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Dimethyl 3-Methylglutaconate: a Useful Reagent for the Diastereoselective Synthesis of Functionalized 5,6-Dihydro-2*H*-Pyran-2-ones

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Abstract: Condensation of dimethyl 3-methylglutaconate with aldehydes leads to the formation of 6-substituted 5,6-dihydro-2*H*-pyran-2-ones through aldolisation followed by cyclization. The conditions of the aldolisation reaction in order to increase diastereoselectivity are described. Chiral aldehydes and aminoaldehydes have been used. The 6-substituted 5,6-dihydro-2*H*-pyran-2-ones prepared from aminoaldehydes could be interesting protease inhibitors.

Introduction

5,6-Dihydro-2*H*-pyran-2-ones are heterocycles found in natural products showing interesting biological activity. For instance, Withaferin A[1] and (+)-Asperlin[2] containing such a ring have been described as antibiotic and antitumoral agents. (+)-Goniotriol[3] was also found to exhibit antitumoral activity. Kawain,[4] another 5,6-dihydro-2*H*-pyran-2-one derivative is available commercially as a psychotrope.

An increasing number of HIV protease inhibitors are currently undergoing clinical evaluation; among these derivatives, non peptidic inhibitors containing 5,6-dihydro-2H-pyran-2-ones showed promising activity.[5,6] The dihydropyrone ring interacts simultaneously with the catalytic aspartic acids and the flap of HIV protease. Substitution at position 6 of the ring is important to fill in the S1 and S2 pockets of the protease.

In an attempt to design new protease inhibitors, we have been looking for a general method of preparation of functionalized δ-pyrones. We have planed to use condensation of dimethyl 3-methylglutaconate **1** with aldehydes to afford 6-substituted 5,6-dihydro-2*H*-pyran-2-one in an one-step procedure.

Wiley and Ellert[7] have studied the condensation of dimethyl 3-methylglutaconate **1** with aliphatic aldehydes and have obtained in the case of n-octanal or n-nonanal 5,6-dihydro-2*H*-pyran-2-ones **2** *via* the dicarboxylic acids **3** (scheme 1). In the case of ramified or small length aldehydes, the cyclisation did not occurred.

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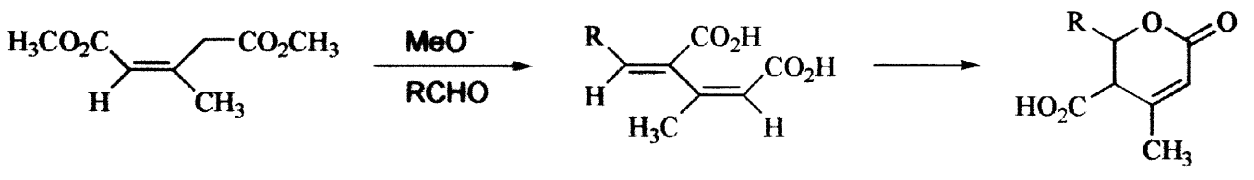
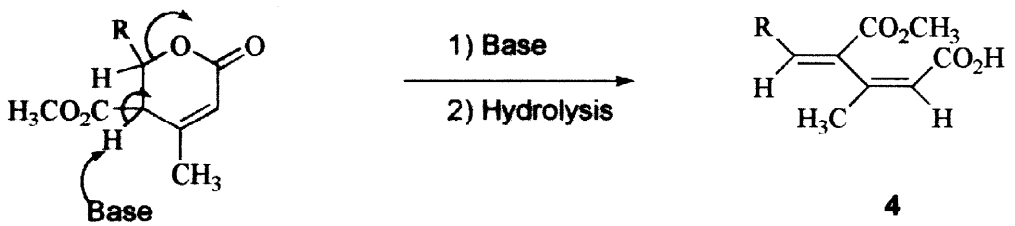


1 3 2

Scheme 1

Maione *et al* have used this procedure to prepare a precursor of Withanolide. [8]

We have studied the reactivity of dimethyl 3-methylglutaconate **1** and showed that condensation of compound **1** with ketones[9] affords 5,6-dihydro-2*H*-pyran-2-ones in low yields (15-40%). We have then observed that the condensation of dimethyl 3-methylglutaconate **1** with aldehydes[10] led to dienoic compounds **4** by opening of the lactone ring under basic conditions (scheme 2).



