The synthesis of some unsaturated 4-substituted-γ-lactones

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The synthesis of conjugated and nonconjugated unsaturated 4-substituted lactones of type 1 and 2 are described. The type 1 lactone was prepared by a two step procedure employing Bredereck's reagent. The type 2 lactone was synthesised by combining the Claisen-Ireland rearrangement and selenolactonisation.

Keywords: unsaturated lactones, synthesis.

Unsaturated γ-lactones are incorporated in the structure of many natural products which show a wide range of pharmacological activities.\textsuperscript{1} On the other hand, unsaturated γ-lactones are also important synths whose reactivity has been investigated.\textsuperscript{2,3a}

As a part of our ongoing interest in the synthesis of some lactonic natural products, we developed the procedure, based on the Suzuki coupling reaction, for the preparation of 4-substituted-α,β-unsaturated lactones. This methodology has been employed in the synthesis of (R)-(-)-isoseridine.\textsuperscript{3b}

Our continuing interest in this area resulted from the requirement for the synthesis of two different 4-substituted unsaturated lactones of type 1 and 2. Relatively simple procedures for their preparation have been developed and some of these results will be discussed in this paper.

The synthesis of type 1 lactone started from the easily available 3 prepared in several steps from dihydroxyacetone.\textsuperscript{4} The protection of the hydroxy group was performed under standard conditions using tert-butyl(dimethyl)chlorosilane (TBDMSCl)/NE\textsubscript{3} in DMF as solvent to afford 4 in 90\% yield (Scheme 1). For the introduction of the double bond into the lactone C5 position, tert-\textit{butoxy} bis(dimethylamino) methane (Bredereck's reagent) was used.\textsuperscript{5} This reagent, which is easily made,\textsuperscript{5b} reacted with the activated methylene group of the lactone 4. Heating Bredereck's reagent and this lactone at 60 °C without solvent produced 5 in 70\% yield. The enamine moiety in 5 was transformed in moderate yield to the exomethylene double bond by reduction with NaCNBH\textsubscript{3} under acidic
conditions. The intermediate 6 was not observed but obviously the reduction of the double bond was followed by the in situ acid catalysed elimination of dimethylamine to afford 7 [(1)R=O-TBDMS-hydroxymethyl]. The enaminic moiety of the lactone 5 is stable enough to allow other transformations in the molecule prior to its further transformations. In some cases this could be very useful since the conjugated double bonds in 7 are expected to be more reactive than in 5. The stability of the conjugated enaminic moiety was demonstrated by deprotection of 5 under standard conditions, tetrabutylammonium fluoride (TBAF)/THF, followed by reaction of the product with CBr₄/PPh₃ to afford the lactonic bromide 9 in 62% overall yield.

![Chemical structures](image)

We showed earlier that the use of Bredereck’s reagent under the described conditions for the introduction of the γ-double bond into the lactone ring was efficient in case of compound 10 as well, Scheme 2.³ The two step procedure afforded lactone 12 in 58% overall yield. These results indicate the possible general applicability of the above reagent for the introduction of the double bond in conjugated lactones.

![Scheme 1](image)
For the synthesis of 4-substituted nonconjugated unsaturated lactones of the type 2, Bredereck's reagent can not be used since it reacts with the activated methylene group leading eventually to conjugation. The potentially useful methodology is presented in Scheme 3.

The acetate 15, prepared by the reaction of aldehyde 13 and Wittig reagent 14, was submitted to the Claisen-Ireland rearrangement under modified conditions to afford ester 16 in 74% yield, accompanied by small amount of amide 17. Hydrolysis of the ester functionality under basic conditions afforded the acid 18. Initially, this acid was submitted to cyclisation in the presence of Pd(II) but unfortunately the expected product 19 was isolated together with two byproducts 12 and 20 in 70% yield.
A two-step procedure employing PhSeBr proved to be more efficient. The cyclisation of the acid 18 in the presence of PhSeBr/NEt3 at room temperature produced the selenolactone 21 in 89% yield (Scheme 3). The oxidation of 21 followed by elimination afforded the unsaturated lactone 19 \( (19) \) \( R=2-(1,3\text{-dioxolane-2-y}) \)ethyl \( (2) \) in 82% yield. The use of anhydrous MgSO4 in the elimination step is important since it is known that primary selenoxides undergo the elimination at slower rate on addition of water.

