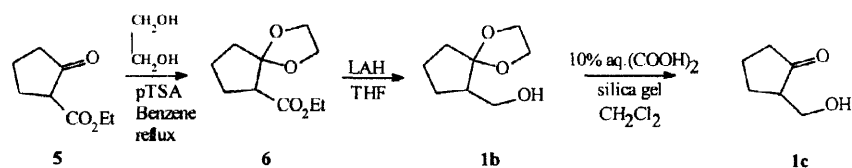

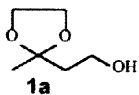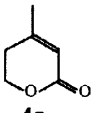
Compound 1f was prepared from iso-pulegol by ozonolysis.[8e]
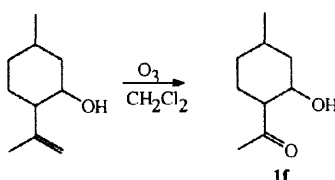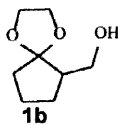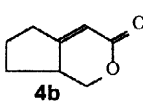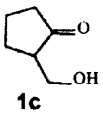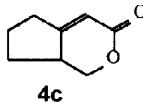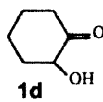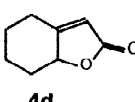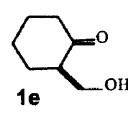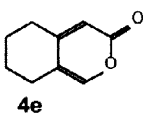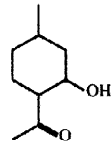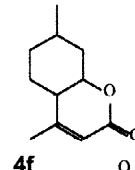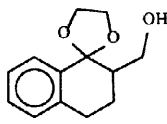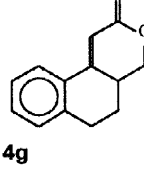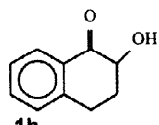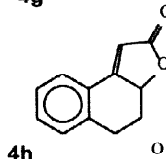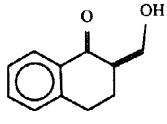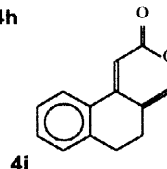
Compound 1g was prepared from α-tetralone by following sequence of reactions. The reaction of α-tetralone with diethyl carbonate gave the β-ketoester 7,[8f] which on treatment with ethylene glycol in the presence of catalytic amount of pTSA afforded 8. The subsequent reduction of the ester group of 8 with LAH furnished 1g.
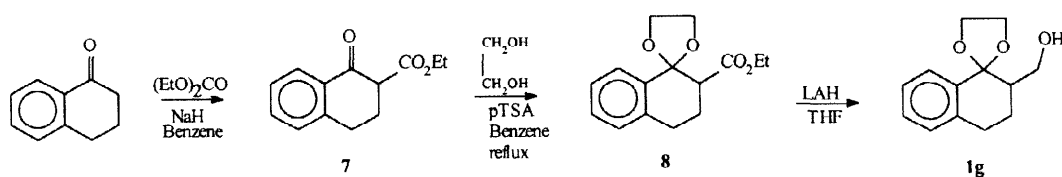
Compound 1h was prepared from α-tetralone by α-hydroxylation using o-iodo benzoic acid.[8g]
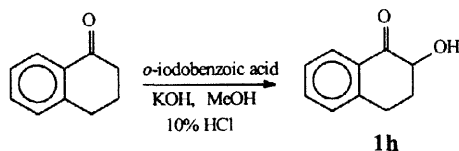
Table-1 : Synthesis of unsaturated lactones **4** from **1** and **2** *via* intramolecular Wittig cyclization.

Entry	Substrate	Reaction time(h)	Annulated Product [a, b]	Yield(%)[c]
1	1a	10	4a	47
2	1b	6	4b	53
3	1c	6	4c	36
4	1d	8	4d	40
5	1e	12	4e	52
6	1f	6	4f	70
7	1g	5	4g	56
8	1h	4	4h	50
9	1i	10	4i	65

(a) Method A was employed in entries 1, 2, 7 and method B was employed in entries 3-6, 8, 9. (b) All compounds have been fully characterized spectroscopically by IR, ^{1}H-NMR, ^{13}C-NMR and MS. (c) : Yields refer to isolated pure products. (d) : The product is a mixture of isomers since the starting material is not optically pure.

When a mixture of compound 1 and (triphenylphosphoranylidene)ethenone 2 was heated in refluxing benzene, the desired lactones 4 were obtained in 36- 70% yields. The conversion of 1 into 4 could be explained by a sequence of reactions as depicted in the Scheme-1. The plausible mechanism can be visualized as initial protonation of (triphenylphosphoranylidene)ethenone 2 by 1 followed by nucleophilic attack of the alkoxy anion to the resulting vinylphosphonium salt leading to the phosphorane 3 which subsequently undergoes ring closure via the intramolecular Wittig reaction to afford the lactone 4. However, our attempt to isolate compound 3 from the reaction of 1 and 2 at room temperature failed due to the instantaneous intramolecular Wittig reaction eventually leading to the product 4.

