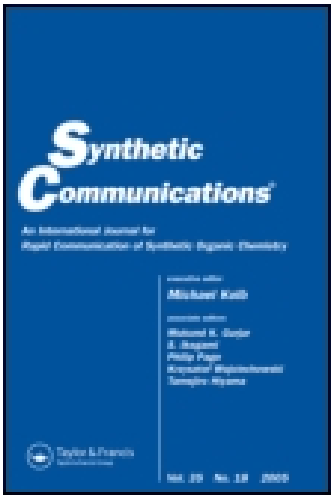


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# Dihydropyran as a Template for Lactone Synthesis

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# Dihydropyran as a Template for Lactone Synthesis

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**Abstract:** 3,4-Dihydro-2H-pyran (DHP) was efficiently transformed into 4-thiophenyl-3,4-dihydro-2H-pyran. This intermediate was converted to the corresponding 1,3-O,S-allylic carbanion with t-butyllithium and selectively alkylated at the carbon $\alpha$ to the sulfur with alkyl halides, an epoxide, and an aldehyde. An one-pot oxidative elimination of the sulfur fragment using vanadium pentoxide generates the desired $\beta$-substituted $\alpha,\beta$-unsaturated $\delta$-valero lactone.

$\beta$-Substituted $\alpha,\beta$-unsaturated $\delta$-valero lactones represent potentially useful intermediates and have a strong structural presence in natural products. Therefore, they have been the target for new synthetic methods.[1–6] We now report a new, straightforward approach to this lactone system using 3,4-dihydro-2H-pyran (DHP) as a readily available and inexpensive template (Scheme 1). In our synthetic approach, the goal was to selectively introduce a sulfide as a carbanion-stabilizing functionality at C-4 that could be removed after an alkylation process.

The availability of the typical array of potential carbon electrophiles for reaction with the resulting carbanion intermediate would ensure the desired flexibility in structural design within the targeted family of unsaturated lactones.

The successful approach was to utilize dithiophenyldibutyl stannane for the reported SN2′ addition of thiophenoxide to allylic acetals.[6–8] The requisite cyclic allylic acetal was prepared through an one-pot sequence of bromoethoxylation of DHP and dehydrobromination (Table 1).[9–11]

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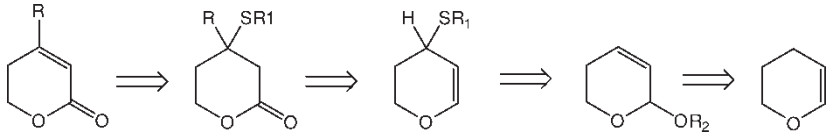



*Scheme 1.*

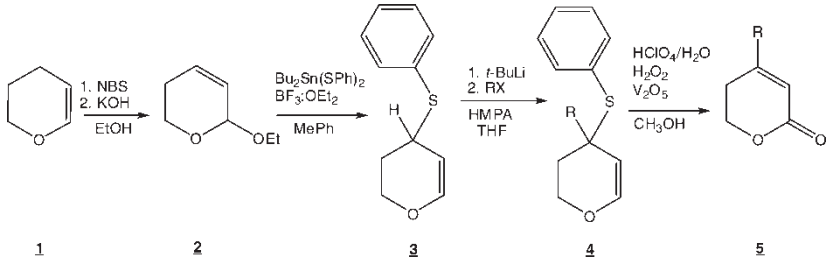
***Table 1.*** NMR data: compound 2

| Product | NMR ($CDCI_3$) | Data |
|---|---|---|
| **2** | $^1$H NMR | $\delta$ 6.1 (1H, m), 5.9 (1H, d), 5.0 (1H, s), 4.0 (1H, td), 3.9 (1H, m), 3.8 (1H, q), (1H, m), 2.3 (1H, m), 2.0 (1H, m), 1.3 (3H, t) |
| | $^{13}$C NMR | (75.5 MHz, $CDCI_3$) $\delta$ 129, 93, 63, 57, 25, 15 |

