Pergamon

Tetrahedron, Vol. 53, No. 51, pp. 17335-17342, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10157-0

Strategic Use of Retro Diels-Alder Reaction in the Construction of β-Carboxy-α-Methylene-γ-Lactones. Total Synthesis of Methylenolactocin and Protolichesterinic Acid

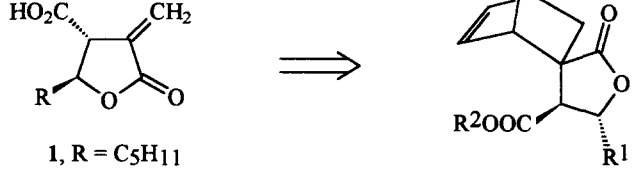
Anjan Ghatak, Subrata Sarkar and Subrata Ghosh*

Department of Organic Chemistry, Indian Association for the Cultivation of Science,
Jadavpur, Calcutta - 700 032 INDIA

Abstract: A facile route for the construction of β-carboxy-α-methylene-γ-lactone unit is described using retro Diels-Alder reaction as the key step. Using this protocol, total synthesis of (±)-methylenolactocin and (±)-protolichesterinic acid has been achieved.

β-Carboxy-α-methylene-γ-lactone is the basic skeleton of a number of biologically active compounds. Of these, methylenolactocin **1** and protolichesterinic acid **2** have elicited considerable interest in recent years. While methylenolactocin, isolated[1] from the culture filtrate of *Penicillium sp*, is an antitumor antibiotic, protolichesterinic acid isolated[2] from the various species of moss *Cetraria*, exhibits antibacterial, antifungal, antitumoral and growth regulating effects. The lactones **1**[3] and **2**[4] have become the subject of intensive synthetic investigation over the years largely due to their biological effects.

Structurally β-carboxy-α-methylene-γ-lactone unit appears to be simple for synthesis. However, the synthesis of lactones **1** and **2** is attended with a number of synthetic challenges. First, the normethylene lactone is susceptible to ring opening as evidenced by the synthetic investigation on the lactone **2** by van Tamelen and Bach.[5] Second, the exo methylene unit present in the lactones **1** and **2** is prone to isomerisation. It appeared to us that the lactone function, if constructed spiro to a ring system as in the structure **3**, would remain locked,



