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Enantiospecific Preparation of the Lactone Fragment of Murisolin◊

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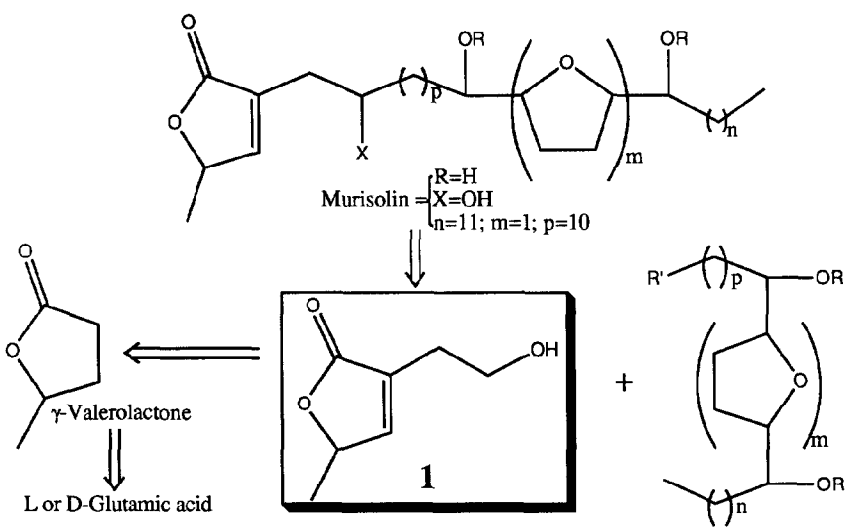
Abstract: *Both enantiomers (R) and (S) of the functionalized unsaturated γ-lactone moiety of the acetogenin murisolin have been enantiospecifically synthezised from L and D-glutamic acid respectively.*

During the course of our study of natural tetrahydrofuran fatty γ-lactones, we were interested in the enantiospecific synthesis of the antibacterial acetogenin murisolin[1] (isolated in this laboratory from *Annona muricata*). This compound possesses six chiral centers, and an interesting unsaturated γ-lactone moiety also present in many other natural products (such as pheromones, ionophores, lignans, etc...). The absolute stereochemistry of the stereogenic centre in the molecule remains unknown, and because this fragment is common to most of the acetogenin compounds[2], we wish to report a convenient procedure which allowed us to obtain the corresponding synthetic intermediate **1** in high yield, as the (R) or (S) forms, with excellent optical purity from L and D- glutamic acid respectively (Scheme I).

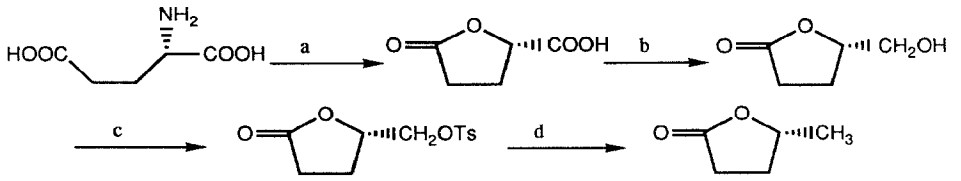
Scheme I



Although the optically pure (R) or (S) forms of γ-valerolactone can be obtained by various methods[3], we used and modified Mori's procedure, as shown in Scheme II, to provide γ-valerolactone in four steps with an overall yield of 38% from the inexpensive starting materials: L and D-glutamic acid. In this procedure is noteworthy the efficient one-pot conversion of a primary tosylate into the corresponding alkane: the un-isolated iodide

intermediate was reduced by tributyltin hydride in the presence of a catalytic amount of AIBN with an excellent yield, and with conservation of the high optical purity of the starting material.