We have demonstrated possible synthetic routes for the preparation of some 4-substituted either conjugated or nonconjugated \( \gamma \)-lactones. The two-step procedure using Bredereck's reagent is the method of choice for the synthesis of unsaturated conjugated lactones of type 1, e.g., \( 7 \). On the other hand, unsaturated nonconjugated lactones of type 2, e.g., \( 19 \), could be prepared employing selenocyclisation of the appropriate acid, easily available via a Claisen-Ireland rearrangement. These lactones could be useful syntheses in the synthesis of some lactone natural products. Currently, the dienophilic and the dipolarophilic reactivity of the \( 7 \) and \( 19 \) are being investigated and these results will be reported in due course.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Mass spectral data were recorded using a VG-AutoSpec spectrometer operating at 70 eV. Nuclear magnetic resonance spectra were recorded at 300 MHz using a General Electric QE300 instrument. Flash column chromatography employed silica gel 60 (230–400 mesh).

5-\( (\text{O-tert-Butyldimethylsilyl)hydroxymethyl})-2(5H)furanone \( (4) \)

tert-Butyldimethylchlorosilane (0.2 g, 1.3 mmol) was added at 0 \( ^\circ \)C to a solution of lactone 3 and DMF (3 ml) followed by the addition of triethylamine (0.15 g, 1.4 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solvent was then evaporated under reduced pressure and dichloromethane added. The mixture was washed with water, dried (MgSO4), the solvent evaporated under reduced pressure and the residue purified by flash chromatography (SiO2; 4:1 v/v petroleum ether-ethyl acetate) to afford the product (0.27 g, 90%) as a colourless oil which solidified upon standing, m.p. 31–32 \( ^\circ \)C. Found: C, 57.65; H, 9.2; C11H20O2Si requires: C, 57.9; H, 8.8%. \( \delta \) (H): 0.99 (s, 6H, SiMe2), 0.90 (s, 3H, t-Bu), 4.56 (s, 2H, TBDMOSOCH2), 4.80 (s, 2H, ring CH2) and 5.97 (s, 1H, =CH). Msr(C): 228 (M+ 4), 171 (71), 143 (45), 113 (66), 75 (94), 59 (23) and 55 (100).

4-\( (\text{O-tert-Butyldimethylsilyl)hydroxymethyl})-5-dimethylaminomethylene-2(5H)furanone \( (5) \)