1, R = C_5H_{11}
2, R = $C_{13}H_{27}$

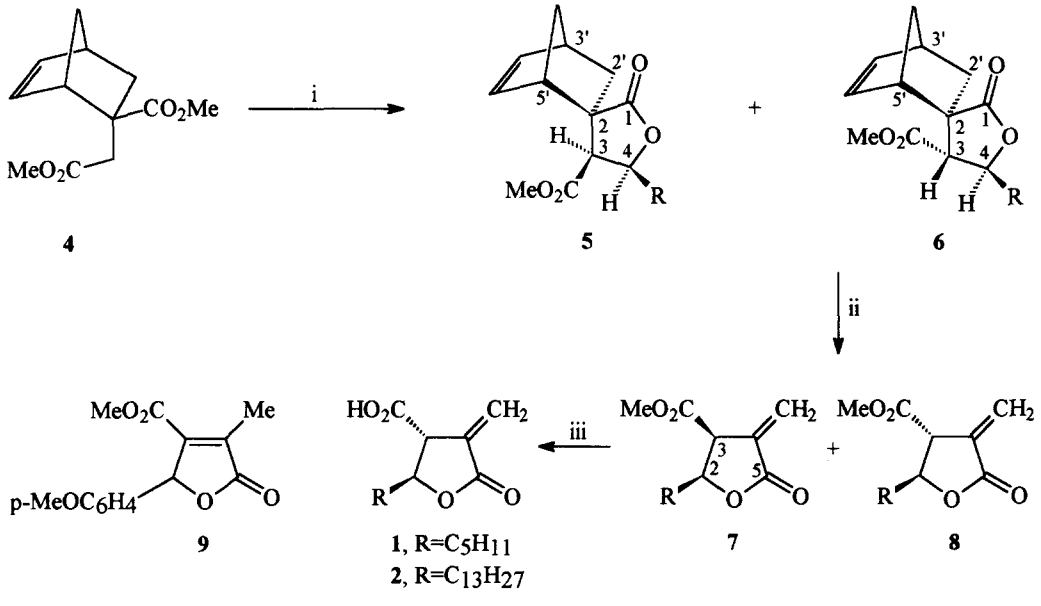
3

thus preventing ring opening. The use of retro Diels-Alder reaction to remove the carbocyclic ring residue from **3** would then be expected to generate the α-methylene lactone.[6] In this paper we describe the results[7] of our investigation based on this concept offering a general facile route for the synthesis of β-carboxy-α-methylene-γ-lactone and the total synthesis of (±)-methylenolactocin and (±)-protolichesterinic acid.

Results and Discussion

The steps involved in our approach is delineated in **Scheme 1**. The ester enolate generated from the dimethyl ester **4** with LDA was allowed to react with butanal. As expected, coupling of the ester-enolate with the aldehyde proceeded smoothly to produce a liquid in 80% yield. The IR (1735 and 1770 cm^{-1}) and the ^{13}C NMR spectra (δ171.0 and 180.0) of the product indicated that during coupling of the enolate with the aldehyde, spontaneous lactonisation had taken place. It was anticipated that lactonisation would proceed to give the thermodynamically more stable *trans* lactone **6a**. However a mixture of all the four possible diastereomeric lactones (only one pair of the diastereomers **5a** and **6a** is shown in **Scheme 1**) was produced as evidenced by the presence of four COOMe signals at δ 3.60, 3.63, 3.66 and 3.73 in ca. 1:2:1.5:5 ratio from ^1H NMR spectrum of the product. Separation of the components of this mixture through column chromatography became impossible. As the *trans* configuration of the C_3 and C_4 substituents in the methyl ester of nor methylene analogue of methylenolactocin is thermodynamically more stable,[3a] we thought that it would be possible to make this mixture enriched with the *trans* component through equilibration. However the composition of the mixture remained unchanged on refluxing with DBU in benzene for 6-7 hours. The resistance of this mixture to undergo equilibration may be attributed as follows. Epimerisation of the component **5** in which the COOMe group lies away from the ethylene bridge would require the COOMe group to occupy the more crowded *endo* position as in **6**. Thus epimerisation of the lactone **5** to the diastereomer **6** is resisted. Since removal of cyclopentadiene unit from this lactone mixture would eventually destroy the chirality at the centre α- to the lactone carbonyl reducing the number of diastereomers from four to two, we decided to carry on the synthesis with this mixture. Flash vacuum thermolysis (FVT) of this mixture at about 500° C effected smooth retro Diels-Alder reaction to produce a mixture of two α-methylene lactones **7a** and **8a**. The presence of two COOMe singlets at δ 3.69 and 3.76 and the three olefinic doublets at δ 5.83 (J=3 Hz), 5.93 (J=3 Hz) and 6.38 (J=3 Hz) in ^1H NMR spectrum of the product indicated it to be a mixture of *cis* and *trans* lactones **7a** and **8a**. Attempted separation through column chromatography led to complete isomerisation of the *exo* methylene. Stereochemical assignment of the individual components of the mixture could not be made at this point. However, the sequence involving coupling of the enolate of the diester **4** with aldehyde followed by retro Diels-Alder reaction demonstrated the feasibility of the above concept to the synthesis of β-carboxy-α-methylene-γ-lactone.

To establish the generality and the synthetic potential of this approach, total synthesis of methylenolactocin and protolichesterinic acid was undertaken. Towards this end hexanal and tetradecanal were chosen as the aldehyde components for coupling with the diester. Exposure of the enolate of the diester **4** with hexanal under the above condition afforded a solid, m.p. 91° C in 79% yield. In this case also the product obtained was a mixture of four diastereomers **5b**, **6b** with two other (not shown) as evidenced from the four COOMe singlets at δ 3.61, 3.65, 3.67 and 3.74 in ca. 1:1.5:1:2 ratio. As in the previous case, composition of this mixture remained unchanged on attempted equilibration with DBU. Flash vacuum thermolysis afforded a mixture of two exo methylene lactones **7b** and **8b** as a liquid in 92% yield in ca. 2:1 ratio from integration of the COOMe signals at δ 3.75 and 3.80 respectively. ^{1}H NMR data, particularly the chemical shifts of the protons of the COOMe group (δ 3.80) and the exo methylene group [δ 5.90 (d, 1H, J=2.5 Hz) and 6.40 (d, 1H, J=2.5 Hz)]



