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Reactions of Pyrrolidine Enamines of Cyclic and Acyclic 3,4-Dioxobutanoic Acid Derivatives with Dimethyl Acetylenedicarboxylate. A New Case of Atropoisomerism.

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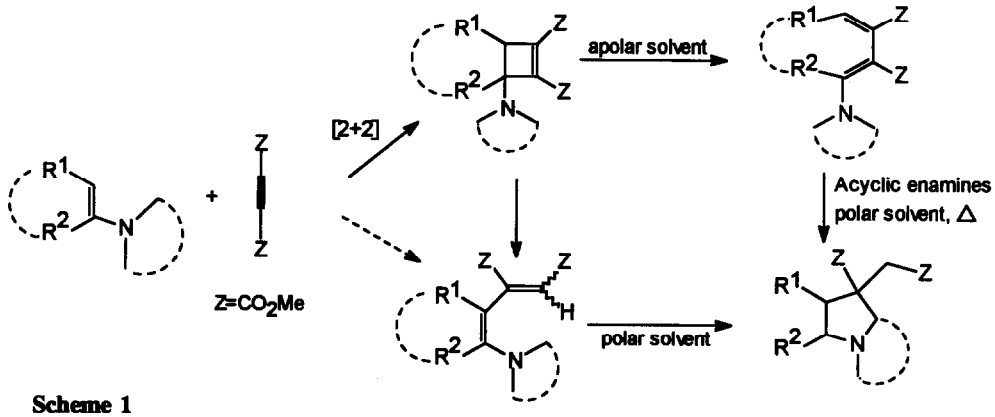
Dedicated to the memory of Professor Francisco Fariña for his contribution to 5-alkoxyfuran-2(5H)-ones chemistry.

Abstract: Reaction conditions and structure of the starting enamines (cyclic or open-chain) determine greatly the final products of the title reactions. Whereas in benzene and acetonitrile, DMAD and **1** give a mixture of the diastereoisomeric dienamines **5**, in methanol they afford pirrolizine **3**. Enaminofuranones **2** and **10** furnish the corresponding "Michael adducts" **7a,b,c** and **11a,b,c** but fail to yield pirrolizines. It has been demonstrated that above **b** and **c** adducts differ exclusively on the arrangement of groups around a chiral axis.

INTRODUCTION

Reactions of tertiary enamines with electron-deficient acetylenes, such as dimethyl acetylenedicarboxylate (DMAD) or propiolate, have been previously reported.[1] It is generally accepted that initially a [2+2] cycloadduct is formed, but the final products differ greatly depending on the starting compound structure and reaction conditions, such as solvent[2] and temperature[3] (Scheme 1).



Scheme 1

Cycloadditions of cyclic ketone enamines to electron-withdrawing substituted acetylenes have been specially studied, because of the ring-enlargement caused by thermal rearrangement of previously formed

bicyclic cyclobutene in apolar solvents.[1a-c,3] These reactions provide a useful methodology to obtain medium-sized heterocycles[4] or azulenes and they are the key step in the synthesis of several natural products such as steganone,[5] velleral[6] and muscone.[7]

Moreover, it has been reported that, in polar solvents, cyclobutene adducts mainly evolve, through the corresponding 1,3-dienamines, to a cyclization product between the α-position of the tertiary amine moiety and the C-3 of the dienamine.[8] In the case of pyrrolidine enamines a pyrrolizine system is formed.[2b]

Reactions of ß-amino α,ß-unsaturated esters with electron-deficient acetylenes have been scarcely studied. As far as we knew, the reaction of ethyl 3-anilinobut-2-enoate published more than twenty years ago,[9] was the only case reported. But recently, when our work was already completed, two papers of Viehe and col.[10], have been appeared in the literature. Antecedents of the same reactions on 4-enaminofuranones have not been found.