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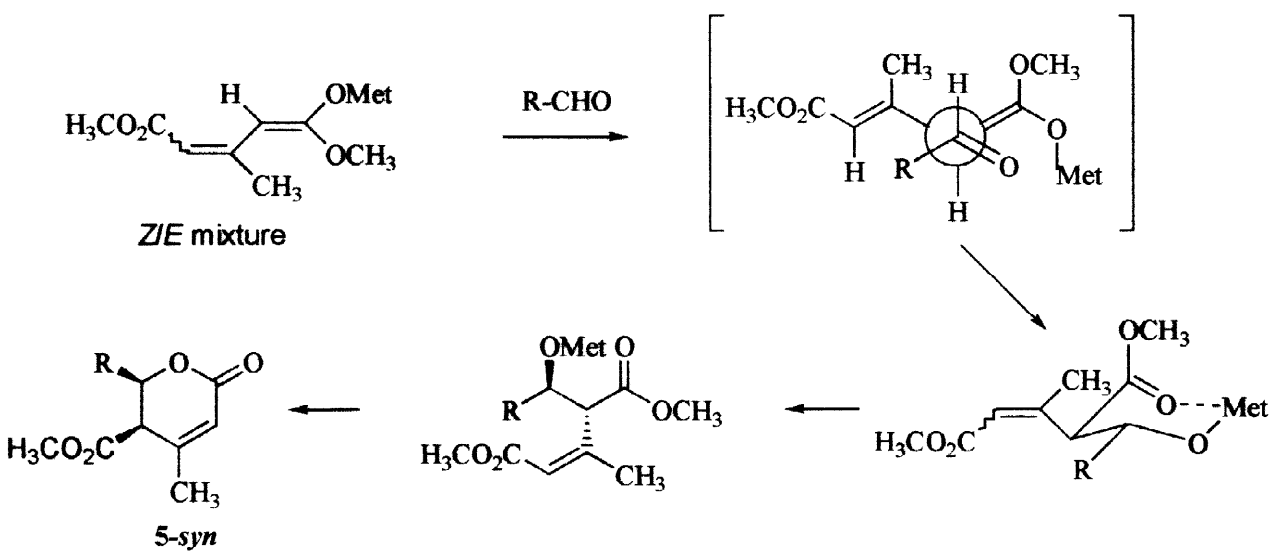
Scheme 2

Following our previous results, the aim of our work was to prepare lactones **5** in an one-step procedure with satisfactory yields and diastereoselectivity. The principle of this reaction is described in scheme 3 and proceeds *via* a directed aldol type condensation followed by cyclization leading to δ-pyrones **5.**



Z/E mixture

5-*syn*

Scheme 3

Results and discussion

Several experiments were run in order to find the best conditions for the aldolisation reaction. In order to prepare the enolate from dimethyl 3-methylglutaconate under kinetic conditions we used lithium bis-trimethylsilylamide (LiHMDS) since this base is strong enough and not too nucleophilic. The reaction was run at –60°C. When benzaldehyde was added no reaction occurred (Table 1). In order to increase the reactivity of the lithium enolate (aggregates),[11] we have used as additive LiBr to form mixed aggregates. Results in Table 1 indicate that in the presence of lithium salt, better yields were obtained, but it did not seem to have any effect on diastereoselectivity. In order to increase both yield and diastereoselectivity, another strategy was performed following the observations of House[12] showing that better yields could be obtained using a Lewis acid in reactions involving preformed lithium enolates. Thus we used anhydrous $ZnCl_2$ to prepare zinc enolates by transmetalation of lithium enolates.

Table 1. Condensation of enolates from dimethyl 3-methylglutaconate on aldehydes to prepare *syn* and / or *anti* lactones **5.**

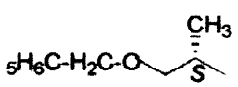
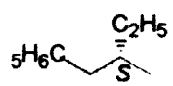
Aldehyde R - CHO	Conditions	Lactone **5** (yield %)	Racemate *syn* %	Racemate *anti* %
R = Propyl	LiHMDS	68	68	32
	LiHMDS + LiBr	90	60	40
	LiHMDS + $ZnCl_2$	80	80	20
R = Heptyl	LiHMDS	80	72	28
	LiHMDS + LiBr	92	70	30
	LiHMDS + $ZnCl_2$	85	85	15
R = Benzyl	LiHMDS	27	92	8
	LiHMDS + LiBr	80	94	6
	LiHMDS + $ZnCl_2$	65	100	0
R = Phenyl	LiHMDS	0	-	-
	LiHMDS + LiBr	30	8	92
	LiHMDS + $ZnCl_2$	31	0	100

Results summarized in table 1 indicate that the best conditions to prepare lactones **5** with satisfactory yields and good diastereoselectivity were obtained with zinc enolates leading mainly to the *syn* racemates. These results indicate that the aldol reaction between the *Z*-enolate derived from dimethyl 3-methylglutaconate and aldehydes according to the Zimmermann-Traxler model leads preferentially to the *anti* aldolate under

kinetic control. Cyclisation of this aldolate then gives rise to the corresponding lactone **5** in which the *syn* product predominates (Scheme 3).