a, R = C_3H_7 ; **b**, R = C_5H_{11} ; **c**, R = $C_{13}H_{27}$; **d**, R = p-$MeOC_6H_4$

Scheme 1 Reagents and conditions: i, LDA, THF-HMPA, -30° C then RCHO, 0° C to rt, 66-80 % ; ii, FVT, ~500° C (0.05 mm), 54-92 % ; iii, 6M HCl, butanone, reflux, 2h, 71-72 %

of the minor component of the mixture was found to be identical to that reported for the methyl ester of methylenolactocin in which the COOMe and C_5H_{11} groups are *trans* to each other. Thus, the minor lactone in the above mixture was assigned the *trans* structure **8b** and hence the major component with COOMe protons at δ 3.76 and methylene protons at δ 5.81 (d, 1H, J=2 Hz) and 6.40 (d, 1H, J=2.5 Hz) was assigned *cis*

structure **7b**. Based on this stereochemical assignment the major and the minor exo methylene lactones in the first example was assigned the *cis* configuration **7a** and the *trans* configuration **8a** respectively. Hydrolysis of the mixture of the two exo methylene lactones **7b** and **8b** in refluxing butanone with 6M HCl following the procedure of Weavers[3e] effected epimerisation of the *cis* isomer **7b** to afford exclusively the *trans* acid **1**, i.e. methylenolactocin in 71% yield.

With tetradecanal, the enolate of the diester **4** gave a mixture of lactones **5c**, **6c** with two others (not shown) in 66% yield as a semisolid mass in ca. 1:1.5:1.5:4 ratio as evidenced by the presence of four COOMe singlets at δ 3.63, 3.65, 3.68 and 3.73 in its ^{1}H NMR spectrum. Flash vacuum thermolysis of this mixture afforded a mixture of two exo methylene lactones **7c** and **8c** in ca. 3:1 ratio (from the integration of the olefinic protons in ^{1}H NMR) in 86% yield. In analogy to the stereochemical assignment to the methylene lactones **7b** and **8b** obtained from flash vacuum thermolysis of **5b** and **6b**, the major lactone [δ 3.73 (s, COOMe), 5.80 (s, 1H) and 6.37 (d, 1H, J=3 Hz)] and the minor lactone [δ 3.78 (s, COOMe), 5.89 (d, 1H, J=3 Hz) and 6.37 (d, 1H, J=3 Hz)] in this case was assigned the *cis* **7c** and *trans* **8c** configuration respectively. Hydrolysis of the lactone mixture in refluxing butanone with 6M HCl effected epimerisation of the *cis* lactone **7c** to produce protolichesterinic acid **2** in 72% yield as a solid, m.p. 103-105° C (lit.[4a] m.p. 104-105° C). IR, ^{1}H NMR and ^{13}C NMR spectra of this sample was found to be identical with those reported in literature.

