Tetrahedron Vol 44, No 17, pp. 5441 to 5449, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF α-METHOXYCARBONYLAMINO- γ-ALKENYL- γ-BUTYROLACTONES - AMIDOALKYLATION OF DIENES WITH THE ADDUCT OF GLYOXYLIC ACID-METHYLCARBAMATE[1]

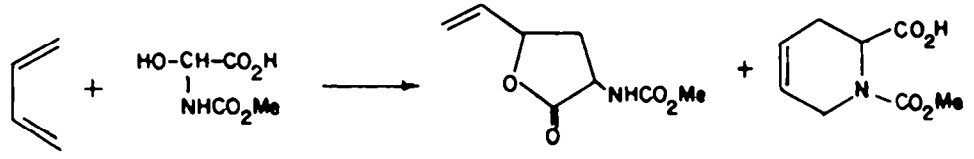
D. BEN-ISHAI* AND S. HIRSH

Department of Chemistry, Israel Institute of Technology, Haifa, Israel.

(Received in USA 3 March 1988)

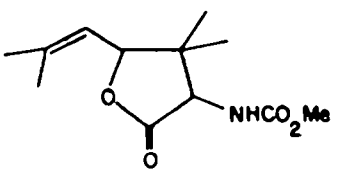
Abstract - Amidoalkylation of 1,3-dienes with glyoxylic acid-methyl carbamate adduct afforded α-methoxycarbonylamino- γ-alkenyl- γ-butyrolactones in 40-80% yield. The lactones were epoxidized to the epoxy lactones or ozonized and rearranged to γ-ketopyrrolidine-2-carboxylic acid derivatives.

In the course of our studies on the chemistry of glyoxylic acid-primary amide adducts and their reactions with aromatics and olefins[2] we were puzzled by the claims[3,4] and our own observations[5] that the yields of the acid catalyzed Diels-Alder reactions of dienes with open chain acylimines as dienophiles are rather low. We have now found that glyoxylic acid - methyl carbamate adduct[6] reacts with butadiene in methylene chloride at room temperature and in the presence of methanesulfonic acid affording the neutral α-methoxycarbonylamino-γ-vinyl-γ-butyro lactone (2) in 65-70% yield and the pipecolic acid derivative, the N-methoxycarbonylaminobaikian (3), in only 7-9% yield:

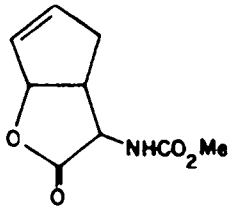


1 2 3

This observation was found to be quite general: piperylene, isoprene, 2,3-dimethylbutadiene, 2,4-hexadiene, 2,5-dimethyl-2,4-hexadiene, cyclopentadiene, 1,3-cyclohexadiene and 1,3-cyclooctadiene all were found to react with the adduct 1 in the acid catalyzed reaction to give lactones as the major reaction products (40-80%). The normal Diels-Alder pipecolic acid derivatives were obtained in less than 20% yield under the reaction conditions mentioned. In the case of 2,5-dimethyl-2,4-hexadiene and cyclopentadiene we observed only the formation of the crystalline lactones 4 and 5:



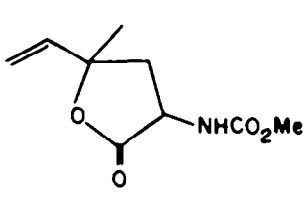
4



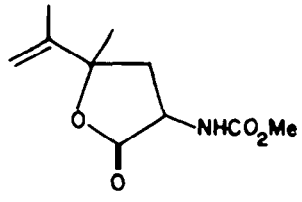
5

An X-ray crystal structure analysis showed lactone 4 to have the cis configuration and in the bicyclic lactone 5 the methoxycarbonylamino group is in the exo position.

According to the ^1H NMR spectra the crude reaction products of all the monocyclic lactones were mixtures of two isomers (cis-trans). The derivatives of butadiene (2) isoprene (6) and 2,3-dimethylbutadiene (7) were characterized as a mixture of two isomers which have not been separated.