As is apparent from Table-1, the intramolecular Wittig cyclization involving phosphorous ylide and ketone is general for the preparation of a variety of lactones. The reaction of 1a without the protection of carbonyl group as ketal with 2 afforded compound 4a in poor yield along with some unidentified side products. The occurrence of a side reaction could possibly be due to the attack of ylide 2 as a base on the acidic sites α-to the carbonyl in the β-hydroxy ketone. Therefore, to circumvent the deleterious side reaction it was thought worthwhile to protect the carbonyl group for a clean transformation. Thus the hydroxy ketal 1a was smoothly converted into anhydromevalonolactone 4a in better yield. It may be pertinent to mention here that a considerable amount of difficulty has been encountered in the standard Intramolecular Horner-Wadsworth-Emmons (IMHWE) olefination reaction in the synthesis of unsaturated lactones.[9] Indeed, an attempt to synthesize compound 4a from the corresponding β-hydroxy carbonyl compound by Horner-Emmons reaction failed. This could perhaps be attributed to the fact that the base sensitive substrates are prone to α-epimerization and/or β-elimination under IMHWE reaction conditions and a plethora of reactions could be expected due to the competition for all possible acidic sites α- to the carbonyl in phosphonate.[10] In this connection the present methodology for 1a to 4a is noteworthy. The efficacy of the present annulation protocol can be clearly visualized in the case of α- or β-hydroxy bicyclic ketones where the corresponding tricyclic unsaturated lactones have been obtained in good yields (entries 7, 8, 9) and the formation of the side products was not observed. A recent publication by Nangia et.al[9b] describes the synthesis of α, β-unsaturated-δ-lactones from β-hydroxy ketone using IMHWE reaction where the formation of tricyclic lactones could not be achieved due to the slower IMHWE reaction and facile enolisation leading to the exclusive β-elimination product. Thus, the present method is quite general and works both for acyclic and cyclic α- or β-hydroxy ketones.

In summary, an efficient annulation protocol for a variety of unsaturated lactones via intramolecular carbonyl olefination using (triphenylphosphoranylidene)ethenone has been developed. This method offers a more general and one-pot synthesis of lactones such as monocyclic (4a), bicyclic (4b-f), tricyclic (4g-i), α,β-unsaturated-γ-butyrolactones (4d, 4h) and α-pyrones (4e, 4i). The strategy described here has significant potential of application to a variety of lactones of biological interest. Currently, studies are in progress in this direction.

Experimental Section

General information : Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin- Elmer model 683 grating infrared spectrometer. Proton and ^{13}C NMR spectra were recorded on Bruker AC-200 NMR spectrometer. The chemical shifts are reported in parts

per million(δ) with tetramethyl silane as an internal standard. Mass spectra were recorded with a Finnigan MAT-1020-B-70eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

Experimental procedure for the preparation of Hydroxy ketones

Preparation of 1b : A mixture of 2-carbethoxy cyclopentanone 5 (1g, 6.4mmol), ethylene glycol (5g, 8mmol) and catalytic amount of pTSA in dry benzene was refluxed using Dean-Stark water separator. After 4 h, the reaction mixture was cooled and to this water was added. The benzene layer was separated and washed with aq.NaHCO$_3$ and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated. The residue thus obtained was purified by column chromatography using pet.ether : ethylacetate (90 : 10) as eluent to afford 1.1g (86%) of 6. A solution of compound 6 in dry THF was added dropwise to the ice-cooled suspension of LAH and the reaction mixture was stirred at room temperature overnight. To this, aq.NaOH solution was added dropwise at 0°C. The white solid thus separated was filtered and washed thrice with THF. The combined THF layers were dried over Na$_2$SO$_4$ and concentrated. Purification of the residue by silica gel column chromatography using pet.ether : ethylacetate (85 : 15) as eluent gave 1b (0.6g, 75%). IR v_{max} /cm^{-1} (Neat) : 3500-3100(b); ^{1}H NMR (CDCl$_3$) δ : 1.5(m, 7H), 2.5(s, 1H, OH), 3.4-3.6(m, 2H), 3.9(s, 4H). Anal. calcd for C$_8$H$_{14}$O$_3$ (158.19) : C, 60.74; H, 8.92. Found : C, 60.47; H, 8.76.