To probe the influence of γ-aromatic substituents on the biological properties, the synthesis of α-methylene lactones **7d** and **8d** was undertaken. Reaction of the enolate of the diester **4** with p-anisaldehyde followed by crystallisation of the crude semisolid mass afforded a solid, m.p. 138-139° C in 73% yield. This solid was found to be a mixture of two lactones **5d** and **6d** in ca. 2:1 ratio (from integration of COOMe signals) with traces of the two other diastereomers. The stereochemical assignment to the major component as *cis* **5d** and *trans* **6d** followed from analogy to the formation of major and minor lactones as in *cis* **5b** and *trans* **6b** from reaction of the enolate of the diester **4** with hexanal. Flash vacuum thermolysis of this lactone mixture afforded, instead of the expected α-methylene lactones **7d** and **8d**, the butenolide **9** in 70% yield. The structure of butenolide **9** could readily be determined from the following spectral data: ^{1}H NMR δ 2.17 (3H, d, J=1.8 Hz), 3.63 (3H, s), 3.70 (3H, s), 5.89 (1H, s), 6.77 (2H, d, J=8.7 Hz), 7.06 (2H, d, J=8.7 Hz) and ^{13}C NMR δ 10.7 (Me), 52.2 (OMe), 55.2 (OMe), 82.2 (OCH), 114.1, 126.0, 126.5 128.5, 136.7, 147.3, 160.3 (CO) and 172.9 (CO). The spontaneous isomerisation of the exo methylene lactones **5d** and **6d** through FVT is probably the result of relief of the strain[8] arising from eclipsing interaction between the bulkier aryl group at C_3 and the COOMe group at C_4 in the *cis* isomer **7d**.

In conclusion, the above investigation demonstrates the feasibility of the synthesis of the very sensitive β-carboxy-α-methylene-γ-lactones through the use of retro Diels-Alder reaction. The potential of the approach has been established through the synthesis of (±)-methylenolactocin and (±)-protolichesterinic Acid.

Experimental section

The compounds described are all racemates. Melting points were taken in open capillary in sulphuric acid bath and are uncorrected. Petroleum refers to the fraction of b.p. 60-80° C. Column chromatography was performed with silica gel 60-120 mesh. IR spectra were recorded as neat for liquids and in KBr pellets for solids. ^{1}H NMR spectra were recorded at 200 MHz and 300 MHz in $CDCl_3$ solution. ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 75 MHz. Peak positions are indicated in ppm downfield from internal TMS in δ units.

***exo*-Methyl-1-(carbomethoxy methyl) bicyclo[2.2.1]hept-4-ene-1-carboxylate (4)** : The *exo*-dimethyl ester **4** was prepared from hydrolysis of the exclusive *exo* Diels-Alder adduct[9] of itaconic anhydride with cyclopentadiene followed by esterification according to the following procedure. To a magnetically stirred solution of itaconic anhydride (3.0 g, 26.76 mmol) in anhydrous THF (15 ml) cooled to 0°C was added freshly distilled cyclopentadiene (3.5 g, 53.52 mmol). The solution was stirred for 10 mins and then anhydrous $AlCl_3$ (0.18 g, 1.38 mmol) was added all at a time. The reaction mixture was left overnight at 0°C and then poured into brine solution (10 ml), extracted with ether (2x25 ml), dried (Na_2SO_4) and concentrated to give the crude cycloadduct. It was taken in a mixture of EtOH (15 ml) and water (40 ml) and $NaHCO_3$ (5.6 g, 66.9 mmol) was added to it in parts when effervesence occurred. The mixture was refluxed for 2 h, cooled to r.t. and extracted with ether (2x10 ml). The aqueous part was acidified by dropwise addition of cold conc. HCl. It was extracted with ethyl acetate (3x20 ml). The organic extracts was washed repeatedly with brine, dried (Na_2SO_4) and concentrated to afford a solid (4.2 g, 80%) m.p. 148-150° C. The diacid (1.5 g, 7.65 mmol) thus obtained was treated with an ethereal solution of diazomethane and the product was purified through column chromatography using petroleum ether (9:1) as eluent to give the dimethyl ester **4** (1.47 g, 86%). ^{1}H NMR (300 MHz) δ 1.37 (1H, d, J = 8.7 Hz), 1.57 (1H, d, J = 8 Hz), 2.32 (1H, d, J = 16.2 Hz), 2.46 (2H, dd, J = 12.3 Hz and 3.6 Hz), 2.69 (1H, d, J = 16.2 Hz), 2.81 (1H, brs), 2.99 (1H, brs), 3.57 (3H, s), 3.65 (3H, s), 6.01-6.04 (1H, m), 6.19-6.22 (1H, m).

