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

SUREN HUSINEC[a] and VLADIMIR SAVIĆ[b]

[a]*Institute of Chemistry, Technology and Metallurgy, Center for Chemistry, Njegoševa 12, P.O.Box 815, YU-11000 Belgrade and* [b]*Faculty of Pharmacy, Department of Organic Chemistry, Vojvode Stepe 450, YU-11000 Belgrade, Yugoslavia*

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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.

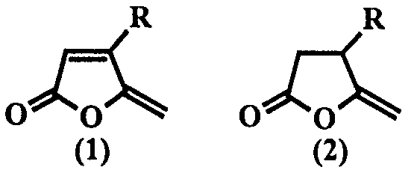
Unsaturated γ-lactones are incorporated in the structure of many natural products which show a wide range of pharmacological ativities.[1] On the other hand, unsaturated γ-lactones are also important synthons whose reactivity has been investigated.[2,3a]

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.[3b]

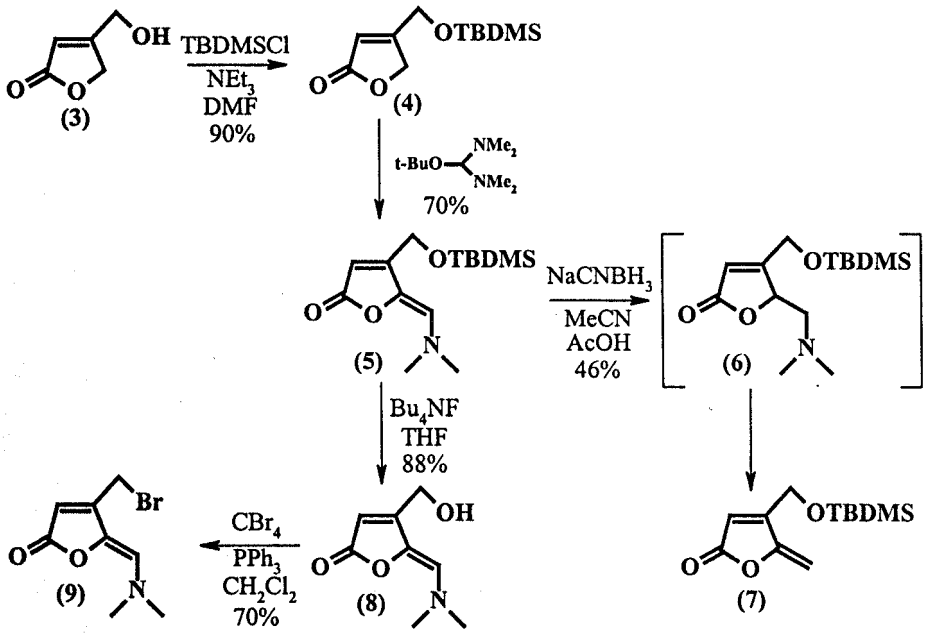
Our continuing interest in this area resulted from the requirement for the synthesis of two different 4-substituted unsaturated lactones of type **1** and **2.** Relatively simple procedures for their preparation have been developed and some of these results will be discussed in this paper.

The synthesis of type **1** lactone stared from the easily available **3** prepared in several steps from dihydroxy acetone.[4] The protection of the hydroxy group was performed under standard conditions using *tert*-butyldimethylchlorosilane (TBDMSCl)/NEt_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*-butoxy bis(dimethylamino)methane (Bredereck's reagent) was used.[5] This reagent, which is easily made,[5b] reacted with the activated methylene group of the lactone **4**. Heating Bredereck's reagent and this lactone at 60 ºC without solvent produced **5** in 70% yield. The enamino moiety in **5** was transformed in moderate yield to the exomethylene double bond by reduction with $NaCNBH_3$ under acidic