Preparation of 1c : To a slurry of 230-400 mesh silica gel (10g) in dichloromethane was added 10% oxalic acid (5ml). After the disappearance of the aq.phase in about 10 min., a solution of the ketal 1b (1.6g, 0.01mol) in dichloromethane was added and the mixture was stirred at room temperature. After the reaction was judged to be complete, 1g of solid Na$_2$CO$_3$ was added and the mixture was filtered. The solid residue was washed with ether several times and the combined filtrates were evaporated in vacuo to give 1c (0.95g, 83%). Spectroscopic properties (IR, ^{1}HNMR) were in accord with those described.[11]

Preparation of 1f : 4g (0.026mol) of iso-pulegol in dry CH$_2$Cl$_2$(70ml) was cooled to -78°C, ozonized gas was bubbled to this solution until the color of the solution became light green (4h). The resulting reaction mixture was allowed to attain room temperature. To this solution were added Zn dust (20g) and HOAc (50ml) and the mixture was stirred for 3h and filtered through a pad of celite. The filtrate was neutralized with 5N NaOH, the organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50ml). The combined organic layers were washed with water, brine and dried over Na$_2$SO$_4$. Evaporation of the solvent and purification of the residue by silica gel column chromatography using pet.ether : ethylacetate (90 :10) as eluent, gave 2.5g (62%) of 1f. IR v_{max} /cm^{-1} (Neat) : 3500-3250(b), 2950(s), 1700(s); ^{1}H NMR (CDCl$_3$) δ : 0.9(d, J = 8Hz, 6H), 2.2(s, 3H), 0.85-2.4(m, 9H), 2.75(s, 1H). Anal. calcd for C$_9$H$_{16}$O$_2$(156.22) : C, 69.19; H, 10.32; Found : C, 69.40; H, 10.57.

Preparation of 1g : To a warm (60°C) suspension of 0.23g (0.01mol) of NaH and 1.77g (0.015mol) of diethyl carbonate in 15ml of dry benzene was added dropwise and with stirring, a solution of 0.73g (0.005mol) of α-tetralone in 5ml of dry benzene. After the mixture had been stirred for 1h at 60°C, it was cooled to 0°C, acidified with acetic acid and poured into ice-HCl mixture. The aqueous layer was washed with benzene and

the combined organic layers were washed with aq.NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄ and concentrated. Purification of the crude product by column chromatography using pet. ether : ethylacetate (95 : 5) gave 0.85g (78%) of 7.

A mixture of β-ketoester 7 (0.8g, 0.0036mol), ethylene glycol (0.45g, 0.0072mol) and catalytic amount of pTSA in dry benzene was refluxed using Dean-Stark water separator. After 4h, the reaction mixture was cooled and to this water was added. The organic layer was separated and the aqueous layer was washed with benzene and the combined organic layers were washed with aq.NaHCO₃, brine and dried over Na₂SO₄. Purification of the residue by column chromatography using pet.ether : ethylacetate (95 : 5) as eluent gave 8 (0.7g, 73%).

The compound 8 (6.4g, 0.03mol) in THF was added dropwise to the ice-cooled suspension of LAH (1.37g, 0.0036mol) in dry THF and the reaction mixture was stirred at room temperature overnight. To this, aq.NaOH solution was added dropwise at 0°C. The white solid thus separated was filtered and washed with THF. The combined organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography using pet.ether : ethylacetate (90 :10) as eluent to give 3.5g (65%) of 1g. IR νₘₐₓ/cm⁻¹ (Neat) : 3600-3100(b) ; ¹H NMR (CDCl₃) δ : 1.9-2.3(m, 5H), 2.95-3.1(m, 4H), 4.95(bs, 1H,), 5.26(t, J = 13.5, 19Hz, 2H), 7.5-7.18(m, 4H, Ar). Anal. calcd for C₁₃H₁₆O₃(220.26) : C, 70.89; H, 7.32; Found : C, 70.59 ; H, 7.58.

Preparation of 1h: 0.15mol of KOH was dissolved in 80ml of methanol with ice cooling and 7.3g (0.05mol) of α-tetralone in 20ml of methanol was added dropwise with stirring. Then solid o-iodo benzoic acid 14g (0.055mol) was added portionwise over 30 min. The reaction mixture was stirred at room temperature overnight. The α-hydroxy dimethylacetal was isolated by removing most of   methanol under reduced pressure and then by addition of water and extractraction with dichloromethane. The dichloromethane layer was dried, concentrated and the residue was purified by column chromatography using pet.ether : ethylacetate (90:10) as eluent. Acid hydrolysis of α-hydroxy dimethyl acetal using 5% H₂SO₄ in CHCl₃ gave 4g (50%) of 1h. Spectroscopic properties (IR, ¹HNMR, MS) were in accord with those described.[12]