Reaction of the enolate of the dimethylester 4 with aldehydes. Spiro[3-carbomethoxy-4-(n-propyl)-5-oxa cyclopentanone]-2,1′-(3′,5′-etheno)cyclopentanes (5a and 6a). To a magnetically stirred solution of diisopropylamine (0.7 g, 6.95 mmol) in anhydrous THF (8 ml) cooled to -78° C under argon atmosphere was added drowpwise n-BuLi (3.8 ml, 6.42 mmol, 1.7 M in hexane). The solution was then warmed to 0° C and again cooled to -78° C. A solution of the diester (1.2 g, 5.35 mmol) in THF (5 ml) was added dropwise. The reaction mixture was then slowly warmed to -30° C and stirred at that temperature for 1.5 h. The temperature of the reaction mixture was again brought down to -78° C and to it a solution of n-butyraldehyde (0.5 g, 6.95 mmol) in THF (3 ml) was added dropwise. The reaction mixture was allowed to attain room temperature and stirred overnight (12-16 hr). After quenching with saturated aqueous ammonium chloride solution, the reaction mixture was extracted with ether (3x10 ml). The organic extract was washed

successively with 10% aqueous HCl (2x5 ml), 5% aqueous $NaHCO_3$, brine and dried (Na_2SO_4). The residual oil after removal of ether was chromatographed [ether-petroleum (1:10)] to afford a colourless liquid (1.13 g, 80%); IR: 1770, 1735 cm^{-1}; ^1H NMR (300 MHz) δ 0.88-0.94 (3H, m), 1.32-1.58 (6H, m), 1.95-2.35 (2H, m), 2.67-3.07 (3H, m), 3.60 (s), 3.63 (s), 3.66 (s) and 3.73 (s) (total 3H), 4.34 (m) and 4.60 (m) (total 1H), 5.97-6.27 (2H, m); ^{13}C NMR (75 MHz) (for major isomer from mixture) δ 13.6 (Me), 19.2 (CH_2), 32.9 (CH_2), 39.8 (CH_2), 42.3 (CH), 47.5 (CH_2), 47.6 (CH), 51.7 (OMe), 52.6, 56.9 (CH), 77.4 (OCH), 134.0, 139.0, 171.0 (CO), 180.0 (CO). Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found : C, 68.26; H, 7.58.

Spiro[3-carbomethoxy-4-(n-pentyl)-5-oxa-cyclopentanone]-2,1'-(3',5'-etheno)cyclopentanes (5b and 6b): Following the above procedure, the spiro lactones (**5b** and **6b**) were obtained as a solid, m.p. 91°C in 79% yield from coupling of the enolate of the diester **4** with hexanal; IR: 1775, 1735 cm^{-1}; ^1H NMR (200 MHz) δ 0.87 (3H, m), 1.23-1.64 (10H, m), 2.04-2.40 (2H, m), 2.63-3.09 (3H, m), 3.61 (s), 3.65 (s), 3.67 (s) and 3.74 (s) (total 3H), 4.31 (m) and 4.52 (m) (total 1H), 5.96-6.39 (2H, m). Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.82; H, 8.28. Found : C, 69.86; H, 8.21.

Spiro[3-carbomethoxy-4-(n-tridecyl)-5-oxa-cyclopentanone]-2,1'-(3',5'-etheno)cyclopentanes (5c and 6c) was obtained in 66% yield as a semisolid mass from reaction of the enolate of the diester **4** with tetradecanal; IR: 1775, 1735 cm^{-1}; ^1H NMR (300 MHz) δ 0.85 (3H, t, J = 6 Hz), 1.23-1.64 (26H, m), 1.97-2.39 (2H, m), 2.67-3.08 (3H, m), 3.61 (s), 3.64 (s), 3.66 (s) and 3.73 (s) (total 3H), 4.32-4.36 (m) and 4.51-4.55 (m) (total 1H), 5.92-6.37 (2H, m); ^{13}C NMR (75 MHz) (for major isomer from mixture) δ 13.9 (Me), 22.5 (CH_2), 25.7 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.46 (CH_2), 29.48 (CH_2), 30.9 (CH_2), 31.7 (CH_2), 42.2 (CH), 47.4 (CH_2), 47.5 (CH), 51.5 (OMe), 52.5, 56.7 (CH), 77.4 (OCH), 133.9, 139.0, 170.9 (CO), 179.8 (CO). Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.20; H, 9.97. Found : C, 74.40; H, 10.08.