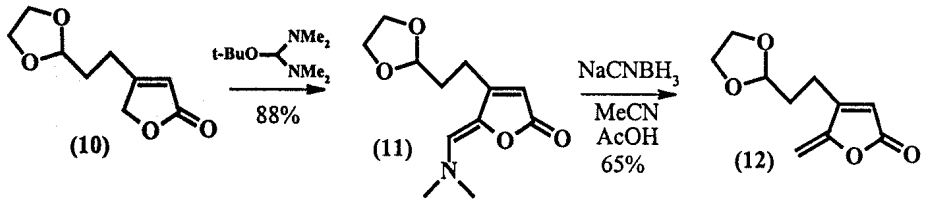
conditions. The intermediate **6** was not observed but obviously the reduction of the double bond was followed by the *in situ* acid catalysed elimination of dimethylamine to afford **7** [(**1**)R=O-TBDMS-hydroxymethyl]. The enamino moiety of the lactone **5** is stable enough to allow other transformations 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 enamino moiety was demonstrated by deprotection of **5** under standard conditions, tetrabutylammonium fluoride (TBAF)/THF, followed by reaction of the product with CBr_4/PPh_3 to afford the lactonic bromide **9** in 62% overall yield.



We showed earlier that the use of Bredereck's reagent under the described conditions for the introduction of the α,β-double bond into the lactone ring was efficient in case of compound **10** as well, Scheme 2.[3a] 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.

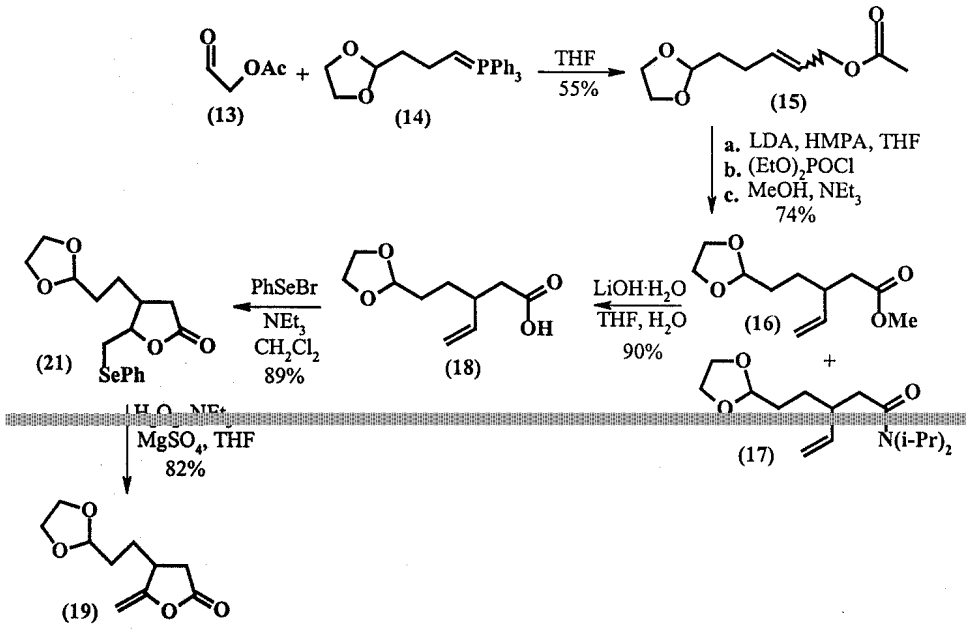


Scheme 1.



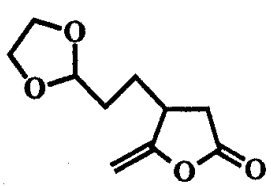
Scheme 2.

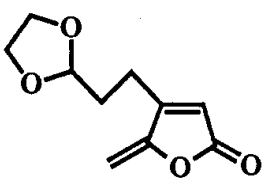
For the synthesis of 4-substituted nonconjugated unsaturated lactones of the type **2** Bredereck's reagent can not be used since it reacts with the activated methylene group leading eventually to conjugation. The potentially useful methodology is presented in Scheme 3.



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[6] 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)[7] but unfortunately the expected product **19** was isolated together with two byproducts **12** and **20** in 70% yield.