The lactone 4 (0.19 g, 0.83 mmol) and bis(dimethylamino)-tert-butoxymethane\(^{5b}\) (0.15 g, 0.92 mmol) were heated under nitrogen atmosphere at 60 \( ^\circ \)C (oil bath temperature) for 3–4 h. The mixture
was dissolved in ether and after the addition of activated charcoal boiled under reflux for 10 min.,
filtered and the solvent evaporated under reduced pressure to afford the product (0.17, 70%) as yellow prisms (petroleum ether–ether), m.p. 107–109 °C. Found: C.59.55; H.8.7; N5.25; C14H12N2O2Si requires: C.59.35; H.8.8; N.4.95%. δ(1H): 0.09 (s, 6H, SiMe3), 0.91 (s, 9H, t-Bu), 3.15 (s, 6H, NMe2),
4.61 (s, 2H, TDBDMSCH2), 5.47 (s, 1H, –CHNMMe2) and 6.21 (s, 1H, –CHCOO). m/z(%): 283 (M+,
5), 149 (8), 75 (100), 57 (8) and 45 (13).
4-[(O-tert-Butyldimethylsilyl)hydroxymethyl]-5-methylene-2(5H)furanone (7)
Sodium cyanoborohydride (0.006 g, 0.09 mmol) was added to a solution of lactone 5 (0.04 g,
0.14 mmol) in acetonitrile (3 ml) followed by the addition of acetic acid (0.2 ml). The mixture was
stirred at room temperature for 1 h, the solution evaporated under reduced pressure and the residue
carefully neutralised by adding 10% aqueous NaHCO3 solution. The resulting mixture was extracted
(ether), the extract dried (MgSO4), the solution evaporated under reduced pressure and the residue
purified by thin layer chromatography (SiO2, 7:3 v/v petroleum ether–ether–acetone) to afford the
product (0.015 g, 46%) as a colourless oil. Found: C.59.75; H.8.25; C12H2O2Si requires: C.60.00; H.8.35%. δ(1H): 0.09 (s, 6H, SiMe3), 0.91 (s, 9H, t-Bu), 4.61 (s, 2H, TDBDMSCH2), 4.82 and 5.15
(2x, 2xH, –CH3) and 6.21 (s, 1H, –CHCOO). m/z(%): 225 (M+–CH3, 3), 183 (55), 155 (16), 113
(100), 99 (8), 83 (10), 75 (58) and 57 (31).
4-Hydroxymethyl-5-dimethylaminomethylene-2(5H)furanone (8)
A mixture of lactone 5 (0.3 g, 1.1 mmol) and tetrabutlammonium fluoride (1.3 ml, 1M in THF,
1.3 mmol) in THF (6 ml) was stirred at room temperature for 1 h. The solution was then evaporated
under reduced pressure and the residue purified by flash chromatography (SiO2, ethyl acetate) to afford the
product (0.16 g, 88%) as yellow needles (ether–dichloromethane) m.p. 101–102 °C. Found:
C.56.55; H.6.5; N8.15; CsH11NO requires: C.56.80; H.6.51; N.8.28%. δ(1H): 3.18 (s, 6H, NMe2),
4.59 (s, 2H, OCH2), 5.47 (s, 1H, –CHN) and 6.26 (s, 1H, –CHCOO). M/z(%): 169 (M+, 72), 149
(25), 82 (31), 67 (10) and 57 (53).
4-Bromomethyl-5-dimethylaminomethylene-2(5H)furanone (9)
Triphenylphosphine (0.24 g, 0.9 mmol) in dichloromethane (2 ml) was added dropwise to a solution
of alcohol 18 (0.14 g, 0.83 mmol) and carbon tetrabromide (0.3 g, 0.9 mmol) in dichloromethane (10 ml)
at 0°C. The mixture was allowed to warm to room temperature and stirred until t.l.c. monitoring indicated the
absence of starting material. The solution was then evaporated under reduced pressure and the residue
purified by column chromatography (Al2O3, ethyl acetate) to afford a mixture of triphenylphosphine oxide and
the product. The triphenylphosphine oxide was separated by crystallisation from ethyl acetate. Evaporation of
the solvent under reduced pressure afforded the product (0.13 g, 70%) as a yellow oil. δ(1H): 3.18 (s, 6H,
NMe2), 4.21 (s, 2H, BrCH2), 5.62 (s, 1H, –CHN) and 6.13 (s, 1H, –CHCOO). M/z(%): 231 (M+–I, 17),
152 (100), 124 (22), 96 (35), 81 (15), 67 (10) and 57 (19).
O-Acetyl-5-(1,3-dioxolan-2-yl)-2-pentenol (15)
Potassium tert-butoxide (23 ml 1 M, 23 mmol) was added dropwise to a stirred mixture of the
appropriate phosphonium bromide 19a (10.7 g, 23 mmol) and THF (60 ml) at room temperature.
Stirring was continued for a further 45 min and the aldehyde 13b (4.2 g, 23 mmol) in THF (10 ml) was
added dropwise. The mixture was stirred for a further 3 h at room temperature, poured into water,
extracted (ether), the extract dried (MgSO4) and the solvent evaporated under reduced pressure. The solid
residue was triturated several times with petroleum ether and the petroleum ether extract was then
evaporated under reduced pressure. The residual oil was purified by distillation to afford the product (2.6 g,
56%), as a mixture of the cis and trans isomers, b.p. (Kugelrohr temp.) 105–110 °C/0.2mmHg. Found: C.60.2; H.8.15; C14H19O4 requires: C.60.0; H.8.0%. δ(1H): 1.74 (m, 2H, CH2CH=CH–), 2.06 (s, 3H, CH3), 2.29 (q, 2H, J=7.5Hz, CH2CH=CH–), 3.91 (m, 4H, OCH2CH2O), 4.64 (q, 2H, J=6.4Hz, CH2OOC), 4.87 (s, 1H, J=6.4Hz, OCHRO) and 5.65 (m, 2H, CH=CH). M/z (%):
199 (M+–I, 1), 141 (6), 112 (6), 99 (28), 86 (13), 79 (6), 73 (100), and 67 (12).
Methyl 3-[(1,3-dioxolan-2-yl)ethyl]-4-pentenoate (16)