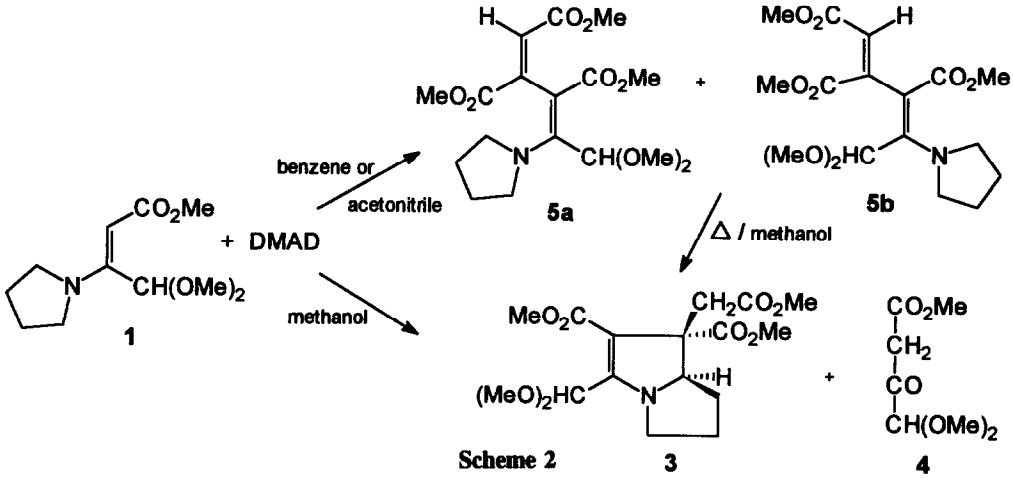
In previous papers we have described a convenient method of preparing methyl (*E*)-4,4-dimethoxy-3-(pyrrolidin-1-yl)but-2-enoate (**1**)[11] and its cyclic analogue, 5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one(**2**).[12] The pyrrolizines that we expect to obtain from the reactions of these substrates with DMAD in polar solvents, are appropriately functionalized and may serve as versatile synthetic intermediates for the construction of fused heterocyclic ring systems. On the other hand, in apolar solvents, the thermal rearrangement of the cycloadduct obtained from enamine **2** would afford the corresponding seven membered ring lactone.

We have studied the reactions whose results are given in this paper, in order to confirm our expectations, and to establish if the open-chain ß-enaminoester **1** and furanone **2** present a different behaviour towards DMAD, as we have demonstrated with other reagents.[13]

RESULTS AND DISCUSSION

Reaction of methyl (E)-4,4-dimethoxy-3-(pyrrolidin-1-yl)but-2-enoate (**1**)

The reaction in methanol of the enamine **1** and DMAD in equimolar amounts, after 24 h at room temperature, affords the pyrrolizine **3** (32%), as sole diastereoisomer with a *cis* relationship between the methoxycarbonyl group and the bridghead hydrogen atom (Scheme 2).



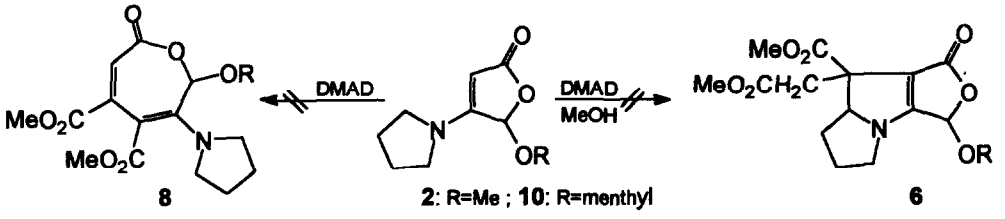
Scheme 2

This assignment is based on the comparison of their ^{1}H and ^{13}C RMN spectral data with those published for analogous compounds.[1d] The great stereoselectivity observed is in accordance with the one reported for the reaction of methyl (*E*)-3-phenyl-3-(pyrrolidin-1-yl)but-2-enoate.[10b] The β-ketoester **4**, formed by hydrolysis of the starting enamine, was also isolated in 25% yield. Enamine **1** reacts with an equimolar amount of DMAD at room temperature in an apolar solvent (benzene), and also in acetonitrile, to give a mixture of stereoisomeric 1,3-dienamines **5a,b** (**a/b**= 1.5). These dienamines, although they could not be separated, were isolated in 71% of combined yield, when the solvent was removed at ambient temperature and the residue was subjected to a fast chromatography on silica gel. The above dienamines mixture was completely transformed in the bicyclic compound **3**, when it was allowed to stand in methanolic solution for five days at room temperature, or instantaneously by heating.