We then chose these conditions[13] for the preparation of different functionalized 5,6-dihydro-2*H*-pyran-2-ones (Table 2).

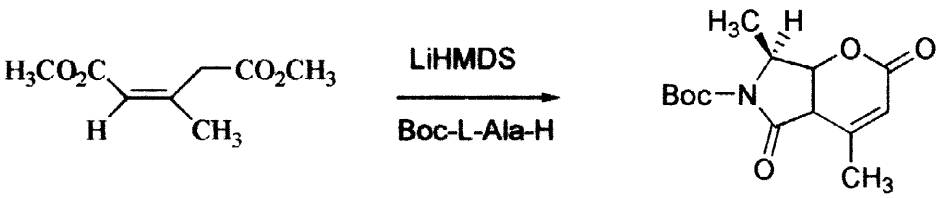
Table 2. Condensation of zinc enolates prepared from dimethyl 3-methylglutaconate with aldehydes

R-CHO	Product **5**	Yield %	Rac-*syn*	Rac-*anti*
R = C_6H_5	**5a**	31	0	100
R = CH_3	**5b**	50	75	25
R = $(CH_2)_2$ CH_3	**5c**	90	70	30
R = $(CH_2)_6$ CH_3	**5d**	80	85	15
R = CH_2- C_6H_5	**5e**	65	100	0
R = CH $(CH_3)_2$	**5f**	80	80	20
R = C $(CH_3)_3$	**5g**	90	0	100
	**5h**	67	70[a]	30[a]
	**5i**	59	55[b]	45[b]

[a] Determined by CAPCELL RP-HPLC analysis with CH_3CN/H_2O 80 : 20 mixture. ^1H NMR of Rac-*syn* indicated the presence of two diastereomers in proportion 70/30. [b]Determined by CAPCELL RP-HPLC analysis with CH_3CN/H_2O 80 : 20 mixture where the four diastereomers were distinct in proportion: 38/17/30/15.

Results summarized in table 2 show that condensation of zinc enolates with aldehydes proceed in satisfactory yields and *syn* diastereoselectivity with the exception of trimethylacetaldehyde bearing a bulky substituant. We could notice the particular reactivity of benzaldehyde that led to the *anti* product in low yield. This result could be explained following the proposed mechanism for the Zn(II)-mediated reaction of lithium enolates with aldehydes assuming that retroaldolisation takes place in this case and undergoes a *syn-anti* equilibration to favour the thermodynamic compound.[14] Furthermore, we noted that at low temperature (below –40° C), the 3,4-olefin of the aldol product has an *E* - geometry that prevents ring closure.[13] When the reaction was run between –30°C and –10°C, the *Z*- and *E*-olefinic products equilibrated and allowed the *Z*-olefin to undergo ring closure.

In an attempt to design protease inhibitor candidates, we planned to prepare functionalized 5,6-dihydro-2*H*-pyran-2-ones from α-aminoaldehydes, following the conditions developed previously. In order to prevent formation, under basic conditions, of the amide leading after cyclisation to the bicyclic compound **6** (scheme 4), we prepared α-aminoaldehydes **7** bearing two protecting groups.



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Scheme 4

We focused our interest onto *N,N*-dibenzylamino aldehydes since these building blocks can be easily prepared from the corresponding α-amino acids. Synthesis of *N,N*-dibenzylamino aldehydes involves three simple steps,[15] namely benzylation, reduction and Swern oxidation of *N,N*-dibenzylamino alcohols.

It is also possible to switch the order of the three steps by reducing first α-amino acids to the corresponding primary α-amino alcohols followed by *N*-benzylation and Swern oxidation.[16]

N,N-dibenzylamino aldehydes are known to undergo aldol reaction with lithium enolates with non chelation control.[15] The formation of the main diastereomer depends on the predominance of the Felkin-Ahn conformation of aldehyde **7a** and to the attack of enolate from the less hindered *Re* face.