(19)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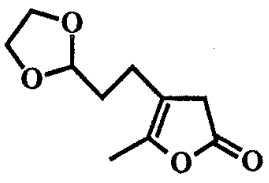
(20)

A two step procedure employing PhSeBr proved to be more efficient. The cyclisation of the acid **18** in the presence of PhSeBr/NEt_3 at room temperature produced the selenolactone **21** in 89% yield (Scheme 3). The oxidation of **21** followed by elimination afforded the unsaturated lactone **19** [(**2**) R=2-(1,3-dioxolan-2-yl)ethyl] in 82% yield. The use of anhydrous $MgSO_4$ in the elimination step is important since it is known that primary selenooxides 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 g-lactones. The two step procedure using Bredereck's reagent is the method of choice for the synthesis of unsaturated conjugated lctones 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 synthones in the synthesis of some lactonic 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 recoreded at 300 MHz using a General Electric QE300 instrument. Flash column chromatography employed silica gel 60 (230–400 mesh).

*5-[(O-tert-Butyldimethylsilyl)hydroxymethyl]-2(5H)furanone (***4***)*

tert-Butyldimethylchlorosilane (0.2 g, 1.3 mmol) was added at 0 °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 12h. The solvent was then evaporated under reduced pressure and dichloromethane added. The mixture was washed with water, dried ($MgSo_4$), the solvent evaporated under reduced pressure and the residue purified by flash chromatography (SiO_2, 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 °C. Found: C,57.65; H,9.2; $C_{11}H_{20}O_3Si$ requires: C,57.9; H,8.8%. d(^{1}H):0.09 (*s*, 6H, $SiMe_2$), 0.90 (*s*, 9H, *t*-Bu), 4.56 (*s*, 2H, $TBDMSOCH_2$), 4.80 (*s*, 2H, ring CH_2) and 5.97 (*s*, 1H, = CH). *M/z*(%): 228 (M^+, 4), 171 (71), 143 (45), 113 (66), 75 (94), 59 (23) and 55 (100).

*4-[(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 °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; $C_{14}H_{25}NO_3Si$ requires: C,59.35; H,8.8; N,4.95%. $\delta(^1H)$: 0.09 (*s*, 6H, $SiMe_2$), 0.91 (*s*, 9H, *t*-Bu), 3.15 (*s*, 6H, NMe_2), 4.61 (*s*, 2H, TBDMSOCH_2), 5.47 (*s*, 1H, = CHNMe_2) 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-(5*H*)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 14 h, the solvent evaporated under reduced pressure and the residue carefully neutralised by adding 10% aqueous $NaHCO_3$ solution. The resulting mixture was extracted (ether), the extract dried ($MgSO_4$), the solvent evaporated under reduced pressure and the residue purified by thin layer chromatography (SiO_2, 7:3 v/v petroleum ether-ethyl acetate) to afford the product (0.015 g, 46%) as a colourless oil. Found: C,59.75; H,8.25; $C_{12}H_{20}O_3Si$ requires: C,60.00; H,8.35%. $\delta(^1H)$: 0.09 (*s*, 6H, $SiMe_2$), 0.91 (*s*, 9H, *t*-Bu), 4.61 (*s*, 2H, TBDMSOCH_2), 4.82 and 5.15 (2x*s*, 2x1H, = CH_2) and 6.21 (*s*, 1H, = CHCOO). *M/z*(%): 225 (M^+–CH_3, 3), 183 (55), 155 (16), 113 (100), 99 (8), 83 (10), 75 (58) and 57 (31).

*4-Hydroxymethyl-5-dimethylaminomethylene-2(5*H*)furanone (***8***)*

A mixture of lactone **5** (0.3 g, 1.1 mmo) and tetrabutylammoniumfluoride (1.3 ml, 1M in THF, 1.3 mmol) in THF (6 ml) was stirred at room temperatutre for 1 h. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (SiO_2, 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; N,8.15; $C_8H_{11}NO_3$ requires: C,56.80; H,6.51; N,8.28%. $\delta(^1H)$: 3.18 (s, 6H, NMe_2), 4.59 (s, 2H, OCH_2), 5.47 (*s*, 1H, = CHN) and 6.26 (*s*, 1H, = CHCOO). *M/z*(%): 169 (M^+, 72), 149 (25), 82 (31), 67 (10) nd 57 (53).