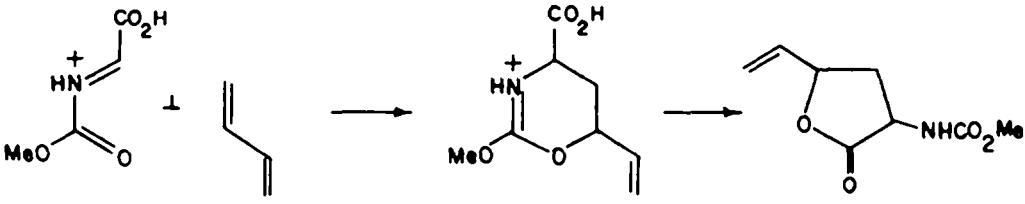
6



7

All the lactones showed characteristic carbonyl absorptions at 1770-1790 cm^{-1} (γ-butyrolactones) and 1720 cm^{-1} (carbamate carbonyl) as well as NH absorptions at 3420 cm^{-1} and 1500 cm^{-1}. In the ^1H NMR spectra the lactones showed characteristic absorption for the carbamate NH at δ 5.20-5.70 (doublet) and the α-hydrogens at δ 4.10-4.80. The γ-hydrogens appeared at δ 4.30-5.20, which appear to be a good support for the regiospecificity of the reaction.

The intermediates in the formation of the γ-alkenyllactones are most probably the oxazine-4-carboxylic acid derivative (e.g. 8) which rearranges to the lactone (2):



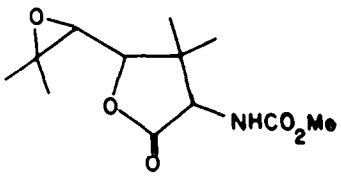
9 8 2

This suggestion is based on the observations made by Seelinger[7] and R.R. Schmidt[8] who have isolated alkenyloxazines in the reactions of N-hydroxymethylbenzamide with dienes. Esters of oxazine-4-carboxylic acid are relatively stable[2] but to the best of our knowledge no free oxazine-4-carboxylic acid of the type involved was reported. We are probably dealing with two competing 4+2 cycloadditions.[1] The major product of the reactions are the lactones (e.g. 2) which are formed by a Diels-Alder type reaction with an inverse electron demand. The acyliminium intermediate (e.g 9) reacts as the electron poor diene while the diene (e.g. butadiene) functions as a dienophile. The kinetically controlled oxazine derivative (e.g. 8) then rearranges to the more stable lactone (e.g. 2).

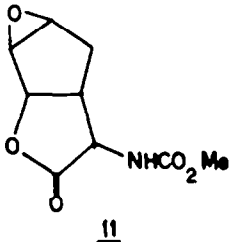
The pipecolic acid derivative (e.g. 3) which is obtained by the normal cycloaddition[3] of the diene with the acyliminium intermediate as a dienophile is the minor product in the reactions discussed.

Epoxidation of six of the vinyl lactones with MCPBA in refluxing methylene chloride afforded the corresponding epoxylactones in good yield. Epoxidation of cis lactone 4 afforded two isomeric epoxides (10) which were separated by trituration and chromatography. The more polar crystalline stereoisomer was shown by X-ray crystal structure analysis to have the 3R5R6S-3S5S6R configuration. Epoxidation of the exo-vinyllactone 5 afforded a major crystalline epoxylactone which is according to an X-ray crystal structure analysis the cis isomer with the epoxide and the lactone rings cis to each other and with the carbamate group exo (11)

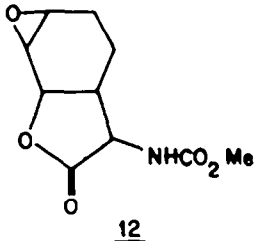
Epoxidation of the vinyllactone obtained from cyclohexadiene afforded a mixture of epoxides the polar stereoisomers which separated as a crystalline products (12) showed by X-ray crystal structure analysis to have the trans configuration. The epoxide and lactone rings are trans to each other with the carbamate group exo to the bicyclic six-five ring system.