Spiro[3-carbomethoxy-4-(p-methoxyphenyl)-5-oxa-cyclopentanone]-2,1'-(3',5'-etheno)cyclopentanes (5d and 6d) was obtained from reaction of the enolate of the diester **4** with p-anisaldehyde as a solid; m.p. 138-139° C in 73% yield; IR: 1770, 1730 cm^{-1}; ^1H NMR (300 MHz) δ 1.47-1.55 (2H, m), 2.06-2.5 (2H, m), 2.96-3.18 (3H, m), 3.28 (s) and 3.35 (s) (total 3H), 3.79 (3H, s), 5.49 (d, J = 5.7 Hz) and 5.69 (d, J = 6.0 Hz) (total 1H), 6.00-6.45 (2H, m), 6.84-6.88 (2H, m), 7.20-7.27 (2H, m); ^{13}C NMR (75 MHz) (for major isomer in mixture) δ 39.9 (CH_2), 42.1 (CH), 48.1 (CH_2), 51.5 (OMe), 52.8, 55.2 (OMe), 59.8 (CH), 77.6 (OCH), 113.6, 126.5, 127.1, 134.2, 139.2, 159.5, 170.1 (CO), 179.9 (CO). Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.48; H, 6.14. Found : C, 69.26; H, 6.22.

General Procedure for Flash Vacuum Thermolysis (FVT). Cycloadducts were carefully vapourised with a free flame and the vapour was passed through a heating column of a gas-phase pyrolysis apparatus at about 500° C, subjected to high vacuum (0.05 mm). The crude product was collected in a trap by cooling it in an ice-bath.

Methyl-2,3-dihydro-4-methylene-5-oxo-2-(n-propyl)-3-furan carboxylate (7a and 8a) was obtained as a liquid by FVT of a mixture of the spiro lactones **5a** and **6a** in 54% yield. The product obtained was found to contain about 30-40% of the unpyrolysed material; IR: 1770, 1740 cm^{-1}; ^1H NMR (300 MHz) (from mixture) δ 0.86 (3H, m), 1.15-1.64 (4H, m), 3.69 (s) and 3.76 (s) (total 3H), 4.39 (m) and 4.81 (m) (total 1H), 5.83 (d, J = 3 Hz) and 5.93 (d, J = 3 Hz) (total 1H), 6.38 (1H, d, J = 3 Hz). An analytically pure sample could not be obtained either through sublimation or through column chromatography.

Methyl-2,3-dihydro-4-methylene-5-oxo-2-(n-pentyl)-3-furan carboxylate (7b and 8b) was obtained as a liquid by FVT of a mixture of the spiro lactones **5b** and **6b** in 92% yield; IR: 1770, 1740 cm^{-1}; ^1H NMR (200 MHz) δ 0.89 (3H, m), 1.30-1.74 (9H, m), 3.75 (s) and 3.80 (s) (total 3H), 4.59 (m) and 4.79 (m) (total 1H), 5.81 (d, J = 2 Hz) and 5.90 (d, J = 2 Hz) (total 1H), 6.40 (1H, d, J = 2 Hz).

Methyl-2,3-dihydro-4-methylene-5-oxo-2-(n-tridecyl)-3-furan carboxylate (7c and 8c) was obtained as a liquid by FVT of a mixture of the spiro lactones **5c** and **6c** in 86% yield; IR 1775, 1745 cm^{-1}; ^1H NMR (300 MHz) δ 0.86 (3H, t, J = 6 Hz), 1.23-1.71 (25 H, m), 3.73 (s) and 3.78 (s) (total 3H), 4.57-4.64 (m) and 4.77 (m) (total 1H), 5.73 (d, J = 3 Hz) and 5.83 (d, J = 3 Hz) (total 1H), 6.38 (1H, d, J = 3 Hz); ^{13}C NMR (75 MHz) δ 13.9 (Me), 22.6 (CH_2), 24.6 (CH_2), 25.4 (CH_2), 29.07 (CH_2), 29.09 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.40 (CH_2), 29.47 (CH_2), 29.52 (CH_2), 29.55 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 35.6 (CH_2), 48.9 (CH), 52.2 (OMe), 78.3 (OCH), 124.8 (CH_2), 132.9, 169.3 (CO), 177.7 (CO). Anal. Calcd. for $C_{20}H_{34}O_4$: C, 70.95; H, 10.13. Found : C, 70.52; H, 10.26.