*4-Bromomethyl-5-dimethylaminomethylene-2(5*H*)furanone(***9***)*

Triphenylphosphine (0.24 g, 0.9 mmol) in dichloromethane (2 ml) was added dropwise to a solution of alcohol **8** (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 solvent was then evaporated under reduced pressure and the residue purified by column chromatography (Al_2O_3, ethyl acetate) to afford a mixture of triphenylphosphine oxide and the product. The triphenylphosphine oxide was separated by crystalisation from ethyl acetate. Evaporation of the solvent under reduced pressure afforded the product (0.13 g, 70%) as a yellow oil. $\delta(^1H)$;3.18 (*s*, 6H, NMe_2), 4.21 (*s*, 2H, $BrCH_2$), 5.62 (*s*, 1H, = CHN) and 6.13 (*s*, 1H, = CHCOO). *M/z*(%): 231 (M^+–1, 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 salt[8] (10.7 g, 23 mmol) and THF (60 ml) at room temperature. Stirring was continued for a further 45min and the aldehyde **13**[9] (2.4 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 ($MgSO_4$) 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 distillaiton to aford 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; $C_{10}H_{16}O_4$ requires: C,60.0; H,8.0%. $\delta(^1H)$: 1.74 (*m*, 2H, CH_2CH_2CH=), 2.06 (*s*, 3H, CH_3), 2.29 (*q*, 2H, *J* 7.5Hz, CH_2CH_2CH=), 3.91 (*m*, 4H, OCH_2CH_2O), 4.64 (*d*, 2H, *J* 6.4Hz, CH_2OCO), 4.87 (*t*, 1H, *J* 6.4Hz, OCHRO) and 5.65 (*m*, 2H, CH=CH). *M/z* (%): 199 (M^+–1, 1), 141 (6), 112 (6), 99 (28), 86 (13), 79 (6), 73 (100), and 67 (12).

*Methyl 3-[2-(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 1h 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 ($MgSO_4$), the solvent evaporated under reduced pressure and the residue purified by flash chromatography (SiO_2, 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 witrhout further purification δ(^{1}H): 1.38–1.78 (*m*, 4H, CH_2CH_2), 2.35 (*m*, 2H, CH_2COO), 2.55 (*m*, 1H, CH_2CHRCH_2), 3.65 (*s*, 3H, COOMe), 3.82–3.98 (*m*, 4H, OCH_2CH_2O), 4.84 (*t*, 1H, *J* 4.2Hz, OCHRO), 5.05 (*m*, 2H, = CH_2) 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-[2-(1,3-dioxolan-2-yl)ethyl]-4-pentenamide (***17***)*

Found: C,67.75; H,10.2; N,4.8; $C_{16}H_{29}NO_3$ requires: C,67.85; H,10.25; N,4.95%. δ(^{1}H): 1.18 and 1.36 (3x*d*, 2x6H, *J* 6.9 and *J* 6.9Hz, N(*iso*-Pr_2), 1.66 (*m*, 4H, CH_2CH_2), 2.29 (*m*, 2H, CH_2CON), 2.61 (*m*, 1H, CH_2CHRCH_2), 3.46 (*m*, 2H, CHNCO), 3.88 (*m*, 4H, OCH_2CH_2O), 4.85 (*t*, 1H, *J* 4.5Hz, OCHRO), 5.06 (*m*, 2H, =CH_2) and 5.65 (*m*, 1H, CH_2=C*H*). *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-[2-(1,3-Dioxolan-2-yl)ethyl]-4-pentenoic acid (***18***)*