10

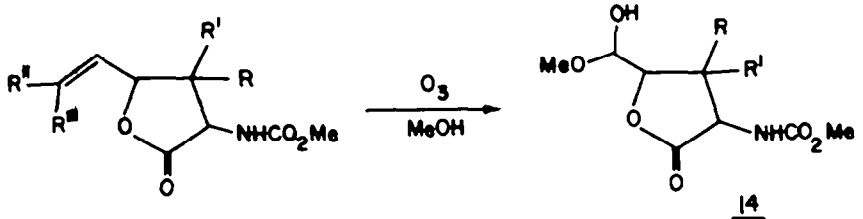


11



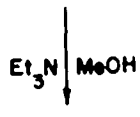
12

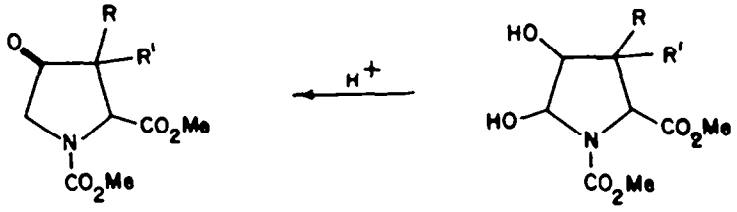
Oxonolysis of three of the alkenyl lactones 2, 4 and 13, in methanol solution, afforded the hemiacetals 14. The hemiacetal were found to rearrange in refluxing methanol and in the presence of a weak base (Et_3N) to the dihydroxypyrrolidine-2-carboxylic acid derivatives 15. Acid catalyzed water elimination converted the 4,5-dihydroxypyrrolidines (15) to the corresponding 4-ketopyrrolidine-2-carboxylic acid derivatives 16: The overall conversion of the alkenyllactones to the pyrrolidone derivatives can be carried out in a one pot reaction and in 65-75% yield.



2, R = R' = R'' = R''' = H
4, R = R' = R'' = R''' = Me
13, R = R'' = H, R' = R''' = Me

14





16

a, R = R' = H
b, R = R' = Me
c, R = H, R' = Me

15

In the case of the vinyllactone 2 starting from a mixture of two isomers afforded a single pyrrrolidone derivative 16a. One chiral center was lost in the conversion of the lactone to the pyrrolidone derivative. The methyl N-methoxycarbonyl-4-pyrrolidone -2-carboxylate (16a) is a known precursor of hydroxyproline. [9]

The pyrrolidone derivative 16c has two chiral centers and was obtained as a mixture of two isomers in about a 1:1 ratio, according to the nmr spectra.

Experimental

General: M.P.'s are uncorrected. The I.R. spectra were recorded on a Perkin-Elmer 298 spectrophotometer; ^{1}H-NMR spectra were obtained on Varian T-60 spectrometer. Chemical shifts are reported in ppm downfield from TMS. ^{13}C NMR were recorded on a Bruker AM-400. Mass spectra were obtained on a Varian MAT-711 spectrometer.

Chromatographic separations were carried out on Florisil 60-100 mash and silica gel 60 70-230 mash.

α-Methoxycarbonylamino- γ-vinyl- γ-butyrolactones-General Procedure:

To a suspension of α-hydroxy-N-methoxycarbonylglycine 1, (0.01 mole) in methylene chloride, or a mixture of methylene chloride:ether, was added methanesulfonic acid (1.5 ml, 0.02 mole). The mixture was stirred and cooled to 0°C when the diene (0.01 mole) neat or as a solution in methylene chloride (10 ml) was added. The reaction mixture was stirred at room temperature for 72 hr and then poured over crushed ice and solid sodium bicarbonate (0.03 mole). The aqueous layer was extracted three times with methylene chloride dried over anhydrous $MgSO_4$, filtered and evaporated.

α-Methoxycarbonylamino- γ-vinyl- γ-butyrolactone (2).

A suspension of α-hydroxy-N-methoxycarbonylglycine 1 (22.35g, 0.15 mole) in methylene chloride (150 ml) and methanesulfonic acid (22.5 ml, 0.3 mole) was treated with a solution of butadiene in methylene chloride (150 ml of a 1 molar solution) as described above. The crude oil was chromatographed over Florisil (60-100 mesh) and the product eluted with methylene chloride to give 18.90g (68%) of product which is according to ^{1}H and ^{13}C NMR a mixture of two isomers. IR($CHCl_3$): 3400 (NH), 1785 (CO lactone), 1725 (CO carbamate) and 1495 (NH). ^{1}H NMR ($CDCl_3$) δ: 6.33-5.66 (m, 2H, CH=, NH); 5.63-4.23 (m, 4H, CH_2=, O-CH-O-, N-CH-CO), 3.75 (s, 3H, OCH_3); 3.20-1.76 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 175.25, 174.85, 156.84, 135.09, 134.70, 119.15, 117.34, 78.10, 77.45, 52.58, 51.68, 49.35, 36.00, 33.93. M.S.(HR) m/z 185.0633 (M^+), calcd for $C_8H_{11}NO_4$ m/z 185.0688 (M^+), 141 (M^+-CO_2), 126 (M^+-CO_2Me). The aqueous alkaline solution was acidified and extracted to give 1.98g (7%) of the crude pipecolic acid derivative 3 (IR, NMR).