The ester 15 (0.89 g, 4.5 mmol) in THF (3 ml) was added dropwise to a stirred solution of LDA (5.7 mmol) prepared from diisopropyl amine (0.58 g, 5.7 mmol) and n-BuLi (3.6 ml 1.6 M in hexane), in THF (10 ml) at -78 °C. The mixture was stirred at -78 °C for 1 h and diethyl chlorophosphate (1.5 g, 9.0 mmol) in HMPA (4 g, 22.5 mmol) was added dropwise. The mixture was then slowly warmed to -15 °C and stirred at that temperature until t.l.c. monitoring indicated the absence of the starting material. MeOH (2.0 g, 62.5 mmol) was added followed by triethylamine (2.7 g, 26.7 mmol) and stirring was continued for 12 h at room temperature and then for 1 h at 60 °C. Water was then added, the organic layer separated and the water layer extracted (ether). The combined organic layers were dried (MgSO₄), the solvent evaporated under reduced pressure and the residue purified by flash chromatography (SiO₂, 4:1 v/v petroleum ether-ether) to afford the product 16 (0.7 g, 74%), as a pale yellow oil together with by product 17 (0.06 g, 5%) obtained as a pale yellow oil. The product contained 5-7% of the ester 15 which could not be separated by flash chromatography, therefore it was used in next step without further purification. χ²(H): 1.38–1.78 (m, 4H, CH₂CH₂), 2.35 (m, 2H, CH₂COO), 2.55 (m, 1H, CH₂CH(RCH₂)₃), 3.65 (s, 3H, COOMe), 3.82–3.98 (m, 4H, OCH₂CH₂O), 4.84 (t, 1H, J 4.2 Hz, OCH₂O), 5.05 (m, 2H, -CH₂) and 5.61 (m, 1H, -CHR). M/z (%): 213 (M−1, 2), 183 (2), 141 (3), 121 (3), 99 (18), 73 (100), 55 (5) and 45 (23).

N,N-Diisopropyl-3-[(1,3-dioxolan-2-yl)ethyl]-4-pentenamide (17)

Found: C 67.75; H 10.2; N 4.8; C₁₀H₁₄NO₂ requires: C 67.85; H 10.25; N 4.95%.
χ²(H): 1.18 and 1.36 (2x, 2x6H), J 6.9 and J 6.9 Hz, N(iso-Pr), 1.66 (m, 4H, CH₂CH₂), 2.29 (m, 2H, CH₂CON), 2.61 (m, 1H, CH₂CH(RCH₂)₃), 3.46 (m, 2H, CHNCO), 3.88 (m, 4H, OCH₂CH₂O), 4.85 (t, 1H, J 4.5 Hz, OCH₂O), 5.06 (2H, -CH₂) and 5.65 (m, 1H, CH₂=CH₂). M/z (%): 282 (M−1, 2), 240 (5), 210 (7), 182 (70), 168 (22), 128 (20), 100 (29), 86 (100), 73 (43), 58 (26) and 43 (46).

3-[(1,3-Dioxolan-2-yl)ethyl]-4-pentenoic acid (18)

A mixture of ester 16 (0.209 g, 1.35 mmol) and aqueous LiOH·H₂O (0.085 g, 2.1 mmol in 2.1 ml H₂O) in THF (3 ml) was stirred at room temperature of 12 h. The mixture was acidified (pH 1–2) with 5% aqueous HCI and then extracted (dichloromethane), the extract dried (MgSO₄), the solvent evaporated under reduced pressure and the residue purified by flash chromatography (SiO₂, 1:1 v/v petroleum ether-ether) to afford the product (0.24 g, 90%), as a colourless oil. Found: C 60.05; H 8.80; C₁₀H₁₅NO₂ requires: C 60.0; H 8.0%.
χ²(H): 1.40–1.78 (m, 4H, CH₂CH₂), 2.30–2.57 (m, 1H and 2H, CH₂CH(RCH₂)₃ and CH₂COO), 3.82–3.99 (m, 4H, OCH₂CH₂O), 4.86 (t, 1H, J 4.4 Hz, OCH₂O), 5.08 (m, 2H, -CH₂) and 5.62 (m, 1H, CH₂=CH₂). M/z (%): 199 (M−1, 7), 141 (7), 99 (55), 80 (21), 73 (86), 67 (17), 55 (25) and 45 (100).