A mixture of ester **16** (0.209 g, 1.35 mmol) and aqueous LiOH· H_2O (0.085 g, 2.1 mmol in 2.1 ml H_2O) in THF (3 ml) was stirred at room temperature of 12 h. The mixture was acidified (pH 1–2) with 5% aqueous HCl and then extracted (dichloromethane), the extract dried ($MgSO_4$), the solvent evaporated under reduced pressure and the residue purified by flash chromatography (SiO_2, 1:1 v/v petroleum ether-ether) to afford the product (0.24 g, 90%), as a colourless oil. Found: C,60.05; H,8.0; $C_{10}H_{16}O_4$ requires: C,60.0; H,8.0%. δ(^{1}H): 1.40–1.78 (*m*, 4H, CH_2CH_2), 2.30 –2.57 (*m*, 1H and 2H, CH_2CHRCH_2 and CH_2COO), 3.82–3.99 (*m*, 4H, OCH_2CH_2O), 4.86 (*t*, 1H, *J* 4.4Hz, OCHRO), 5.08 (*m*, 2H, =CH_2) and 5.62 (*m*, 1H, CH_2=C*H*). *M/z*(%): 199 (M^+–1, 7), 141 (7), 99 (55), 80 (21), 73 (86), 67 (17), 55 (25) and 45 (100).

*4-[2-(1,3-Dioxolan-2-yl)ethyl]-5-phenylselenylmethyl-2(3*H*)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 (SiO_2, 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; $C_{16}H_{20}O_4Se$ requires: C,54.1; H,5.6%. δ(^{1}H): 1.59 (*m*, 4H, CH_2CH_2), 2.27 and 2.78 (2x*dd*, 2x1H, *J* 17.3 and 7.4Hz and *J* 17.3 and 8.4Hz, CH_2COO), 2.38 (*m*, 1H, CH_2CHRCH_2), 3.16 (*m*, 2H, CH_2Se), 3.82–3.96 (*m*, 4H, OCH_2CH_2O), 4.33 (*m*, 1H, $PhSeCH_2CH$), 4.82 (*t*, 1H, *J* 4.1Hz, OCHRO), 7.28 (*m*, 3H, ArH) and 7.55 (*m*, 2H, ArH). *M/z*(%): 356 (M^+1, 29), 199 (7), 185 (16), 157 (15), 137 (19), 99 (21), 91 (23), 73 (100), 55 (20) and 45 (32).

*4-[2-(1,3-Dioxolan-2-yl)ethyl]-5-methylene-2(3*H*)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 $MgSO_4$ 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_2, 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; $C_{10}H_{14}O_4$ requires: C,60.6; H,7.07%. δ(^{1}H): 1.59–1.85 (*m*, 4H, CH_2CH_2), 2.36 and 2.81 (2x*dd*, 2x1H, *J*18.0 and 6.4Hz and *J*17.9 and 9.5Hz, CH_2COO), 3.11 (*br m*, 1H, CH_2CHRCH_2), 3.84–4.02 (*m*, 4H, OCH_2CH_2O), 4.34 and 4.77 (2x*d*, 2x1H, *J*1.9 and *J*1.9Hz, $=CH_2$) and 4.87 (*t*, 1H, *J*4.1Hz, OCHRO). *M/z*(%): 197 (M^+–1, 6), 160 (22), 149 (25), 127 (18), 111 (29), 97 (46), 85 (57), 71 (76), 57 (100) and 43 (63).

И З В О Д

СИНТЕЗА НЕКИХ НЕЗАСИЋЕНИХ 4-СУПСТИТУИСАНИХ-γ-ЛАКТОНА

СУРЕН ХУСИНЕЦ[а] и ВЛАДИМИР САВИЋ[б]

[а]*Институт за хемију, технологију и металургију, Центар за хемију, Његошева 12, п.пр. 815, 11000 Београд* и [б]*Фармацеутски факултет, Институт за органску хемију, Војводе Степе 450, 11000 Београд*

Развијени су релативно једноставни синтетски путеви за добијање конјугованих и неконјугованих δ-лактона који имају структуре типа **1** и **2**. Лактон типа **1** је синтетисан увођењем егзоцикличне двоструке везе уз коришћење Bredereck-овог реагенса, док је лактон типа **2** добијен применом Claisen-Ireland-овог премештања и селенолактонизације.

(Примљено 16. јула, ревидирано 1. октобра 1999)

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