α-Methoxycarbonylamino- γ-(1-propenyl)butyrolactone

This compound was prepared from α-hydroxy-N-methoxycarbonylglycine 1 (7.5g, 0.05 mole) in methylene chloride - dry ether (100 ml 1:1), methanesulfonic acid (7.5 ml, 0.1 mole) and piperylene (5 ml, 0.05 mole) as described above by general procedure. The oily crude product (8.7g) was chromatographed on a Florisil column and the product eluted with methylene chloride (1:1). The oily product (4.27g, 43%) is according to the ^{1}H NMR a mixture of one main compound and a minor isomer. IR ($CHCl_3$): 3440 (NH), 1785 (CO lactone), 1730 (CO carbamate), 1505 (NH). ^{1}H NMR ($CDCl_3$) δ : 6.20-5.50 (m, 3H, CH=CH, NH), 5.23-4.15 (m, 2H, OCH-O-, N-CH-CO), 3.72 (s, 3H, CH_3), 3.16-1.88 (m, 2H, CH_2), 1.80 (d, J=5, 3H, CH_3-C=). ^{13}C NMR ($CDCl_3$) : 174.98, 156.97, 132.49, 130.16, 127.96, 78.62, 78.09, 73.31, 52.58, 51.81, 49.73, 36.65, 34.71,17.61. M.S.(HR) m/z 155.0923 (M^+-CO_2), calcd for (M^+-CO_2)=155.0942, 140 (M^+-CO_2Me). (Found: N, 6.70%; $C_9H_{13}NO_4$ requires: 7.03%).

The aqueous solution was acidified and extracted to give a crude oil (0.79g, 8%) which was the pipecolic acid derivative (IR, NMR).

α-Methoxycarbonylamino- γ-methyl- γ-vinyl- γ-butyrolactone (6).

A mixture of α-hydroxy-N-methoxycarbonylglycine 1 (11.23g, 0.075 mole) in methylene chloride-dry ether (100 ml 1:1), methanesulfonic acid (7.5 ml, 0.1 mole) was treated with isoprene (5 ml, 0.05 mole) as described above in the general procedure. The crude oily product (7.6g) was chromatographed over Florisil and the product eluted with methylene chloride. The pure product (4.9g, 49%) was a mixture of two isomers according to the NMR spectra. IR($CHCl_3$): 3420 (NH), 1775 (CO), 1725 (CO) 1500 (NH). ^1H NMR ($CDCl_3$) δ : 6.34-5.70 (m, 2H, CH=C, NH); 5.60-5.20 (m, 2H, CH_2=C); 4.84-4.30 (m, 1H, N-CH-CO), 3.74 (s, 3H, OMe); 3.40-1.95 (m, 2H, -CH_2-); 1.60 (s, 3H, CH_3-C=). M.S. (HR) m/z 199.0852 ($C_6H_{13}NO_4$ requires 199.0845).

Acidification of the aqueous solution afforded the pipecolic acid derivative (1.2g, 12%) (IR. NMR).

α-Methoxycarbonylamino- β-methyl- γ-(1-propenyl)- γ-butyrolactone.

A mixture of α-hydroxy-N-methoxycarbonylglycine (1), (4.5g. 0.03 mole), methanesulfonic acid (4.5 ml 0.06 mole) in methylene chloride-ether (60 ml, 1:1) and t-t-2,4-hexadiene (3.45 ml, 0.03 mole) was treated as described above in the general procedure. The crude oil obtained (3.7g, 58%) was purified on a Florisil column. The product (2.57g, 40%) was eluted with methylene chloride. Trituration of the oil with dry ether gave a crystalline product (m.p. 82-86°C) which is a major isomer contaminated with a minor isomer. IR($CHCl_3$) : 3440 (NH), 1785 (CO lactone), 1730 (CO carbamate), 1500 (NH). ^1H NMR ($CDCl_3$) δ: 6.28-5.40 (m, 3H, CH=CH, NH); 4.68-4.03 (m, 2H, =C-CH-O, NH-CH-CO); 3.78 (s, 3H, OMe); 2.73-2.03 (m, 1H, CH); 1.85 (d, J=5, 3H, =C-CH_3); 1.33 (d, J=6, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ : 133.44, 130.28, 127.06, 126.49, 124.21, 84.46, 57.70, 53.27, 52.66, 44.25, 40.61, 38.78, 17.81, 13.60, 13.04, 12.96. M.S. (H.R) m/z 213.1037 (M^+) ($C_{10}H_{15}NO_4$ requires 213.1001). The aqueous solution afforded on acidification the pipecolic acid derivative (0.23g, 4%) (I.R., NMR).