4-[(1,3-Dioxolan-2-yl)ethyl]-5-phenylselenymethyl-2(3H)dihydrofuranone (21)

Triethylamine (0.056 g, 0.55 mmol) was added to a solution of the acid 18 (0.1 g, 0.5 mmol) and dichloromethane (5 ml). The mixture was stirred 20 min at room temperature and cooled at -78 °C. PhSeBr (0.12 g, 0.5 mmol) was then added in one portion, the mixture stirred for 30 min at -78 °C, allowed to warm to room temperature and stirred for a further 30 min. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (SiO₂, 1:4 v/v petroleum ether-ether) to afford the product (0.16 g, 89%) as a pale yellow oil. Found: C 53.95; H 5.4; C₁₆H₂₀O₄Se requires: C 54.1; H 5.6%. χ²(H): 1.59 (m, 4H, CH₂CH₃), 2.27 and 2.78 (2x, 2xH), J 17.3 and 7.4 Hz and J 17.3 and 8.4 Hz, CH₂COO), 2.38 (m, 1H, CH₂=CH₂CH₂), 3.16 (m, 2H, CH₂=Se), 3.82–3.96 (m, 4H, OCH₂CH₂O), 4.33 (m, 1H, PhSeCH₂CH₂), 4.82 (t, 1H, J 4.1 Hz, OCH₂O), 7.28 (m, 3H, ArH) and 7.55 (m, 2H, ArH). M/z (%): 356 (M⁺, 29), 199 (7), 185 (16), 157 (15), 137 (19), 99 (21), 91 (23), 73 (100), 55 (20) and 45 (32).

4-[(1,3-Dioxolan-2-yl)ethyl]-5-methylene-2(3H)dihydrofuranone (19)

Hydrogen peroxide (0.8 ml of 30% solution) was added to a stirred solution of selenide 21 (1.25 g, 3.5 mmol) in THF (40 ml) at 0 °C followed by the addition of excess MgSO₄ and triethylamine
(0.43 g, 4.2 mmol). The mixture was warmed to room temperature and then stirred for 12 h. The inorganic salts were filtered off and washed with dry THF. The filtrate was refluxed for 4 h, the solvent evaporated under reduced pressure and the residue purified by flash chromatography (SiO<sub>2</sub>; 1:4 v/v petroleum ether-ether) to afford the product (0.54 g, 82%) as a colourless oil. Found: C 60.7; H 7.25; C<sub>16</sub>H<sub>14</sub>O<sub>4</sub> requires: C 60.6; H 7.07%. α(H): 1.59–1.85 (m, 4H, CH<sub>2</sub>), 2.36 and 2.81 (2xd, 2xH, 6H, J 8.0 and 6.4Hz and J 7.9 and 9.5Hz, CH<sub>2</sub>COO), 3.11 (br m, 1H, CH<sub>2</sub>CHRCH<sub>2</sub>), 3.84–4.02 (m, 4H, OCH<sub>2</sub>CH<sub>2</sub>), 4.34 and 4.77 (2xd, 2xH, J 8.0 and J 9.5Hz, –CH<sub>2</sub>) and 4.87 (t, 1H, J 4.1Hz, OCH<sub>2</sub>), M/z (%): 197 (M<sup>+</sup>–1, 6), 160 (22), 149 (25), 127 (18), 111 (29), 97 (46), 85 (57), 71 (76), 57 (100) and 43 (63).

ИЗВОД

СИНТЕЗА НЕКИХ НЕЗАСИЋЕНИХ 4-СУПСТИТУИСАНИХ-9-ЛАКТОНА

СУРЕН ХУСИНЕЦ<sup>4</sup> и ВЛАДИМИР САВИЋ<sup>5</sup>

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Развијен су релативно једноставни синтетски путеви за добијање конјугованих и неконјугованих 9-лактона који имају структуре типа 1 и 2. Лактон типа 1 је синтетисан увршењем епоксициклне диоксыдне целе уз коришћење Bredereck-овог регенеза, док је лактон типа 2 добијен примењом Claisen-Ireland-овог премештања и селенолактонизације.

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