Methyl-3-methyl-5-(p-methoxyphenyl)-2-oxo(5*H*)-furan-4-carboxylate (9) was obtained as a liquid by FVT of a mixture of the lactones **5d** and **6d** in 70% yield; IR: 1765, 1730 cm^{-1}; ^1H NMR (300 MHz) δ 2.17 (3H, d, J = 1.8 Hz), 3.63 (3H, s), 3.70 (3H, s), 5.89 (1H, s), 6.77 (2H, d, J = 8.7 Hz), 7.06 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz) δ 10.7 (Me), 52.2 (OMe), 55.2 (OMe), 82.2 (OCH), 114.1 (CH), 126.0, 126.5, 128.5 (CH), 136.7, 147.3, 160.3 (CO), 172.9 (CO). Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.10; H, 5.38. Found : C, 64.33; H, 5.65.

Synthesis of methylenolactocin (1) : A solution of the mixture of the methyl esters **7b** and **8b** (0.03 g, 0.13 mmol) in butanone (2 ml) containing HCl (6M, 6 drops) was heated under reflux for 2h. Water (5 ml) was added and the organic solvent was removed. The aqueous residue was extracted with CH_2Cl_2 (3x10 ml) and the solvents were evaporated. The crude product was dissolved in toluene (15 ml) and extracted with 5% $NaHCO_3$ (3x20 ml). Concentration of the toluene extract afforded the unhydrolysed ester **7b** and **8b** (0.02 g). The basic extract was then acidified with HCl, extracted with CH_2Cl_2 (3x10 ml). The organic extract was dried (Na_2SO_4) and concentrated to give methylenolactocin **1** [0.01 g, 71% (based on recovered ester)]; ^1H NMR (200 MHz) δ 0.88-0.89 (3H, m), 1.17-1.51 (6H, m), 1.68-1.75 (2H, m), 3.58-3.63 (1H, m), 4.06 (br), 4.79-4.82 (1H, m), 6.01 (1H, d, J = 1.4 Hz), 6.44 (1H, d, J = 1.6 Hz); ^1H NMR data are comparable with that reported in literature.[3f]

Protolichesterinic acid (2) : Following the above procedure, the ester **7c** and **8c** (0.05 g, 0.15 mmol) was hydrolysed to produce a solid which was recrystallised from ethyl acetate-petroleum to give protolichesterinic acid **2** [0.02 g, 72% (based on recovered ester)], m.p. 103-105° C (lit[4a] m.p. 104-105° C). IR: 3000-2850, 1745, 1710 cm^{-1}; ^1H NMR δ (300 MHz) 0.89 (3H, t, J = 6 Hz), 1.26-1.51 (22H, m), 1.71-1.76 (2H, m), 3.63 (1H, m), 4.20 (br), 4.83 (1H, m), 6.02 (1H, d, J = 2.1 Hz), 6.47 (1H, d, J = 2.4 Hz); ^{13}C NMR (75 MHz) δ 14.0 (Me), 22.5 (CH_2), 24.6 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.50 (CH_2), 29.54 (CH_2), 31.8 (CH_2), 35.6 (CH_2), 49.4 (CH), 78.8 (OCH), 125.6 (CH_2), 132.4, 168.1 (CO), 173.4 (CO). ^1H and ^{13}C NMR data are comparable to that reported in literature.[4a]

Acknowledgement : Financial support from the Department of Science and Technology, New Delhi is gratefully acknowledged. AG and SS wish to thank the Council of Scienctific and Industrial Research, New Delhi for Senior Research Fellowships.