Scheme II

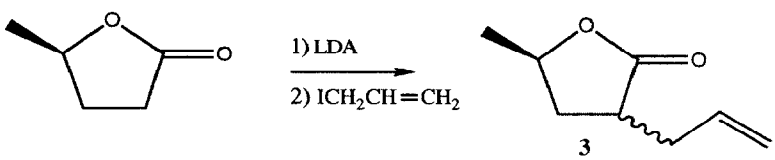


Conditions : a)$NaNO_2$, H^+, 63%; b)$BH_3.SMe_2$,100%, c)TsCl, pyridine 77%; d)NaI, AIBN cat., nBu_3SnH 79%.

Alkylation[4] of γ-valerolactone at the 3-position is known to be sluggish unless a very active electrophile is utilized or the lactone is activated via an electron withdrawing group at the 3-position. The first choice of an α-halo-acetaldehyde-dimethyl acetal, as the alkylating reagent of the preformed enolate of the lactone, gave a mixture of several compounds without significant traces of the desired product. Instead the product of self-condensation of the starting material, **2**, was isolated[10], independent of experimental conditions (time, temperature, concentration, stoechiometry).

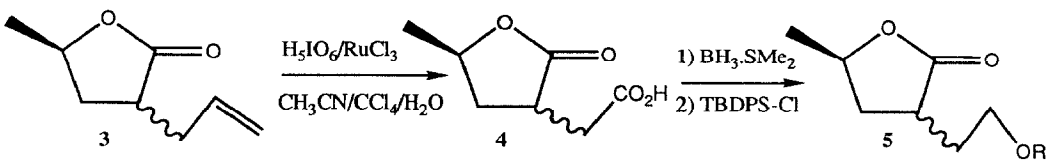
We therefore used allyl iodide[5], a more reactive and easily handled reagent. After enolization and alkylation of (R) or (S) γ-valerolactone, we obtained the alkylated products **3** in 90% overall yield as a cis/trans (25:75) mixture (Scheme III). This ratio could be displaced to 5:95 in favour of the trans isomer by decreasing the temperature of the reaction, but because both diastereoisomers will give the same compound after introduction of the double bond, we used directly the inseparable mixture for the following step.

Scheme III



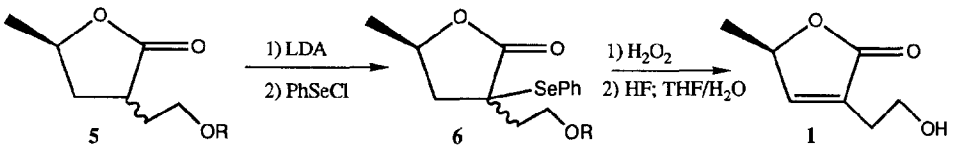
The oxidative cleavage of the double bond was readily achieved in one hour at room temperature with a catalytic amount of $RuCl_3$ in the presence of an excess of periodic acid to give the pure carboxylic acid **4** in quantitative yield[6]. The latter compound **4** was then reduced[7] with $BH_3.SMe_2$, to afford the corresponding alcohol, which was then directly protected as the silylated ether **5** with tert-butyl-diphenyl-chlorosilane[8] (Scheme IV) in 74% yield for the last two steps.

Scheme IV



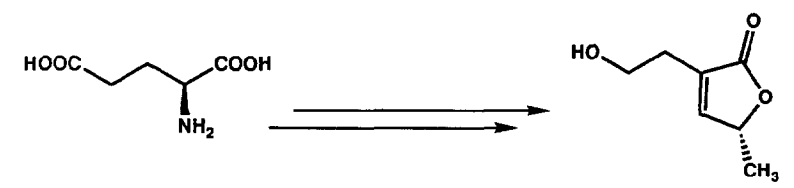
The latter compound **5** was then submitted to a procedure[9] for introducing the double bond. Treatment of **5** with LDA, followed by addition of phenylselenylchloride gave the seleno-derivative **6**. Oxidation in one hour at room temperature by H_2O_2 of the crude seleno-derivative **6** gave the desired α,β-unsaturated γ-lactone in a 71% overall yield for the last two steps[10]. It is noteworthy to remark the exclusive formation of the *endo*-double bond after the elimination step (the isomer corresponding to the formation of the *exo*-double bond could not be detected either by NMR or TLC). Deprotection of the hydroxyl group was achieved with a solution of HF 40% aq. in THF at room temperature to afford the alcohol **1** in quantitative yield[11](Scheme V).