Another way to prepare *N,N*-diprotected aminoaldehydes is represented by the Garner aldehyde **7d** prepared in enantiomerically pure form in four steps from serine.[17]

Addition of zinc enolate prepared from dimethyl 3-methylglutaconate, on aldehydes **7a-d** was performed in the conditions used previously. We noticed that in these conditions of temperature (-30°C), aminoaldehydes were not reactive enough. In order to prepare the desired lactones, the reaction was run at higher temperature from - 10° to + 20°C. The significant results are summarized in Table 3.

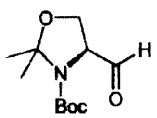
Addition of zinc enolate, prepared from dimethyl 3-methylglutaconate, on aldehyde **7a** provided mainly the (*S, R, R*)-configurated adduct **5j** . This result indicated that the reaction was run under thermodynamic control leading mainly to the δ-lactones of *anti* configuration.

In order to ascertain this hypothesis, an experience was run in case of *N*-protected phenylalaninal **7c** at lower temperature (- 30°C) for a long time (16h). In this case the stereoselectivity can be reversed leading mainly to the *syn* diastereomer (64/36) in 56% yield.

In the same way, the Garner aldehyde **7d** led to the *syn* lactone **5m** (72/28) when the reaction took place at 0°C for 6 hours and the *anti* product was obtained (68/32) when the reaction was carried out at room temperature for 8 hours.

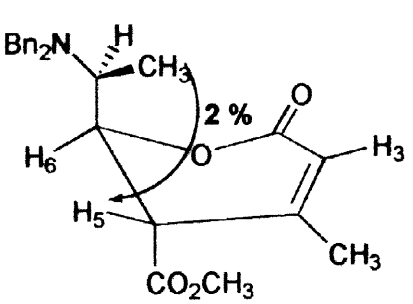
These two experiences proved that at low temperature the δ-lactones of *syn*-configuration are obtained under kinetic control while *anti*-products predominated at room temperature and corresponded to the thermodynamic compounds.[18]

Table 3. Reaction of dimethyl 3-methylglutaconate with aldehydes **7a-d**

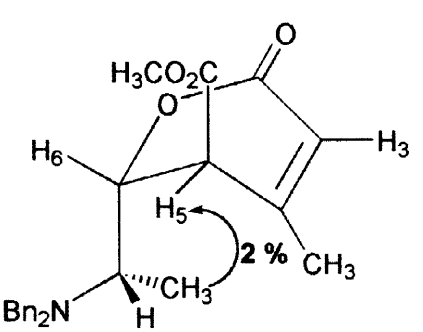
Entry	Aldehyde	Configuration[a]	Product	Yield[b] %	*anti* : *syn* Ratio[c]	*Main isomer* isolated $[\alpha]_D^{25}$ (c, $CHCl_3$)
1	Bn_2-Ala-H **7a**	2*S*	**5j**	63	83/17	- 57° (0.105) *S R R*[d]
2	Bn_2-Ala-H **7b**	2*R*	**5k**	65	80/20	+60°4 (0.101) *R S S*
3	Bn_2-Phe-H **7c**	2*S*	**5l**	50	68/32	+144° (0.098) *S S S*[d]
4	 **7d**	2*S*	**5m**	60	57/43	- 85° (0.100) *anti*

[a] Configuration of starting chiral aldehyde. [b]Isolated yield of diastereomeric mixture. [c]Determined by C18 RP-HPLC analysis with CH_3CN/H_2O 80 : 20 mixture. [d] Relative configuration determined by X-ray crystallographic analysis.

Both diastereomers can be separated by silica gel column chromatography. Coupling constants between H-5 and H-6 (1Hz) indicate that the conformation of the main isolated products **5j** and **5l** is established as pseudoboat with H-5 and H-6 in equatorial position. This was confirmed by ^1H DIFNOE NMR and NOESY experiments where no correlations were observed between H-5 and H-3, indicating for H-5 an equatorial position (scheme 5). The NOE observed between CH_3 and H-5 allowed the relative *S, S, S* or *S, R, R* configurations.



5j (*S, S, S*)



5j (*S, R, R*)

Scheme 5

In order to define unambiguously the relative configuration of lactones **5**, an X-ray crystallographic analysis was performed.[19]

Crystalline **5j** (m.p. 115°C) was subjected to X-ray crystallographic analysis. The resulting RASMOL drawing showed that **5j** has the relative *S, R, R* configuration (figure 1).