The behavior of methyl (*E*)-4,4-dimethoxy-3-(*N*-piperidyl)but-2-enoate towards DMAD parallel that observed with enamine **1**. Thus, the reaction in benzene afforded the corresponding dienamines,[14] and in methanol as solvent lead to the indolizine derivative[15] generated by α-cyclization.

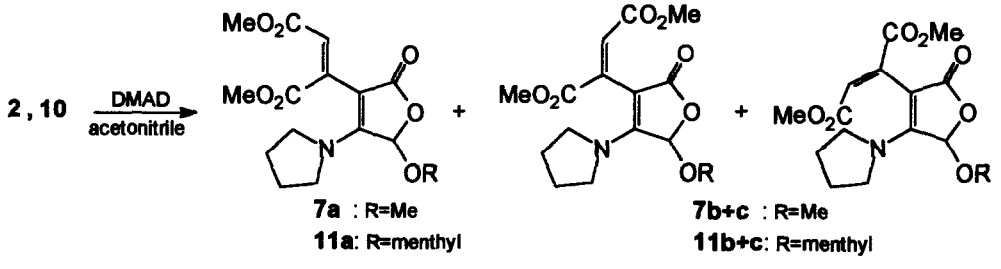
Reaction of 5-alkoxy-4-(pyrrolidin-1-yl)furan-2(5H)-ones

In order to obtain furopyrrolizines **6**, we attempted the reaction of enamine **2** with DMAD in methanol. Surprisingly, either at room temperature or under heating, the enamine **2** is fully recovered and the same occurs in acetonitrile at room temperature.[16]



Scheme 3

However, by prolonged heating in acetonitrile, with an excess of DMAD, the enamine **2** was completely transformed in the three isomeric products **7a,b,c** (Scheme 4). Chromatographic separation affords pure **7a** and a mixture of **7b** and **7c**. All the attempts to separate the above mixture were unsuccessful.



Scheme 4

Structure of **7a** was easily established on the basis of olefinic proton chemical shift (Table I), molecular formula and ^{13}C RMN data. However, from the spectroscopic data of **7b+7c** it can not be

determined unequivocally their structures (Tables I and II). ^{1}H RMN spectrum of **7b+7c** mixture indicated

Table 1: ^{1}H NMR data of compounds **7** and **11**.

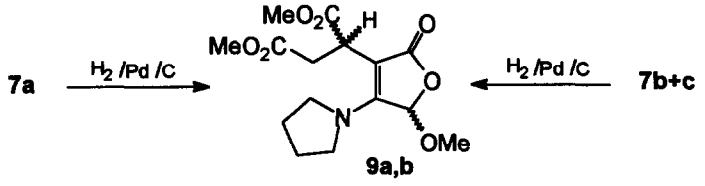
	7a	**7b+7c**	**11a**	**11a+11b**
HC=	5.87*	7.02, 6.98	5.82*	7.01, 6.97
H-5'	5.65*	5.80	5.78*	5.87
CO_2CH_3	3.84, 3.76	3.81, 3.73, 3.72	3.84, 3.75	3.81, 3.72

* Values with an asterisk may be interchanged within the same column.

Table 2: ^{13}C NMR data of compounds **7** and **11**.

	7a	**7b+7c**	**11a**	**11b+11c**
C-2'	169.8	166.8	169.9	170.1
$\underline{C}O_2CH_3$	167.2, 165.1	165.1, 164.9	167.6, 165.3	166.8, 165.3, 164.8
C-4'	158.7	158.5	159.9	159.7
C-2	137.6	136.6, 136.0	138.4	136.3, 136.1
C-3	124.1	130.2, 129.4	123.9	129.7, 129.6
C-5'	97.7	97.9, 97.8	96.9	96.8
C-3'	90.6	89.7, 88.6	91.1	89.6
$CO_2\underline{C}H_3$	52.5, 51.7	53.0, 51.9	52.7, 51.9	52.7, 51.6

the presence of two olefinic protons (7.02 and 6.98 ppm) that is compatible with the following mixtures: one of them formed by the ring-expanded compound **8** and a diastereoisomer of **7a**, with the opposite double bond configuration (**7b** or **7c**), and the other one composed of **7b** and **7c**. The definitive assignment of the structures **7b,c** was achieved by chemical correlation. The formation of diastereoisomers **9a,b** by Pd/C catalytic hydrogenation, from either **7a** or a **7b+7c** mixture, confirms that these two late compounds are