α-Methoxycarbonylamino- γ-methyl- γ-(2-propenyl)- γ-butyrolactone (7).

A mixture of the α-hydroxy-N-methoxycarbonylglycine 1 (14.9g, 0.1 mole) methansulfonic acid (15 ml, 0.2 mole) and 2,3-dimethyl-1,3-butadiene (11.2 ml, 0.1 mole) was treated as described above in the general procedure. The crude product (19.7g) was chromatographed over Florisil and eluted with methylene chloride-hexane. The oily product (10.65g, 50%) was a mixture of two isomers. Trituration with hexane afforded a solid, m.p. 83-86°C which was still a mixture of about 2:1 of the two isomers. IR ($CHCl_3$): 3420 (NH), 1770 (CO lactone), 1720 (CO carbamate) and 1500 cm^{-1} (NH). ^1H NMR ($CDCl_3$) δ : 5.76-5.30 (m, 1H, NH); 5.30-4.90 (m, 2H, CH_2=C); 4.90-4.22 (m, 1H, N-CH-CO); 3.80 (s, 3H, OMe); 3.38-2.18 (m, 2H, -CH_2-); 1.92 (s, 3H, CH_3-C=); 1.70 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ : 156.72, 144.67, 111.51, 110.74, 85.61, 85.36, 52.58, 51.29, 40.41, 39.50, 26.68, 25.13, 19.04, 18.26. MS (HR) m/z 213.1003. ($C_{10}H_{15}NO_4$ requires 213.1001).

The aqueous solution afforded on acidification the pipecolic acid dee. (1.55g, 7%) (IR, NMR).

α-Methoxycarbonylamino- β,β-dimethyl- γ-isobutenyl- γ-butyrolactone (4).

A mixture of α-hydroxy-N-methoxycarbonylglycine 1 (7.5g, 0.05 mole), methanesulfonic acid (7.5 ml, 0.1 mole) and 2,5-dimethyl-2,4-hexadiene (7.5 ml 0.05 mole) in methylene chloride-ether (100 ml, 1:1) was treated according to general procedure described above. The crude product (9.1g) was triturated with hexane to give a crystalline compound (4.78g, 40%),

m.p. 106-108°C after crystallization from methylene chloride-ether. The hexane solution was evaporated to give 2.05g of a mixture of two isomers. The crystalline product is according to an X-ray crystal structure analysis the α, γ cis isomer. IR($CHCl_3$): 3410 (NH), 1770 (CO lactone), 1720 (CO carbamate) and 1500 cm^{-1} (NH). ^1H NMR ($CDCl_3$) δ: 5.25-5.04 (m, 2H, CH=C, NH); 4.88 (d, J=9, 1H, O-CH-O-), 4.50 (d, J=9, 1H, N-CH-CO); 3.76 (s, 3H, OMe); 1.96 (s, 3H, CH_3-C=); 1.92 (s, 3H, CH_3-C=); 1.22 (s, 3H, CH_3); 0.92 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 174.72, 157.36, 141.95, 117.21, 82.50, 61.39, 52.58, 45.72, 26.16, 22.54, 18.52, 15.15. M.S. (H.R.) m/z 197.1420 (M^+-CO_2). (Found: C, 59.56%; H, 7.93%; N, 5.74%. $C_{12}H_{19}NO_4$ requires: C, 59.73%; H, 7.94%; N, 5.81%.

N-Methoxycarbonyl-(2-hydroxy-3-cyclopentenyl) glycinelactone (5).