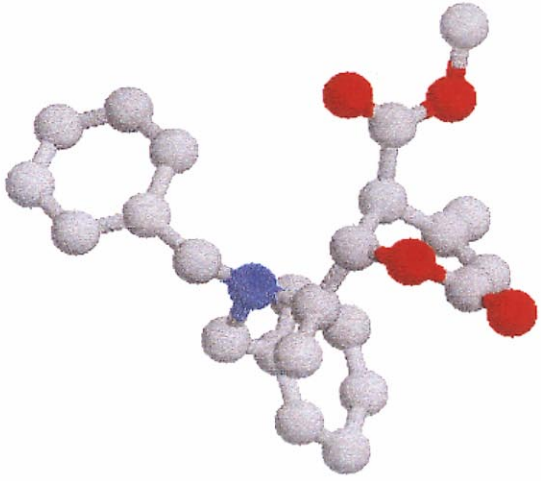


Figure 1. X-ray crystallographic structure of **5j**

Concerning compound **5k**, melting point is similar to the **5j** one and by comparison with $[\alpha]_D$ of **5j,** we can predict that lactone **5k** is the enantiomer of **5j** with a relative *R, S, S* configuration.

Crystalline **5l** (m.p. 119-120°C) was also subjected to X-ray crystallographic analysis. The stereochemistry (*S, S, S*) was the same as predicted on the basis of the addition reaction mechanism.

In the case of lactone **5m**, we can noticed that diastereoselectivity is poor. The configuration of main diastereomer was determined by ^{1}H NMR but complete assignement was not achieved because of instability.

Conclusion

Dimethyl 3-methylglutaconate represents an useful reagent for the preparation of functionalized δ-lactones in an one-step procedure. Condensation of enolate prepared from compound **1** with aldehydes afforded the desired lactones in satisfactory to good yields with a *syn* diastereoselectivity. When aminoaldehydes were used, the condensation was achieved at higher temperature leading mainly to the *anti* diastereomer under thermodynamic control. The stereoisomers can be separated by silica gel column chromatography and the relative configuration was established by X-ray crystallographic analysis. These functionalized 5,6-Dihydro-2*H*-pyran-2-ones could be interesting candidates for the design of protease inhibitors.

Experimental

General. ^{1}H-NMR (300 MHz) spectra were recorded in $CDCl_3$ on a BRUCKER AM300 instrument. Chemical shifts are given in ppm (δ), using tetramethylsilane (TMS) as internal standard. Optical rotations were measured on a ROUSSEL JOUAN polarimeter. IR spectra were recorded on PERKIN-ELMER FT/IR-1600 instrument. Tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl. Column chromatographies were performed with silica gel 60 (70-230 mesh, Merck).

General procedure for the preparation of lactones 5a-i:
To a solution of dimethyl 3-methylglutaconate 60: 40 (*Z*:*E*) mixture (2.5 mmol) in THF (5 ml) was added lithium bis(trimethylsilyl)amide in THF (2.8 mmol) at –35°C under nitrogen and the reaction mixture was stirred for 0.5 h. Then the solution was cooled to –65°C and a 0.5M $ZnCl_2$ solution in THF (5 ml) was added. After stirring for 15 min, aldehyde (1.25mmol) in THF was added. The mixture was allowed to warm to –10°C and then stirred 7 h between –30°C and –10°C. The reaction mixture was cooled to –40°C and quenched with a solution of saturated NH_4Cl (10 ml) The product was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent gave an oil which was purified by chromatography on silica gel to provide lactones **5**.

5-methoxycarbonyl-4-methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (5a). The crude product was chromatographed on silica gel (petroleum ether:diethyl ether 30:70) to afford the *trans* racemate (31%) as a white solid m.p. 81-82°C. IR (KBr) 1735, 1717, 1645, 1255, 1030 cm^{-1}. ^{1}H-NMR: δ 2.0 (3H, s), 3.63 (1H, d, *J*= 8.5 Hz), 3.67 (3H, s), 5.7 (1H, d, *J* =8.5 Hz), 6.0 (1H, d, *J* =1.6 Hz), 7.35(5H, s).

4,6-dimethyl-5-methoxycarbonyl-5,6-dihydro-2*H*-pyran-2-one (5b). The two diastereomers have been isolated after chromatography on silica gel (petroleum ether:diethyl ether 10:90).