Scheme V

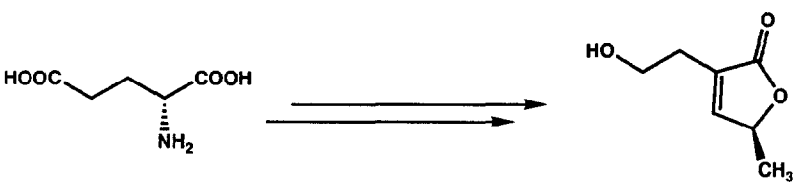


Using this approach, both isomers (R) and (S) of **1** were obtained in high chemical purity and with excellent ee[10,12]: **1**(R) was obtained from L-glutamic acid with an ee=99% and **1**(S) from D-glutamic acid with an ee=99% (Scheme VI).

Scheme VI



L-Glutamic acid (R)-2-(2'-hydroxyethyl)-4-methyl-γ-butyrolactone



D-Glutamic acid (S)-2-(2'-hydroxyethyl)-4-methyl-γ-butyrolactone

Conclusion : In this paper we have demonstrated that (R) or (S)-2-(2'-hydroxyethyl)-4-methyl-γ-butyrolactone **1** can easily be prepared with a high optical purity and good chemical yield from L and D-glutamic acid. These compounds will serve as very versatile intermediates in the synthesis of natural products. The detailed results of the preparation of murisolin from **1** will be reported later in a full paper[13].

References and notes:

◊. Part 8: for part 7 see: Laprévote O.; Roblot F.; Hocquemiller R.; Cavé A.; Charles B.; Tabet J-C. *Phytochemistry*, **1991**, in press.
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10. All new compounds were fully characterized by elemental analysis (C, H), ^{1}H-NMR, ^{13}C-NMR, MS, IR: Data for **2** as an unseparable diastereoisomeric mixture: ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm; 1.33-1.46(m, 6H), 1.66-1.72(m, 1H), 2.23-2.28(m, 1H), 2.40-2.46(m, 1H), 2.93-3.05(m, 2H), 3.33-3.38(m, 1H), 4.56-4.65(m, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ ppm; 20.5, 22.4, 29.6, 31.3, 32.8, 32.9, 73.7, 93.8, 169.3, 172.9; IR (sol. in $CHCl_3$) cm^{-1}: 1730, 1670, 1375, 1330, 1000; MS-ci-CH_4: m/z 183 (MH^++1, 100%); MS-ei-70ev: m/z 182 (M^+, 100%), 167(5), 140(22), 122(32), 110(95), 109(69), 95(37), 83(56), 82(46), 67(27), 55(46), 43(22). Data for **1**(identical for both enantiomers): ^{1}H-NMR (200 MHz, $CDCl_3$, ref. to $CHCl_3$) δ p-pm; 1.38(d, J=6.8Hz, 3H), 2.54(tdd, J=6.00,1.4,1.6 Hz, 2H), 2.61(s,1H), 3.81(t, J=6.8 Hz, 2H), 5.04(qdd, J=6.8,1.4, 1.6 Hz,1H), 7.18(q, J=1.4 Hz,1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ ppm; 18.7, 28.4, 59.9, 78.0, 130.7, 151.6, 174.4; IR (sol. in CCl_4) cm^{-1}: 3400, 1740, 1650, 1370, 1310, 1080, 1020; MS-ei-70ev: m/z 143(MH^++1,14%), 112(37), 97(42), 81(15), 67(51), 53(35), 43(100), 31 (81); UV (Sol. in $CHCl_3$): 248 nm (ε=64) ; **1**(R) from L-glutamic acid: $[\alpha]^{20}$=+56 (c=1.53 , $CHCl_3$), ee=99%; **1**(S) from D-glutamic acid: $[\alpha]^{20}$=-56 (c=1.50 , $CHCl_3$), ee=99%.
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