To a cooled mixture (0°-5°C) of α-hydroxy N-methoxycarbonylglycine 1 (14.9g, 0.1 mole) and methanesulfonic acid (15 ml, 0.2 mole) in THF (100 ml) was added a solution of cyclopentadiene (8.3g, 0.1 mole) in THF (100 ml). The mixture was stirred at room temp. for 24 hr and neutralized with $NaHCO_3$. The THF was evaporated and the residue was treated with crushed ice and hydrochloric acid and extracted with methylene chloride (3 x 100 ml). The methylene chloride solution was dried over $MgSO_4$, filtered and evaporated. The oily residue (13.0g) was triturated with dry ether to give a solid material (7.80g, 41%), m.p. 79-82°C after crystallization (CH_2Cl_2-ether). This product is the pure exo isomer according to an X-ray crystal structure analysis. The ether solution after evaporation gave a mixture of two isomers (2.76g, 14%). IR($CHCl_3$): 3420 (NH), 1770 (CO lactone), 1720 (CO carbamate) and 1500 cm^{-1} (NH). ^1H NMR ($CDCl_3$) δ: 6.22-5.33 (m, 4H, CH=CH, NH, =C-CH-O-); 4.02 (t, J=7, 1H, HC-CH-NH); 3.70 (s, 3H, OMe); 3.36-2.92 (m, 1H, CH); 2.90-2.60 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 175.24, 156.97, 140.78, 136.51, 129.26, 127.96, 87.55, 87.03, 57.38, 53.75, 52.58, 43.52, 52.58, 43.52, 40.54, 37.17, 31.99. M.S.(H.R.) m/z 153.0776 (M^+-CO_2). (Found: C, 54.57; H, 5.56; N, 7.02; $C_9H_{11}NO_4$ requires: C, 54.82; H, 5.62; N, 7.10%).

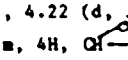
N-Methoxycarbonyl-(2-hydroxy-3-cyclohexenyl)-glycine lactone.

This compound was prepared from α-hydroxy-N-methoxycarbonylglycine 1 (7.45g, 0.05 mole), 1,3-cyclohexadiene (5.0 ml, 0.05) mole and methanesulfonic acid (7.5 ml, 0.1 mole) in methylene chloride - dry ether (100 ml, 1:1) according to the general procedure described above. The crude product (4.57g) was chromatographed over Florisil and eluted with methylene chloride-hexane (1:1). The product (3.28g, 36%) is a mixture of two isomers (NMR). IR($CHCl_3$): 3420 (NH), 1775 (CO lactone), 1720 (CO carbamate), 1500 cm^{-1} (NH). ^1H NMR ($CDCl_3$) δ: 6.38-5.60 (m, 3H, CH=CH, NH); 5.26-4.88 (m, 1H, N-CH-CO), 3.80 (s, 3H, OMe), 3.13-2.58 (m, 2H, $-CH_2$-C=), 2.58-1.77 (m, 3H, $-CH_2$-CH-). M.S (H.R.) m/z 166.0863 (M^+-CO_2). (Found: C, 56.66; H, 6.25; N, 6.56. $C_{10}H_{13}NO_4$ requires: C, 56.86; H, 6.20; N, 6.63%). Acidification of the aqueous solution afforded the pipecolic acid derivative (IR, NMR) as an oil which was purified on a silica gel column (1.36g, 13%).

Epoxidation of the vinyllactones - General Procedure: A mixture of the lactone (0.01 mole), p-chloroperbenzoic acid (PCPBA) (1.2 moles) in methylene chloride (40 ml) was refluxed overnight. The solution was washed with aqueous bicarbonate (10%, 3 x 20 ml), dried and evaporated.

5-6-Epoxy-4-hydroxy-3,3,6-trimethyl-2-methoxycarbonylaminoheptanoic acid lactone (10). The lactone 4 (0.78g, 0.003 mole) in methylene chloride (15 ml) was epoxidized as described above. The solid product (0.65g, 79%) was triturated with ether to give a solid (0.23g) which was crystallized from ether (m.p. 165-167°C) to give one isomer which is according to an X-ray crystal structure analysis 3R5R6S-3S5S6R. The ether solution was evaporated and the mixture separated on a Florisil column with methylene chloride as eluent. The second less polar isomer was eluted first (0.21g, 25%)) followed by an additional fraction of the more polar isomer (0.11g). The total yield of the polar isomer was 41%. IR($CHCl_3$): 3420 (NH), 1795 (CO lactone) 1735 (CO carbamate), 1515 cm^{-1} (NH). ^1H NMR (polar isomer) δ : 5.33 (d, J=8, 1H, NH), 4.40 (d, J=8, 1H, -CH-)-CO), 3.93 (d, J=8, 1H, (N-CH-CO), 3.68 (s, 3H, MeO), 2.80 (d, J=8, 1H), 1.40 (s, 6H, ), 1.26 (s, 3H, Me), 1.02 (s, 3H, Me). M.S(H.R) m/z 257.1310 ($C_{12}H_{19}NO_5$ requires: m/z 257.1263).