***Syn*-4,6-dimethyl-5-methoxycarbonyl-5,6-dihydro-2*H*-pyran-2-one.** white solid m.p. 89-90°C. IR (KBr) 1724, 1701, 1654, 1384, 1256 cm^{-1}. ^{1}H-NMR: δ 1.45 (3H, d, *J* =6.6 Hz), 2.0 (3H, d, *J* =1.4 Hz), 3.05 (1H, d, *J* = 3.9 Hz), 3.75 (3H, s), 4.65 (1H, qxd, *J* =7 Hz, *J'*=4 Hz), 5.95 (1H, m).

***Anti*-4,6-dimethyl-5-methoxycarbonyl-5,6-dihydro-2*H*-pyran-2-one**. colorless oil, IR (KBr) 1723, 1705, 1651, 1386, 1260, 1019 cm^{-1}. ^{1}H-NMR: δ 1.43 (3H, d, *J* =6.6 Hz), 2.0 (3H, s), 3.22 (1H, dxd, *J* = 7.9 Hz, *J'*= 0.7 Hz), 3.8 (3H, s), 4.85 (1H, m), 5.95 (1H, m).

5-methoxycarbonyl-4-methyl-6-propyl-5,6-dihydro-2*H*-pyran-2-one (5c) was obtained in 90% yield and the two diastereomers were separed by chromatography on silica gel (petroleum ether:diethyl ether 10:90).

***Syn*-5-methoxycarbonyl-4-methyl-6-propyl-5,6-dihydro-2*H*-pyran-2-one** was obtained as a white solid, m.p. 62-63°C. IR (KBr) 1723, 1703, 1654, 1384, 1255, 1020 cm^{-1}. ^{1}H-NMR: δ 0.9-1.0 (3H, m), 1.4-1.85 (4H, M), 2.0 (3H, d, J=1.4 Hz), 3.1 (1H, d, J = 3.8 Hz), 3.75 (3H, s), 4.45 (1H, m), 5.95 (1H, s).

***Anti*-5-methoxycarbonyl-4-methyl-6-propyl-5,6-dihydro-2*H*-pyran-2-one** was obtained as a colorless oil, IR (KBr) 1723, 1705, 1651, 1386, 1260, 1019 cm^{-1}. ^{1}H-NMR: δ 0.9-1.0 (3H, m), 1.4-1.85 (4H, M), 2.0 (3H, d, J=1.4 Hz), 3.25 (1H, d, J = 7.6 Hz), 3.75 (3H, s), 4.7 (1H, m), 5.95 (1H, s).

6-heptyl-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (5d) was obtained in 85% yield and the two diastereomers were separated by chromatography on silica gel (petroleum ether:diethyl ether 40:60).

Syn-**5d** as white solid, m.p. 70-71°C. IR (KBr) 1723, 1705, 1651, 1386, 1260, 1019 cm^{-1}. ^{1}H-NMR: δ 0.85 (3H, m), 1.3-1.9 (12H, M), 2.0 (3H, s), 3.1 (1H, d, J = 3.7 Hz), 3.75 (3H, s), 4.45 (1H, m), 5.95 (1H, s).

Anti-**5d** as a colorless oil, IR (KBr) 1723, 1705, 1651, 1386, 1260, 1019 cm^{-1}. ^{1}H-NMR: δ 0.85 (3H, m), 1.3-1.9 (12H, M), 2.0 (3H, s), 3.1 (1H, d, J = 3.7 Hz), 3.75 (3H, s), 4.7 (1H,m), 5.95 (1H, s).

6-benzyl-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (5e) was obtained in 65% yield after chromatography on silica gel (petroleum ether:diethyl ether 40:60) as the *syn*-product. White solid, m.p. 106-107°C. IR (KBr) 1725, 1702, 1656, 1384, 1251, 1200, 1030 cm^{-1}. ^{1}H-NMR: δ 2.0 (3H, s), 3.0 (1H, dxd, J = 12Hz, J'=7.6 Hz), 3.06 (1H, d, J =3.5 Hz), 3.18 (1H, dxd, J =14 Hz, J'= 6.8 Hz), 3.8 (3H, s), 4.6 (1H, dxt, J =3.5 Hz, J'=7.1 Hz), 5.95 (1H, s), 7.3 (5H, M).

6-isopropyl-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (5f) was obtained in 80% yield and the two diastereomers were separated by chromatography on silica gel (petroleum ether:diethyl ether 30:70).

Syn-**5f** as white solid, m.p. 95-99°C. IR (KBr) 1723, 1712, 1697, 1654, 1386, 1253, 1200 cm^{-1}. ^{1}H-NMR: δ 1.0 (3H, d, J=6.7 Hz), 1.1 (3H, d, J=6.7 Hz), 1.88-2.1 (1H, m), 2.0 (3H, s), 3.25 (1H, d, J=3.5 Hz), 3.75 (3H, s), 4.0 (1H, dxd, J =10 Hz, J'= 3.5 Hz), 5.95 (1H, s).