Scheme 5

stereoisomers of **7a**.[17] The existence of two "real" rotamers of *E* configuration on exocyclic double bond is only possible if a chiral axis exists because hindered rotation around the σ C_2-C_3· bond.[18] The severe steric crowding around this axis forcing the furanone ring to take a position out of the butendioate plane and therefore inducing the existence of atropisomerism.

Unlike dienamines **5**, dienaminofuranones **7** fail to be transformed in pyrrolizines **6**. In fact, a mixture of **7a,b,c** remained unaltered after 48 h in refluxing *n*-butanol.

All chiral products described up to now are racemic mixtures. With the aim to obtain non racemic

compounds and to attain to rotamers separation, we carried out the reaction of DMAD with enantiomerically pure menthyloxyenamine **10**, recently described by us.[19]

The reaction of **10** with DMAD in refluxing acetonitrile for five days afforded the expected "Michael adducts" **11a-c**.[20] The results obtained in this case parallel those of the racemic enamine **2**, but unfortunately, the isolation of pure diastereoisomers was not achieved.

In summary, the results described herein indicate that the final products obtained in the reactions with DMAD depend greatly on the enaminoester structure (cyclic or open-chain). The reaction of **1** with DMAD provides a convenient entry to functionalized pyrrolizine that is a valuable intermediate, in particular for the synthesis of fused heterocyclic ring systems. It is remarkable the different reactivity of both types of enamines: whereas **1** reacts readily at room temperature, **2** and **10** need prolonged heating to be transformed. The atropisomerism observed in *E* Michael adducts **7b,c** and **11b,c** is noteworthy, since no other cases of this kind have been described.

EXPERIMENTAL PART

Column chromatography was performed on 230-400 mesh silica gel (Merck) and analytical TLC on Merck DC-Alufolien with F_{254} silica gel 60. Melting points were determined on a Gallenkamp apparatus in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-200-SY instrument in $CDCl_3$. J values are given in Hz. Multiplicities in ^{13}C spectra were determined by DEPT experiments. IR spectra were recorded on a Perkin-Elmer model 681 spectrophotometer, ν values in cm^{-1}. Mass spectra were recorded on a Hewlett-Packard 5985 spectrometer using electron impact at 70 eV. Microanalyses were performed with a Heraus analyzer.

Reactions of methyl (E)-4,4-dimethoxy-3-(pyrrolidin-1-yl)but-2-enoate (1) with DMAD.

A) To a solution of **1** (0.76 g, 3.31 mmol) in methanol (8.2 ml) was added DMAD (0.47 g, 3.31 mmol). The mixture was stirred for 24 h at room temperature. After solvent evaporation in vacuo, ^1H NMR analysis of the residue showed only the presence of methyl 4,4-dimethoxy-3-oxobutanoate (**4**) and pyrrolizine **3**. These compounds were separated and purified by flash column chromatography (ethyl acetate/hexane 2:1).