References and notes

1. Park, B. K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot.* **1988**, *41*, 751.
2. i) For isolation and structure elucidation see: a) Zopf, W. *Liebigs Ann. Chem.* **1902**, *324*, 39; **1904**, *336*, 46. b) Asahina, Y.; Asano, M. *J. Pharm. Soc. Jpn.* **1927**, *539*, 1; *Chem. Abstr.* **1928**, *22*, 4470. c) Asano, M.; Kanematsu, T. *Chem. Ber.* **1932**, *65B*, 1175. ii) For biological properties see: a) Berdy, J. *Handbook of Antibiotic Compounds*; CRC Press: Boca Raton, FL, 1982; Vol. IX and references cited therein. b) Cavalitto, C. J.; Fruehauf, McK. D.; Bailey, J. N. *J. Am. Chem. Soc.* **1948**, *70*, 3724. c) Shibata, S; Miura, Y.; Sugimura, H.; Toyoizumi, Y. *J. Pharm. Soc. Jpn.* **1948**, *68*, 300; *Chem Abstr.*, **1951**, *45*, 6691i. d) Fujikawa, F.; Hitosa, Y.; Yamaoka, M.; Fujiwara, Y.; Nakazawa, S.; Omatsu, T.; Toyoda, T. *Ibid.* **1953**, *73*, 135.; *Chem. Abstr.* **1954**, *48*, 230a. e) Borkowski, B.; Wozniak, W.; Gertig, H.; Werakso, B. *Diss. Pharm.* **1964**, *16*, 189; *Chem. Abstr.* **1965**, *62*, 1995b. f) Sticher, O. *Pharm. Acta. Helv.* **1965**, *40*, 183; *Chem. Abstr.* **1965**, *63*, 8778d. g) Sticher, O; *Pharm. Acta. Helv.* **1965**, *40*, 385;.*Chem. Abstr.* **1965**, *63*, 12026c. h) Hirayama, T.; Fujikawa, F.; Kasahara, T.; Otsuka, M.; Nishida, N.; Mizuno, D. *Yakugaku Zasshi* **1980**, *100*, 755; *Chem. Abstr.* **1980**, *93*, 179563f. i) Huneck, S.; Schreiber, K. *Phytochemistry* **1972**, *11*, 2429.
3. a) de Azevedo, M. B. M.; Murta, M. M.; Greene, A. E. *J. Org. Chem.* **1992**, *57*, 4567. b) Honda, T.; Kimura, N. *J. Chem. Soc. Chem. Commun.* **1994**, 77. c) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 23. d) Zhu, G.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1087. e) Mawson, S. D.; Weavers, R. T. *Tetrahedron* **1995**, *51*, 11257. f) Maiti, G.; Roy, S. C. *J. Chem. Soc. Perkin Trans 1* **1996**, 403. g) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G. *J. Chem. Soc. Chem. Commun.* **1996**, 1289. h) Saicic, R. N.; Zard, S. Z. *J. Chem. Soc.Chem. Commun.* **1996**, 1631. i) Sarkar, S.; Ghosh, S. *Tetrahedron Lett* **1996**, *37*, 4809.
4. Murta, M. M.; de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 7573 and the references cited therein. b) Deshpande, P. K.; La Loggia, A. J.; Sibi, M. P. *Synlett* **1996**, 343.
5. van Tamelen, E. E.; Bach, S. R. *J. Am. Chem. Soc* **1958**, *80*, 3079.
6. For an account of the use of retro Diels-Alder reaction in the synthesis of α-methylene lactones see: Ichihara, A. *Synthesis* **1987**, 207.
7. Part of the results had appeared as a preliminary communication . See ref. 3i
8. A similar relief of eclipsing interaction between substituents through enolisation in a substituted cyclopentanone derivative has been observed. See: Haque, A.; Ghatak, A.; Ghosh, S.; Ghoshal, N. *J. Org. Chem.* **1997**, *62*, 5211.
9. Fotiadu, F; Michel, F.; Buono, G. *Tetrahedron Lett.* **1990**, *31*, 4863.

(*Received in UK* 15 *August* 1997; *accepted* 9 *October* 1997)