Anti-**5f** as a colorless oil, IR (KBr) 1723, 1712, 1697, 1654, 1386, 1253, 1200 cm^{-1}. ^{1}H-NMR: δ 1.0 (3H, d, J =6.7 Hz), 1.1 (3H, d, J =6.7 Hz), 1.88-2.1 (1H, m), 2.0 (3H, s), 3.4 (1H, d, J =7.4 Hz), 3.8 (3H, s), 4.5 (1H, dxd, J =7.9 Hz, J'= 4.9 Hz), 5.95 (1H, m).

6-*t*-butyl-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (5g) was obtained in 90% yield after chromatography on silica gel (petroleum ether:diethyl ether 50:50) as the *anti*-product. White solid, m.p. 80-82°C. IR (KBr) 1728, 1708, 1654, 1386, 1305, 1163, 1062 cm^{-1}. ^{1}H-NMR: δ 1.0 (9H, s), 2.0 (3H, s), 3.35 (1H, d, J = 6.6 Hz), 3.8 (3H, s), 4.5 (1H, d, J =6.7 Hz), 5.95 (1H, m).

6-[(*S*)-1'-benzyloxyethyl]-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (5h) that could not be separated. The ratio of the *syn* and *anti* product (70/30) has been determined by CAPCELL-HPLC analysis

with CH_3CN/H_2O 80:20 mixture. The *syn* stereochemistry was attributed on the basis of characteristic ^1H NMR coupling constant *J* H5-H6 = 3.4 Hz (δ = 3.2 ppm).

5-methoxycarbonyl-4-methyl-6-[(*S*)-1'-phenypropyl]-5,6-dihydro-2*H*-pyran-2-one (5i) was obtained after chromatography on silica gel (petroleum ether:ethyl acetate 90:10) in 59% yield as a mixture of two diastereomers where the *syn* product crystalized. White solid, m.p. 96°C. $[\alpha]_D$ = + 89° (c = 0.104, $CHCl_3$). IR (KBr) 3062, 3029,1738, 1714, 1495, 1382, 1257, 1037 cm^{-1}. ^{1}H-NMR: δ 0.71 (3H, t, *J*=7.37 Hz), 1.73 (1H, m), 1.92 (3H, d, *J*=1.12 Hz), 2.19 (1H, m), 2.76 (1H, txd, *J*=3.6 Hz, *J'*=10.63 Hz), 2.86 (1H, d, *J*=2.46 Hz), 3.65 (3H, s), 5.0 (1H, dxd, J=2.46 Hz, *J'*=9.87 Hz), 5.95 (1H, d, *J*=1.12 Hz), 7.08-7.4 (5H, m).

Condensation of dimethyl-3-methylglutaconate with α-aminoaldehydes 7a-d: The procedure is the same as used for the preparation of lactones **5a-i** but the reaction mixture was stirred 8h between –5°C and + 20°C before being quenched with aqueous NH_4Cl at room temperature.

6-[1'-(*S*)-*N,N*-dibenzylaminoethyl]-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (7a) was obtained after chromatography on silica gel (petroleum ether:ethyl acetate 80:20) in 50% yield as a mixture of two diastereomers where the *anti* product was obtained after recrystalisation from petroleum ether:diethyl ether 40:60 in a pure form. White solid, m.p. 115°C. $[\alpha]_D$ = - 57° (c = 0.105, $CHCl_3$). IR (KBr) 3080, 3060, 3027, 1726, 1654, 1601, 1494, 1384, 1255, 1143 cm^{-1}. ^{1}H-NMR: δ 1.24 (3H, d, *J*=6.71 Hz), 1.44 (3H, d, *J*= 1.1 Hz), 2.88 (1H, qxd, *J*=6.71 Hz, *J'*=10.26 Hz), 3.32 and 3.65 (4H, AB System, J_{AB}= 13.23 Hz), 3.72 (4H, m), 4.76 (1H, dxd, *J*=1 Hz, *J'*=10.26 Hz), 5.63 (1H, d, J=1.10 Hz), 7.22-7.36 (10H, m).