4-(Phenylthio)-3,4-dihydro-2H-pyran (Table 2) produced a 1,3-O,S-allylic carbanion when treated with *t*-butyl lithium (Scheme 2). Alkylation of the allylic carbanion occurred selectively $\alpha$ to the sulfur[12] at C-4 (Table 2). Using a mixture of vanadium pentoxide and hydrogen peroxide for oxidative elimination,[13] the desired $\beta$-substituted $\alpha,\beta$-unsaturated $\delta$-lactones[5] were generated in satisfactory yields (Scheme 2, Tables 3 and 4).

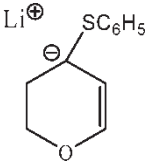
***Table 2.*** NMR data: compound 3

| Product | NMR ($CDCI_3$) | Data |
|---|---|---|
| **3** | $^1$H NMR | $\delta$ 7.4 (2H, m) 7.3 (3H, m), 6.5 (1H, d), 4.9 (1H, m), 4.2 (2H, td), (1H, m), 3.9 (1H, m), 2.2 (1H, m), 1.9 (1H, d) |
| | $^{13}$C NMR | (75.5 MHz, $CDCI_3$) $\delta$ 146, 135, 131, 129, 127, 100, 62, 38, 26 |




*Scheme 2.*

***Table 3.*** Results of electrophilic additions to 1,3-O,S-allylic carbanion

| Strating material | Electrophile | Product | Yield (%) | Rx time (min) | NMR ($CDCl_3$) | Data |
|---|---|---|---|---|---|---|
|  | $CH_3I$ | **4a** | 88 | 5 | $^1$H NMR | $\delta$ 7.5 (2H, m) 7.3 (3H, m), 6.4 (1H, d), 4.7 (1H, d), 4.3 (1H, td), 4.0 (1H, m), 2.0 (1H, m), 1.3 (3H, s) |
| | | | | | $^{13}$C NMR | $\delta$ 145, 138, 133, 130, 129, 108, 64, 45, 36, 30 |
| | n-BuBr | **4b** | 96 | 10 | $^1$H NMR | $\delta$ 7.5 (2H, m) 7.3 (3H, m), 6.4 (1H, d), 4.6 (1H, d), 4.3 (1H, m), 4.0 (1H, m), 1.9 (2H, m), 1.5 (4H, m) 1.5(4H, m) 1.3 (2H, m), 0.9 (3H, t) |
| | | | | | $^{13}$C NMR | $\delta$ 145, 138, 131, 130, 129, 106, 107, 64, 49, 41, 34, 27, 24, 15 |
| |  | **4c** | 90 | 60 | $^1$H NMR | $\delta$ 7.5 (2H, m) 7.3 (3H, m), 6.4 (1H, d) 4.4 (1H, d), 4.3 (1H, td), 4.0 (1H, m), 2.2 (1H, td), 1.8 (2H, m), 1.1(3H, d), 1.0 (3H, d) |
| | | | | | $^{13}$C NMR | $\delta$ 145, 138, 131, 130, 129, 106, 64, 55, 36, 31, 19, 18 |

(*continued*)