Dimethyl 3-dimethoxymethyl-1-methoxycarbonylmethyl-5,6,7,7a-tetrahydro-1H-pyrrolizine-1,2-dicarboxylate (3).- Yellow solid, recrystallized from cyclohexane mp 86-7 °C. Yield 32% (0.39 g). IR (KBr): 1740, 1680, 1585. ^1H RMN: 5.83 (s, 1H, $\underline{H}C(OCH_3)_2$); 4.43 (dd, 1H, H_{7a}, J=4.9 and J=10.9); 3.71 (d, 1H, $C\underline{H}_2CO_2CH_3$, J=17.5); 3.71, 3.67, 3.66 (3s, 3x3H, CO_2CH_3); 3.65 (m, 2H, NCH_2); 3.54, 3.43 (2s, 2x3H, OCH_3); 3.35 (m, 1H, CH_2N); 2.60 (d, 1H, $C\underline{H}_2$-CO_2CH_3); 1.82 (m, 3H, CH_2); 1.43 (m, 1H, CH_2). ^{13}C NMR: 174.8, 172.5, 165.5 (C=O); 161.2 (C-3); 102.8 (C-2); 99.7 ($\underline{C}H(OCH_3)_2$); 71.8 (C-7a); 57.0 (C-1); 55.4, 53.9, 52.4, 51.6, 50.4 (OCH_3); 47.0 (C-5); 36.8 ($\underline{C}H_2CO_2CH_3$); 26.8, 24.6 (C-6, C-7). MS, m/z (relative intensity): 371 (M^+, 9), 356 (3), 340 (9), 324 (11), 280 (100), 236 (32); 75 (31), 59 (75).

Methyl 4,4-dimethoxy-3-oxobutanoate (4).[21] - Oil. Yield 25% (0.14 g).IR (film): 1765, 1740. ^1H NMR: 4.58 (s, 1H,$\underline{H}C(OCH_3)_2$); 3.73 (s, 3H, CO_2CH_3); 3.59 (s, 2H, CH_2); 3.43 (s, 6H, OCH_3). ^{13}C NMR: 197.6 (C-3), 167.1 (C-1), 103.5 (C-4), 54.7 (OCH_3), 51.9 ($CO_2\underline{C}H_3$), 43.9 (C-2).

B) To a solution of methyl (*E*)-4,4-dimethoxy-3-(pyrrolidin-1-yl)but-2-enoate (**1**) (1.23 g, 5.3 mmol) in acetonitrile or benzene (13.2 ml) was added an equimolar amount of DMAD in the same solvent (0.6 ml). Stirring was maintained during 48 h at room temperature. The solvent was removed under reduced pressure

below 30 °C. The residual oil was quickly purified by column chromatography (ethyl acetate:dichloromethane 1:5) to afford a mixture 60:40 of methyl hexa-2,4-dienoates (**5a** and **5b**) respectively (1.41 g, 71% yield), and traces of pyrrolizine **3**.

Methyl (2*E*, 4*E*) and (2*Z*, 4*Z*)-6,6-dimethoxy-3,4-di(methoxycarbonyl)-5-(pyrrolidin-1-yl)-hexa-2,4-dienoates (5a and 5b).- IR (film): 1730, 1685, 1595, 1555. ^{1}H NMR (**5a**): 6.49 (broad, 2x1H, HC=, $\underline{H}C(OCH_3)_2$); 3.76, 3.63, 3.60 (3s, 3x3H, CO_2CH_3); 3.41 (s, 6H, OCH_3) 3.40 (m, 4H, CH_2N); 1.90 (m, 4H, CH_2); (**5b**): 5,32 (s, 1H, HC=); 5.07 (s, 1H, $\underline{H}C(OCH_3)_2$); 3.77, 3.63, 3.60 (3s, 3x3H, CO_2CH_3); 3.43 (s, 6H, OCH_3); 3.40 (m, 4H, CH_2N); 1.90 (m, 4H, CH_2); ^{13}C NMR:(**5a**) 168.8, 165.4 (C=O), 159.2 (C-5), 142.8 (C-3), 122.2 (C-2), 103.5 (C-6), 94.7 (C-4), 55.5, 52.1 (OCH_3) 51.7 (CH_2N), 50.8, 50.4 (OCH_3), 24.6 (CH_2); (**5b**) 168.7, 165.5 (C=O), 160.5 (C-5), 146.0 (C-3), 116.1 (C-2), 104.0 (C-6), 95.9 (C-4), 55.8, 52.3 (OCH_3) 52.1 (CH_2N), 51.5, 50.0 (OCH_3), 24.2 (CH_2). MS, m/z (relative intensity): 371 (M^+, 9), 356 (9), 340 (14), 296 (19), 280 (37), 84 (56), 75 (100).