6-[1'-(*R*)-*N,N*-dibenzylaminoethyl]-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (7b) was obtained after chromatography on silica gel (petroleum ether:ethyl acetate 90:10) in 67% yield as a mixture of two diastereomers where the *anti* product was obtained after recrystallisation from petroleum ether:diethyl ether 40:60 in a pure form. White solid, m.p. 117°C. $[\alpha]_D$ = + 60.4° (c = 0.101, $CHCl_3$). IR (KBr) 3060, 3025, 1727, 1602, 1494, 1438, 1255, 1143 cm^{-1}. ^{1}H-NMR: δ 1.24 (3H, d, *J*=6.7 Hz), 1.43 (3H, d, *J*= 1.32 Hz), 2.88 (1H, qxd, *J*=6.7 Hz, *J'*=10.23 Hz), 3.32 and 3.75 (4H, AB System, J_{AB}= 13.32 Hz), 3.72 (4H, m), 4.77 (1H, dxd, *J*=1.25 Hz, *J'*=10.23 Hz), 5.63 (1H, d, *J*=1.32 Hz), 7.22-7.37 (10H, m).

6-[1'-(*S*)-*N,N*-dibenzylamino-2'-phenylethyl]-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (7c) was obtained after chromatography on silica gel (petroleum ether:ethyl acetate 90:10) in 50% yield as a mixture of two diastereomers where the *anti* product was obtained after recrystallisation from petroleum ether:diethyl ether 40:60 in a pure form. White solid, m.p. 119.5°C. $[\alpha]_D$ = + 144° (c = 0.104, $CHCl_3$). IR (KBr) 3094, 3058, 3035, 1736, 1601, 1454, 1377, 1260, 1066 cm^{-1}. ^{1}H-NMR: δ 1.71 (3H, d, *J*=1.14 Hz), 3.06 (1H, dxd, *J*=3.76 Hz, *J'*=11 Hz), 3.17 (2H, m), 3.34 (3H, s), 3.55 and 4.15 (4H, AB System, J_{AB}=13.74 Hz), 3.74 (1H, d, *J*=9.85 Hz), 4.5 (1H, dxd, *J*=9.85 Hz, *J'*=3.76 Hz), 5.72 (1H, d, *J*=1.14 Hz), 7.1-7.37 (15H, m). LRMS (EI): m/z (%) 470 (M+1; 0.14), 469 (M^+; 0.06), 438 (0.35), 393 (0.8), 378 (21), 346 (4.5), 300 (38.5), 208 (2), 181 (5), 91 (100), 65 (8).

Syn-**7c** was purified on silica gel preparative TLC (iPr_2O: petroleum ether=60:40). IR (KBr) 3060, 3027, 1735, 1601, 1494, 1380, 1260, 1099 cm^{-1}. ^{1}H-NMR: δ 1.49 (3H, s), 3.02-3.24 (3H, m), 3.55 (1H, d, *J*=4.25 Hz), 3.57 and 3.75 (4H, AB System, J_{AB}=13.66 Hz), 3.63 (3H, s) 4.97 (1H, dxd, *J*=4.25 Hz, *J'*=7.02 Hz), 5.64 (1H, s), 7.08-7.38 (15H, m). ^{13}C-NMR: δ 21.42, 32.48, 46.16, 52.14, 54.14, 60.30, 78.78, 117.71, 126.29–129.57.

6-[4'-(*S*)-*N*-*tert*-butoxycarbonyl-2',2'-dimethyl-1',3'-oxazolidin-4'-yl]-5-methoxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (7d) was obtained after chromatography on silica gel (petroleum ether:ethyl acetate 70:30) in 60% yield as a mixture of two diastereomers where the *anti* product was obtained as a white solid m.p. 76°C. $[\alpha]_D$ = - 85° (c = 0.10, $CHCl_3$). IR (KBr) 2977, 1738, 1692, 1648, 1436, 1388, 1217, 1100 cm^{-1}. ^{1}H-NMR: δ 1.49 (9H, s), 1.52 (3H, s), 1.59 (3H, s), 2.12 (3H, d, *J*=0.85 Hz), 3.20 (1H, d, *J*=0.95 Hz), 3.76 (3H, s), 3.91 (1H, dxd, *J*=9.47 Hz, *J'*=4.9 Hz) 4.08-4.22 (2H, m), 4.76 (1H, dxd, *J*=0.95 Hz, *J'*= 10.05 Hz), 5.95 (1H, d, *J*=0.85 Hz). LRMS (EI): m/z (%) 354 (M-15; 0.5), 296 (0.43), 254 (7), 222 (1), 200 (8.5), 169 (2.5), 162 (3.3), 144 (13), 111 (61), 100 (68), 83 (10), 57 (100).

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