***Table 3.*** Continued

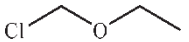
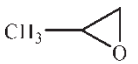
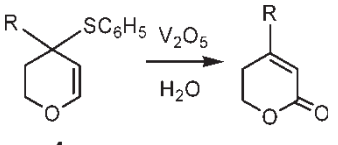
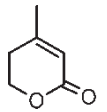
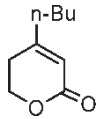
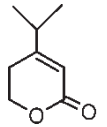
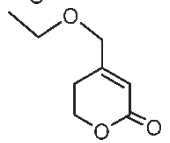
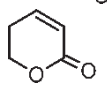
| Strating material | Electrophile | Product | Yield (%) | Rx time (min) | NMR ($CDCl_3$) | Data |
|---|---|---|---|---|---|---|
| |  | **4d** | 95 | 5 | $^1$H NMR | $\delta$ 7.6 (2H, m) 7.4 (3H, m), 6.4 (1H, d), 4.6 (1H, d), 4.4 (1H, td), 4.1 (1H, m), 3.5 (2H, m), 3.4 (1H, d), 3.3(1H, d) 2.1 (1H, td), 1.8 (1H, m), 1.2 (3H, t) |
| | | | | | $^{13}$C NMR | $\delta$ 146, 138, 132, 130, 129, 104, 75, 67, 63, 49, 31, 16 |
| |  | **4e** | 85 | 15 | Two isomers (1.1:1)$^1$H NMR | $\delta$ 7.6 (2H, m) 7.3 (3H, m), 6.5 & 6.3 (1H, d), 4.8 & 4.5 (1H, d), 4.4 (1H, m), 4.2 (1H, m), 4.0 (1H, m) 3.2 & 3.1 (1H, borad s) 3.1 & 2.9 (1H, m) 2.1 & 2.0 (1H, m), 2.0 (1H, m) 1.9 & 1.8 (1H, m), 1.6 (1H, t), 1.2 & 1.1 (3H, d) |
| | | | | | $^{13}$C NMR | $\delta$ 146, 145, 138, 131, 130, 129, (106, 105), (66, 65), (63, 62), (50, 49), (48, 47), (35, 34), (25, 24) |
| | $CH_3CHO$ | **4f** | 65 | 5 | Two isomers (1.1:1)$^1$H NMR | $\delta$ 7.5 (2H, m) 7.3 (3H, m), 6.5 & 6.4 (1H, d), 4.6 & 4.2 (1H, d), 4.5–4.4 (1H, m), 4.2 (1H, m), 3.6 (1H, m) 3.0 (1H, borad s) 2.3 & 2.0 (1H, td), 1.8 (1H, t), 1.2 & 1.1 (3H, d) |
| | | | | | $^{13}$C NMR | $\delta$ 148, 145, 138, 131 130, 129, (103, 100), (70, 69), (64, 63), (57, 56), (29, 28), (17, 16) |

***Table 4.*** Result of oxidations to produce lactones

| Starting material | Lactone | Product | Yield (%) | NMR ($CDCI_3$) | Data |
|---|---|---|---|---|---|
|  **4** **5** |  | **5a** | 47 | $^{1}$HNMR | $\delta$ 5.8 (1H), 4.4 (2H, td), 2.4 (2H, td), 2.0 (3H, s) |
| | | | | $^{13}$CNMR | $\delta$ 157, 117, 67, 54, 29, 24 |
| |  | **5b** | 52 | $^{1}$HNMR | $\delta$ 5.7 (1H, s), 4.4 (2H, td), 2.4 (2H, t) 2.2 (2H, t) 1.5 (2H, m) 1.3 (2H, m) 0.9 (3H, t) |
| | | | | $^{13}$CNMR | $\delta$ 165, 162, 116, 66, 36, 29, 28, 22, 13 |
| |  | **5c** | 50 | $^{1}$HNMR | $\delta$ 5.8 (1H, s) 4.4 (2H, td), 2.5 (1H, m), 2.4 (2H, t), 1.2 (3H, d), 1.1 (3H, d) |
| | | | | $^{13}$CNMR | $\delta$ 168, 166, 114, 67, 34, 26, 20 |
| |  | **5d** | 54 | $^{1}$HNMR | $\delta$ 6.1 (1H, s), 4.4 (2H, t), 4.1 (2H, s), 3.5 (2H, q), 2.4 (2H, t), 1.3 (3H, m) |
| | | | | $^{13}$CNMR | $\delta$ 164, 159, 115, 95, 71, 66, 25, 15 |
| |  | **5g** | 48 | $^{1}$HNMR | $\delta$ 7.0 (1H, m), 6.0 (1H, m), 4.4 (2H, t), 2.3 (2H, m) |
| | | | | $^{13}$CNMR | $\delta$ 164, 146, 122, 67, 25 |