Reactions of 5-methoxy-4-(pyrrolidin-1-yl)furan-2(5H)-one (2) with DMAD.

A) A solution of **2** (99 mg, 0.54 mmol) and DMAD (77 mg, 0.54 mmol) in methanol (1.4 ml) was stirred 12 h at room temperature and no changes were observed on the starting compounds (TLC). The solution was then heated 4 days under reflux and the solvent was removed at vacuo. Column chromatography of the residue affords a 55:45 mixture of dimethyl (*E*)- and (*Z*)-2-methoxybut-2-endioate (132? mg, mmol) and furanone **2** (91 mg, 0.52 mmol).

B) A solution of **2** (549 mg, 3 mmol) and DMAD (852 mg, 6 mmol) in acetonitrile (7.5 ml) was heated for 100 h under reflux. The disappearance of the starting enamine **2** was monitored by TLC (ethyl acetate/hexane 4:1). The solvent was removed and the residue separated by column chromatography to yield compounds **7a** and **7b**+**7c**.

Dimethyl (*Z*)-2-[5'-methoxy-2'-oxo-4'-(pyrrolidin-1''-yl)-2',5'-dihydrofuran-3'-yl]butendioate (7a).- White solid, recrystallized from toluene mp 129-33 °C. 33% Yield. IR (nujol): 1745, 1730, 1665, 1580. ^{1}H NMR: 5.87, 5.65 (2s, 2x1H, HC=, $\underline{H}C\text{-}OCH_3$); 3.84, 3.76 (2s, 2x3H, CO_2CH_3); 3.52 (s, 3H OCH_3); 3.51 (m, 1H, CH_2N); 3.41 (m, 3H, CH_2N), 1.97 (m, 4H, CH_2). ^{13}C NMR: 169.8, 167.2, 165.1 (C=O), 158.7 (C-4'), 137.6 (C-2), 124.1 (C-3), 97.7 (C-5'), 90.6 (C-3'), 55.1, 52.5, 51.7 (OCH_3), 50.2 (CH_2N), 24.9 (CH_2). EM, m/z (relative intensity): 325 (M^+, 100), 294 (40), 266 (21), 250 (15), 70 (32), 59 (39).UV (methanol):217 (7540), 278 (15350), 336 (7540).Analysis calcd. for $C_{15}H_{19}O_7N$: C, 55.38; H, 5.85; N, 4.31. Found: C, 55.56; H, 5.88; N, 4.60.

Dimethyl (*E*)-2-[5'-methoxy-2'-oxo-4'-(pyrrolidin-1''-yl)-2',5'-dihydrofuran-3'-yl]butendioate (7b) +**(7c).**-Yellow solid, recrystallized from carbon tetrachloride mp 113-5 °C. 26% Yield. IR (KBr): 1740, 1725, 1625, 1600. ^{1}H NMR: 7.02, 6.98 (2s, 2x1H, HC=); 5.80 (s, 2x1H $\underline{H}C\text{-}OCH_3$); 3.81, 3.73 (2s, 2x6H, CO_2CH_3); 3.51, 3.49 (2s, 2x3H, OCH_3); 3.48 (m, 2H, CH_2N); 3.30 (m, 4H, CH_2N); 3.05 (m, 2H, CH_2N); 1.93 (m, 2x4H, CH_2). ^{13}C NMR: 166.8, 165.1, 164.9 (C=O), 158.5 (C-4'), 136.6, 136.0 (C-2), 130.2, 129.4 (C-3), 97.9, 97.8 (C-5'), 89.7, 88.6 (C-3'), 53.7, 53.0, 51.9 (OCH_3), 49.4, 49.0 (CH_2N), 25.0 (CH_2). EM, m/z (relative intensity): 325 (M^+, 22), 310 (20), 294 (9), 266 (9), 250 (10), 70 (31), 59 (100). UV (methanol): 223 (9950), 284 (18950), 366 (2250). Analysis calcd. for $C_{15}H_{19}O_7N$: C, 55.38; H, 5.85; N, 4.31. Found: C, 55.25; H, 5.91; N, 4.81.