The less polar isomer showed a similar I.R. and NMR spectra.

N-Methoxycarbonyl-(3,4-epoxy-2-hydroxycyclopentyl)glycine lactone (11). This epoxylactone was prepared from the lactone 5 (1.5g, 0.008 mole) according to the general procedure described above. The oily product was triturated with ether to give a solid (0.88g, 54%) which was crystallized from ether (m.p. 119-121°C). The product is one isomer according to ^{13}C NMR and an X-ray crystal structure analysis. The ether solution was evaporated to give a mixture of two isomers (0.3g, 19%). IR($CHCl_3$): 3420 (NH), 1790 (CO lactone), 1730 (CO carbamate), 1510 cm^{-1} (NH). ^1H NMR ($CDCl_3$) δ: 5.80-5.38 (m, 1H, NH), 5.04 (d, J=8, 1H, -CHO), 4.22 (d, J=8, 1H, N-CH-CO), 4.10 (d, J=8, N-CH-CO), 3.70 (s, 4H, OMe, -CH-), 3.30-1.90 (m, 4H, ). ^{13}C NMR ($CDCl_3$) δ: 175.63, 159.98, 81.86, 59.45, 57.25, 52.28, 41.57, 30.95. M.S.(H.R) m/z 213.0638 ($C_9H_{11}NO_5$ requires 213.0633). (See X-ray crystal structure).

N-Methoxycarbonyl-(3,4-epoxy-2-hydroxycyclohexyl)glycine lactone (12). Epoxidation of lactone (cyclohexyl) (1.88g, 0.009 mole) was accomplished according to the general procedure described above. The oily product which was chromatographed over Florisil (0.97g, 48%) was triturated with ether-hexane and crystallized from ether to give a pure isomer (m.p. 112-114°C) according to an X-ray crystal structure analysis. The ether solution was a mixture of isomers. IR($CHCl_3$): 3420 (NH), 1790 (CO), 1725 (CO) and 1505 cm^{-1} (NH). ^1H NMR ($CDCl_3$) : 5.33-4.98 (m, 1H, NH), 4.76-4.13 (m, 2H, -CH-O, N-CH-CO), 3.63 (s, 3H, OMe), (- ), 2.80-1.43 (m, 5H, $(CH_2)_3$-CH). M.S. (H.R) m/z 227.0787 ($C_{10}H_{13}NO_5$ requires: m/z 227.0789).

Epoxidation of lactone 2, lactone 6 and lactone 7 afforded oily mixtures of isomers which did not separate on Florisil columns.

Ozonolysis of the vinyllactones - General Procedure. A mixture of the lactone (0.01 mole) in dry methanol (30ml) was placed in a three necked flask equipped with a thermometer, an inlet tube and an outlet tube. The flask was cooled to -70°C and reaction mixture was magnetically stirred while ozone was bubbled through the solution until a blue-violet colour appeared. The ozone was formed at 95V and a pressure of 3.5 psi. The excess ozone was removed by the bubbling of oxygen (disappearance of the blue colour). The ozonide solution was decomposed with dimethylsulfide (1.4 eq) and stirred for an additional 3 hr at room temp. The methanol was then evaporated and the product treated as described below.

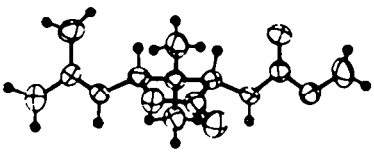
Methyl N-methoxycarbonyl-4-pyrrolidone-2-carboxylate (16a). The crude hemiacetal 14a, (3.47g, 93%), obtained by the ozonolysis of the vinyllactone 2 (3.15g, 0.017 mole) in dry methanol according to the general procedure, was redissolved in dry methanol (30 ml), triethylamine (1 ml) was added and the solution was refluxed overnight. The oily product (15a) obtained after the removal of the methanol (2.06g, 89%) was dissolved in methylene chloride (150 ml)

methanesulfonic (1.5 ml, 0.018 mole) was added and the solution was refluxed for 48hr. The organic layer was washed with water (3 x 50 ml), separated and dried. The crude product (1.46g, 90%) was chromatographed over Florisil and eluted with methylene chloride to give the pyrrolidone derivative (1.3g, 80%). IR($CHCl_3$): 1765 (CO pyrrolidone), 1745 (CO ester), 1710 cm^{-1} (CO carbamate). ^1H NMR($CDCl_3$)δ: 5.00-4.66 (m, 1H, N-CH-CO), 3.93 (s, 2H, N-CH_2-CO), 3.78 (s, 3H, Me), 3.00-2.64 (m, 2H, CH_2CO). M.S(HR) m/z 201,0642 ($C_8H_{11}NO_5$ requires 201.0633).