## EXPERIMENTAL

### One-Pot Synthesis of 2-Ethoxy-5,6-dihydro-2H-pyran (2)

3,4-Dihydro-2H-pyran (45.6 mL, 0.500 mol) was added to a three-necked flask (1 L) containing absolute ethanol (400 mL). The solution was cooled to 0°C, and N-bromo succinimide (89.0 g, 0.50 mol) added over 3 h. The resulting faint yellow solution was stirred for an additional 30 min at 0°C. Potassium hydroxide flakes (125 g, 2.0 mol) were added, and the solution was stirred as it warmed to room temperature. The solution was then refluxed until none of the initial bromoethoxy addition product could be detected by GC-MS (10 h). The reaction mixture was filtered on a sintered-glass funnel, extracted with diethyl ether (500 mL), and washed with water (3 × 500 mL). The dried (anhydrous sodium sulfate) solution was filtered and evaporated, and the 2-ethoxy-5,6-dihydro-2H-pyran was distilled (**2**, 152–155°C, atm, 33.3 g, 52% yield).

### Synthesis of 4-(Phenylthio)-3,4-dihydro-2H-pyran (3)

To a solution of 2-ethoxy-5,6-dihydro-2H-pyran (**2**, 10 g, 0.078 mol) in toluene (500 mL, −80°C, $N_2$ atmosphere), $Bu_2Sn(SPh)_2$ in toluene (24.1 mL, 1.62 M, 0.039 mol) was added. $BF_3 \cdot OEt_2$ (34.6 mL, 0.273 mol) was added rapidly, and the solution was allowed to stir (−80°C, 2 h). Pyridine (22.1 mL, 0.273 mol) and NaOH (1 M, 50 mL, 0.10 mol) were added, and the reaction mixture warmed to room temperature slowly over 3 h. The solution was filtered on a sintered-glass funnel and then washed with 1 M NaOH (3 × 300 mL). The organic layer was dried with anhydrous $Na_2SO_4$, and the solvent was removed in vacuo (98% yield). The product was distilled (90°C, 3 mm Hg) to yield 4-(phenylthio)-3,4-dihydro-2H-pyran (**3**, 12.6 g, 84% yield).

### Addition of Electrophiles to 4-Lithio-4-thiophenyl Pyran: Preparation of 4-Methyl-4-thiophenyl Pyran (4a)

4-(Phenylthio)-3,4-dihydro-2H-pyran 3 (1.0 g, 0.0052 mol) was added to anhydrous THF (25 mL) and HMPA (5 mL) at −80°C under an atmosphere of $N_2$. *t*-BuLi (3.37 mL, 1.7 M in hexane, 0.057 mol) was added dropwise over 1 h. The solution turned dark and was allowed to stir for an additional 30 min at −80 °C. When methyl iodide (0.35 mL, 0.057 mol) was added slowly, the solution turned light yellow. The reaction mixture was then allowed to warm to room temperature over 1 h, extracted with ether (2 × 25 mL), and washed several times with water. The organic layer was dried with anhydrous $Na_2SO_4$, and the solvent was removed in vacuo (92%

yield). The product was purified by column chromatography on silica (Fisher, 60–200 mesh, 85% petroleum ether–15% $CH_2Cl_2$) to yield 4-methyl-4-(phenylthio)-3-4-dihydro-2H-pyran (**4a**, 0.94 g, 88% yield).