The (triphenylphosphoranylidene)ethenone 2 was prepared as per literature procedure.[13]

General procedure for the preparation of unsaturated lactones

Method A : A mixture of (triphenylphosphoranylidene)ethenone 2 (5mmol) and hydroxy ketal 1 (5mmol) in dry benzene (10ml) was refluxed under nitrogen atmosphere for the indicated length of time. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure. The residue was treated with 50ml of 0.1N HCl and stirred at room temperature for 3h. The acid was neutralised by slow addition of aq. NaHCO₃. The aq.layer was extracted with benzene (3 x 15ml) and the combined organic layers were washed with water (15ml), brine (15ml), dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was purified by neutral alumina column chromatography using pet.ether : ethylacetate (80 : 20) as eluent.

Method B : A mixture of (triphenylphosphoranylidene)ethenone **2** (5mmol) and hydroxy ketone **1** (5mmol) in dry benzene (10ml) was refluxed under nitrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure. The crude material was purified by neutral alumina column chromatography using pet.ether : ethylacetate (80 : 20) as eluent.

The physical and spectroscopic data for compounds **4a**[14a], **4b**[9b], **4d**[14b] and **4e**[14c] were in accord with those described. The data for the unknown lactones are given below.

4f : IR ν_{max} /cm^{-1} (Neat) : 1700; ^{1}H NMR (CDCl$_3$) δ : 1.0(d, J = 6.5Hz, 3H), 1.9(s, 3H), 1.1-2.3(m, 8H), 4.0(td, 1H, J = 4, 7Hz), 5.8(d, 1H, J = 1.3Hz). ^{13}C NMR(CDCl$_3$) δ : 18.98, 21.3, 25.40, 30.38, 33.44, 39.58, 41.34, 79.90, 116.30, 160.59, 164.20. Mass : (m/z, rel. int) M$^+$ 180(36), 152(5), 137(13), 123(10), 109(52), 96(26), 95(100), 82(30), 81(33), 67(48). Anal. calcd for C$_{11}$H$_{16}$O$_2$ (180.24) : C, 73.30; H, 8.95. Found : C, 73.72; H, 8.93.

4g : IR ν_{max} /cm^{-1} (Neat) : 1730; ^{1}H NMR (CDCl$_3$) δ : 1.9-2.1(s, 2H), 2.1-2.5(t, 2H, J = 8Hz), 2.5-3.1(t, J = 10Hz, 2H), 4.2(s, 1H), 6.5(s, 1H), 7.0-7.5(m, 4H). ^{13}C NMR(CDCl$_3$) δ : 24.42, 27.88, 65.79, 85.54, 122.37, 126.07, 126.51, 126.79, 127.33, 134.13, 134.96, 140.49, 187.00. Mass : (m/z, rel. int) M$^+$ 160(60), 142(48), 129(100), 128(59), 115(33), 102(8.6), 91(17), 77(10). Anal. calcd for C$_{13}$H$_{12}$O$_2$ (200.23) : C, 77.98; H, 6.04. Found : C, 78.15; H, 6.34.

4h : IR ν_{max} /cm^{-1} (Neat) : 1740, 1630; ^{1}H NMR (CDCl$_3$) δ: 1.7-1.9(m, 4H), 5.05(m, 1H), 6.1(s, 1H), 7.15-7.7(m, 4H). ^{13}C NMR(CDCl$_3$) δ : 27.90, 30.34, 80.30, 109.80, 127.18, 127.30, 129.50, 13178, 138.20, 166.50. Mass : (m/z, rel. int) M$^+$ 186(100), 158(67), 157(96), 141(67), 130(71), 129(94), 128(84), 116(39), 115(69). Anal. calcd for C$_{12}$H$_{10}$O$_2$ (186.20) : C, 77.40; H, 5.41. Found : C, 77.30; H, 5.66.

4i : m.p : 100°C ; IR ν_{max} /cm^{-1} (Nujol) : 1720, 1630, 1540; ^{1}H-NMR (CDCl$_3$) δ : 2.7(t, 2H, J = 8Hz), 2.95(t, 2H, J = 8Hz), 6.25(d, 1H, J = 10Hz), 7.3(m, 4H), 7.8(m, 1H). ^{13}C NMR(CDCl$_3$) δ : 23. 98, 27.04, 111.82, 113.43, 122.69, 126.74, 127.59, 127.70, 129.97, 136.89, 145.56, 154.64, 161.63. Mass : (m/z, rel. int) M$^+$ 198(83), 170(100), 169(43), 141(74), 115(34), 77(6), 70(15). Anal. calcd for C$_{13}$H$_{10}$O$_2$ (198.21) : C, 78.77; H, 5.09. Found : C, 79.00; H, 5.34.

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