Dimethyl 2-[5'-methoxy-2'-oxo-4'-(pyrrolidin-1''-yl)-2',5'-dihydrofuran-3'-yl]butandioate (9a,b)

A) A suspension of **7a** (27 mg, 0.083 mmol), ethanol (0.1ml) and 10% Pd/C (0.4 mg) was hydrogenated under atmospheric pressure at room temperature. After 150 min with stirring, the reaction mixture was filtered and the solvent removed in vacuo. The residue contains only compounds **9a** and **9b** in a ratio 87:13 (^{1}H NMR). Cuantitative yield (27 mg).IR (film): 1755, 1725, 1630. ^{1}H NMR, (**9a**): 5.61 (s, 1H HC-OCH_3); 4.21 (dd, 1H, $CHCO_2CH_3$, J=6.5, J=7.4); 3.73 (m, 2H, CH_2N); 3.58 (m, 2H, CH_2N); 3.69, 3.67 (2s, 2x3H, CO_2CH_3); 3.45 (s, 3H, OCH_3); 3.27 (dd, 1H, $CH_2CO_2CH_3$, J=17.2, J=6.5); 2.89 (dd, 1H, $CH_2CO_2CH_3$, J=17.2, J=7.4); 1.99 (m, 4H, CH_2).(**9b**) 5.62 (s, 1H HC-OCH_3); 4.20 (dd, 1H, $CHCO_2CH_3$, J=7.6, J=6.5); 3.72 (m, 4H, CH_2N); 3.69, 3.65 (2s, 2x3H, CO_2CH_3); 3.42 (s, 3H, OCH_3); 3.27 (dd, 1H, $CH_2CO_2CH_3$, J=17.1, J=6.5); 2.86 (dd, 1H, $CH_2CO_2CH_3$, J=17.1, J=7.4); 1.99 (m, 4H, CH_2). ^{13}C NMR, (**9a**): 172.9, 172.5, 171.9 (C=O), 157.4 (C-4'), 98.1 (C-5'), 91.2 (C-3'), 53.9, 52.5, 51.6 (OCH_3), 49.2 (CH_2N), 36.5 (C-2), 34.2 (C-3) 25.1 (CH_2). EM, m/z (relative intensity): 327 (M^+, 36), 312 (6), 296 (14), 295 (32), 268 (45), 254 (13), 236 (100), 183 (4), 70 (6), 59 (8).

B) Following the above procedure from a mixture of **7b** and **7c**, a 47:53 diastereoisomeric mixture (**9a** and **9b**) of the hydrogenated compound was also obtained in cuantitative yield.

Reaction of (5S)-5-(l-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5H)-one (10) with DMAD in acetonitrile.

A solution of **10** (1.991 g, 6.5 mmol) and DMAD (3.681 g, 26 mmol) in acetonitrile (31.5 ml) was kept under reflux for 5 days. After solvent removal, the residue was chromatographed on silica gel (hexane/ketone/ethyl acetate 8:1:1) to afford compounds **11a**, (**11b+11c**) and an unknown compound in a 47:25:28 ratio (^{1}H NMR).

Dimethyl (*Z*)-2-[5'-(*l*-menthyloxy)-2'-oxo-4'-(pyrrolidin-1''-yl)-2',5'-dihydrofuran-3'-yl]butendioate (11a).- 24% Yield. IR ($CHCl_3$): 1725, 1635, 16150. ^{1}H NMR: 5.82, 5.78 (2s, 1H, 1H, HC=, $HCOCH_3$); 4.1-3.2 (m, 1H ment., 4H, CH_2); 3.84, 3.75 (2s, 2x3H, CO_2CH_3); 2.3-0.6 (m, 18H, ment., 4H, CH_2). ^{13}C NMR: 169.9, 167.6, 165.3 (C=O), 159.9 (C-4'), 138.4 (C-2), 123.9 (C-3), 96.9 (C-5'), 91.1 (C-3'), 79.6 (CH ment.), 52.7, 51.9 (OCH_3), 50.4 (CH_2N), 48.2 (CH ment.), 42.3 (CH_2 ment.), 33.9 (CH_2 ment.), 31.6 (CH, ment.), 25.1 (CH_2), 25.1 (CH, ment.), 22.7 (CH_2, ment.), 22.2, 21.2, 15.7 (CH_3, ment.).