### Oxidation and Elimination to Lactone (5a, Anhydromevalonolactone)

4-Methyl-4-(phenylthio)-3,4-dihydro-2H-pyran **4a** (1 g, 0.0049 mol) was added to methanol (25 mL). The solution was cooled to 0°C, and $HClO_4$ (70%, 0.25 mL, 0.0029 mol), was introduced. Vanadium pentoxide (0.089 g, 0.0005 mol) was added to a 0°C hydrogen peroxide solution (35% in water, 1.61 mL, 0.0196 mol) and stirred until the $V_2O_5$ dissolved and produced a red solution. The $V_2O_5$/hydrogen peroxide solution was added dropwise to the reaction mixture containing the pyran. Stirring was maintained at ~5°C until no starting material was lift, as monitored by thin-layer chromatography (TLC). The solution was extracted with ethyl acetate (2 × 25 mL) and washed with saturated sodium bicarbonate. The organic layer was dried, and the solvent was removed in vacuo (**5a**, 0.26 g, 47% yield).

All new compounds (**3, 4a–f**, and **5c,d**) exhibited high resolution mass spectra (MAT95, Mass Spectral Services, Department of Chemistry, UMTC) from samples of >90% purity by HPLC. All mass spectra were consistent (±0.0005 amu) with the molecular weight of the proposed structures. The NMR spectrum of **5 g** was identical to one obtained from a commercially available sample (Sigma-Aldrich), and the reported values for **5a** and **5b** match those found in the literature.[3,5]

## RESULTS AND DISCUSSION

### 4-(Thiophenyl)-3,4-dihydro-2H-pyran

Dithiophenyldibutyl stannane was produced from dibutyl tin oxide[6] and used directly as a solution in toluene. The tin reagent was stable over several weeks but reacted readily under the acidic conditions used for addition to the allylic acetal. Using a rapid introduction of boron trifluoride etherate (3.5 equiv; −80°C) nearly eliminated the production of unwanted by-products. The yield and purity of the addition products were improved when pyridine and sodium hydroxide were added to the cold (−80°C) reaction mixture before it was allowed to come slowly to room temperature. Removal of the fine precipitate of tin oxide was most effective if both the organic and aqueous layer were filtered. A further filtration of tin oxide from the organic layer may be necessary after additional washes with aqueous sodium hydroxide. A final distillation of the product was necessary to obtain material of suitable purity for anion generation.

### Anion Generation and Subsequent Addition

Considerable effort at experimental optimization of the reaction conditions for anion generation and subsequent addition resulted in the recommended use of a THF/hexane solution of *t*-butyllithium in the presence of HMPA. Electrophile reactivity followed generally predictable patterns, with methyl iodide reacting in a few minutes and n-butyl bromide, chloromethylethyl ether, propylene oxide, and 2-bromopropane reacting more slowly but completely. Benzyl bromide, benzaldehyde, and styrene oxide reactions were slow (styrene oxide) or generated considerable by-products. Although an addition product was observed with acetaldehyde, no addition was observed with 3-pentanone or cyclohexanone, presumably because the rate of addition is slower than the removal of the proton $\alpha$ to the ketone carbonyl.

Purification of the addition products can be effectively accomplished by column chromatography on silica (Fisher, 60–200 mesh, 85% petroleum ether–15% methylene chloride). Under these conditions, the aldehyde and epoxide addition products were transformed to the bicyclic acetals. A deactivated alumina column (Fisher, 60–325 mesh, activity grade II) proved effective (15% petroleum ether–85% methylene chloride) in avoiding cyclization.

### Conversion to the Unsaturated γ-Lactone

Of the variety of methods that were evaluated for the generation of the desired unsaturated lactones, the most satisfying protocol used hydrolytic conditions (aqueous perchloric acid) in the presence of vanadium pentoxide and hydrogen peroxide. Purification of the products could be accomplished by distillation, flash chromatography, or preparative-layer chromatography on silica (E.M. Reagents, Kieselgel 60 –Preparative 254/366, short UV visualization of the unsaturated lactone).

## CONCLUSION

A set of experimental protocols has now resulted in an attractive process for the generation of $\beta$-substituted $\alpha,\beta$-unsaturated $\delta$-valero lactones with varying functionality at the $\beta$-position, using DHP as an inexpensive synthetic template.

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