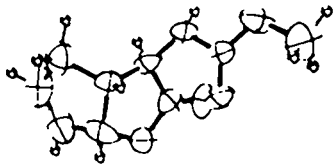
Methyl N-methoxycarbonyl-3,3-dimethyl-4-pyrrolidone 2-carboxylate (16b). This compound was prepared from the lactone 11 by ozonolysis, rearrangement of the hemiacetal and water elimination as described above. The product which was obtained in 73% yield (from the hemiacetal) was purified on a Florisil column and eluted with methylene chloride (m.p. 46-47°C). IR($CHCl_3$): 1760 (CO), 1740 (CO ester), 1710 (CO carbamate). ^1H NMR ($CDCl_3$)δ:4.38 (s, 1H, N-CHCO), 3.93 (s, 2H, N-CH_2-CO), 3.66 (s, 3H, OMe), 3.63 (s, 3H, OMe), 1.26 (s, 3H, CH_3), 1.08 (s, 3H, CH_3). M.S.(HR) m/z 229.0962 ($C_{10}H_{15}NO_5$ requires m/z 229.0950).

Methyl N-methoxycarbonyl-3,4-pyrrolidone 2-carboxylate (16c). The crude hemiacetal (14b) was obtained by the ozonolysis of the lactone 4 (1.88g), as described above, and was treated with triethylamine (1 ml) in refluxing methanol (24 hr). The rearranged product was according to the nmr, a mixture of isomers. It was dissolved in methylene chloride (30 ml), methanesulfonic acid (1.8 ml) was added and the mixture was refluxed (48 hr) to give the pyrrolidone derivative (1.02g). The oily product was purified on a Florisil column and eluted with methylene chloride. It is according to the nmr a mixture of two isomers (cis-trans, 1:1) I.R.($CHCl_3$): 1760 (CO), 1745 (CO), 1705 cm^{-1} (CO carbamate). ^1H NMR ($CDCl_3$) : 4.80 (d, J=8, 1H, N-CH-CO); 4.25 (d, J=4, 1H, N-CH-CO), 3.76 (s, 2H, N-CH_2CO), 3.66 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.30-2.30 (m, 1H, CHCO) 1.30 (d, J=6, 3H, CH_3), 1.10 (d, J=6, 3H, CH_3). M.S. (H.R.) m/z 215.0787; ($C_9H_{13}NO_5$ requires 215.0793).

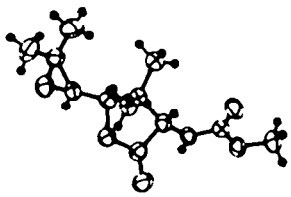
X-ray crystal structures



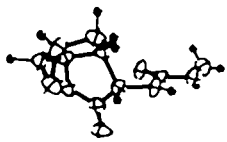
4



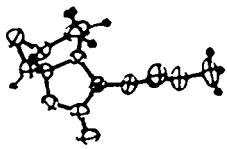
5



10



11



12

References

1. For a preliminary report of this work see: D. Ben-Ishai and S. Hirsh, Tetrahedron Lett., 1983, 24, 955.
2. D. Ben-Ishai, R. Moshenberg, and J. Altman, Tetrahedron, 1977, 33, 1533.
3. S.M. Weinreb and J.I. Levin, Heterocycles, 1979, 12, 949.
4. H.E. Zaugg, Synthesis, 1984, 181.
5. D. Ben-Ishai and Z. Bernstein, unpublished results.
6. D. Ben-Ishai, I. Satati, and Z. Bernstein, Tetrahedron, 1976, 32, 1571.
7. W. Seelinger and W. Diepers, Liebigs Ann. Chem., 1966, 697, 171.
8. R.R. Schmidt, Chem. Ber., 1970, 3242.
9. R. Kuhn and G. Oswald, Chem. Ber., 1956, 89, 1423.