Dimethyl (*E*)-2-[5'-(*l*-menthyloxy)-2'-oxo-4'-(pyrrolidin-1''-yl)-2',5'-dihydrofuran-3'-yl]butendioate (11b)+(11c).-Yellow solid, recrystallized from cyclohexane mp 118-9 °C. 12% Yield. IR (KBr): 1735, 1720, 1625, 1600. ^{1}H NMR: 7.01, 6.97 (2s, 2x1H, HC=); 5.87 (s, 2H $HCOCH_3$); 3.81, 3.72 (2s, 2x6H, CO_2CH_3); 3.7-2.9 (m, 2x1H, ment., 2x4H, CH_2); 2.4-0.7 (m, 2x18H ment., 2x4H, CH_2). ^{13}C NMR: 170.1, 166.8, 165.3, 164.8 (C=O), 159.7 (C-4'), 136.3, 136.1 (C-2), 129.7, 129.6 (C-3), 96.8 (C-5'), 89.6 (C-3'), 77.7 (CH ment.) 52.7, 51.6 (OCH_3), 49.1 (CH_2N), 48.1 (CH ment.), 41.9 (CH_2 ment.), 33.8 (CH_2 ment), 31.4, 24.8 (CH ment.), 22.6 (CH_2), 22.0, 21.1, 15.6 (CH_3 ment.). EM, m/z (relative intensity): 449 (M^+, 20), 311 (100), 294 (16), 282 (61), 279 (33), 70 (24), 59 (13). Analysis calcd. for $C_{24}H_{35}O_7N$: C, 64.14; H, 7.80; N, 3.13. Found: C, 64.23; H, 8.00; N, 3.20.

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14. Significative ^{1}H NMR data of Methyl 6,6-dimethoxy-3,4-di(methoxycarbonyl)-5-(*N*-piperidyl)-hexa-2,4-dienoates; (2*E*, 4*E*)-isomer: 6.49 (s, 2H, HC=, C<u>H</u>$(OCH_3)_2$; (2*Z*, 4*Z*): 5.29, 5.23 (2s, 2H, HC=, C<u>H</u>$(OCH_3)_2$).
15. ^{1}H NMR data of dimethyl 3-dimethoxymethyl-1-methoxycarbonylmethyl-2,3-dehydro-1*H*-indolizidine-1,2-dicarboxylate: 5.83 (s, 1H, C<u>H</u>$(OCH_3)_2$), 4.43 (dd, 1H, H_{8a}, J=10.9, 4.9), 3.80 (d, 1H, C<u>H</u>$_2CO_2CH_3$, J=17.8), 3.71, 3.67, 3.66 (3s, 3x3H, CO_2CH_3), 3.54, 3.43 (2s, 2x3H, OCH_3), 2.61 (d, 1H, C<u>H</u>$_2CO_2CH_3$, J=17.8), 2.0-1.4 (m, 6H).
16. In these conditions, intact enamine **2** was recovered. In contrast, to the result with enaminoester **1**, wherein was isolated the hydrolysis product **3** of unreacted starting compound.
17. ^{13}C RMN spectrum of **7b+7c** mixture is compatible with the proposed assignment.
18. ^{1}H NMR spectra of **7b+7c** mixture are recorded at temperatures ranging from 287 to 333 °K, in toluene-d_8 as solvent. The signals of all significative protons, including those of the methoxy groups, are observed for both rotamers at lowest temperature (287 °K). However, at 323 °K the coalescence of the above signals was observed, because rotation around C_2-C_3 becomes posible (rotation barrier ≈17 Kcal./mol).
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20. Separation of **11b** from **11c** was not possible. Compound **11a** is contaminated with an unknown product, which may correspond, by its ^{1}H NMR signals (6.62, 6.54, 5.76, 5.70, 3.78, 3.75, 3.74, 3.67, 3.64, 3.53, 3.52 ppm and the corresponding of pyrrolidine and menthyl groups), to an 2:1 adduct of DMAD and **10** as diastereoisomeric mixture.
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