Ring Chain Transformation of γ-Keto-δ-crotonolactones: A Convenient Synthesis of 1,4-Piperazinones, 1,4-Thiazinones and 1,4-Diazepinones

Costas D. Apostolopoulos, Minas P. Georgiadis and Elias A. Couladouros*

Chemistry Laboratories, Agricultural University of Athens, Iera Odos 75, Botanicos 118.55, Athens, Greece

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Dedicated to the memory of Nicholas Alexandrou

A new procedure for the efficient synthesis of 1,4-piperazinones, 1,4-thiazinones and 1,4-diazepinones is presented. The reaction is based on a ring chain transformation of γ-keto-δ-crotonolactones induced by 1,2- or 1,3-diamino- (or thiamino-) binucleophiles. The reaction sequence of this transformation is also discussed.

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Introduction.

Recently, ring chain transformation of butenolides, pentenolides or α,β-unsaturated lactams with 1,2-binucleophiles such as hydrazines, thiamines or hydroxylamines, have led to the formation of interesting heterocycles, such as pyrazolidinones [1,2], isoxazolidinones [3], benzodiazepinones [4], 1,4-diazepinones and 1,4-thiazepinones [5] (Scheme 1, eq. 1).

Generally, this transformation proceeds *via* conjugate addition to the double bond of **1**, leading to the formation of intermediate **2**, by which subsequent attack of the remaining nucleophile to the carbonyl function is finally converted to the ring system **3**. Preparation of 1,4-thiazepin-5-ones is also achieved by a similar reaction sequence using 2-amino-1-mercaptanes as nucleophiles and α,β-unsaturated carboxylates as acceptors [6,7]. Furthermore, the latter substrates, upon reaction with 1,2-diamines [8], furnish 1,4-diazepin-5-ones *via* a reverse order of these reactions, *i.e.* formation of the amide and subsequent addition of the other amine moiety to the C-C double bond. It is noteworthy that the above 7-membered heterocycles are formed from the addition of the binucleophile to the conjugated system at positions 2 and 4.

Lactone **4** is a relatively new species, which can be easily prepared from the well known 2*H*-pyran-3(6*H*)-ones in high yield [9]. In the course of our ongoing investigation concerning the applicability of **4** as a potent synthon for the synthesis of several products [9,10], we report herein the synthesis of piperazinones, thiazinones and diazepinones *via* a similar ring chain transformation using γ-keto-δ-crotonolactones of the general formulae **4** as substrates (Scheme 1, equation 2). In contrast to the hitherto used substrates, on this particular one, position 3 is relatively more electrophilic than position 4 [10c]. As a consequence, binucleophiles are attacking the unsaturated systems at positions 3 and 2 providing thus an entry to 6- and 7-membered heterocycles. The latter might be of practical interest, since a number of pharmacologically active compounds is represented in this class of heterocycles [4,11,12].

Results and Discussion.

The reactivity of γ-keto-δ-crotonolactone **4** with *O*-, *S*- and *N*-1,2-binucleophiles was examined and the results are summarized in Table 1. Diol **6** was not nucleophilic

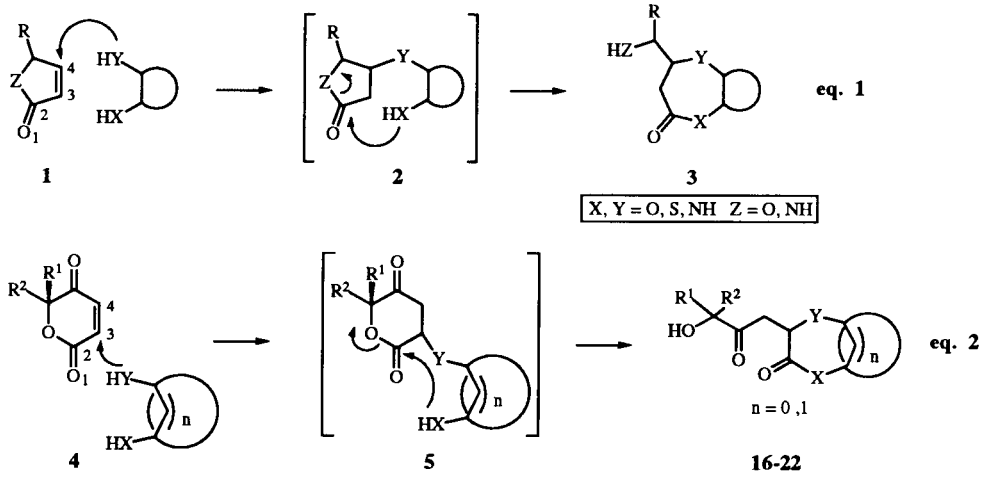
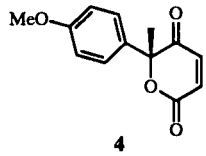
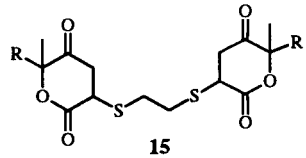
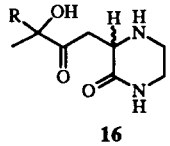
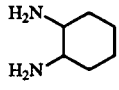
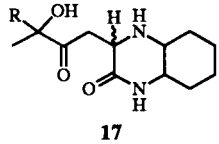
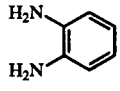
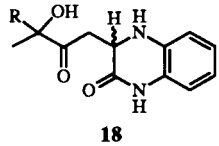
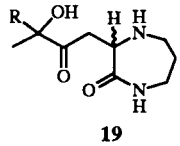
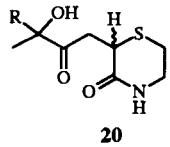
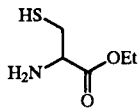
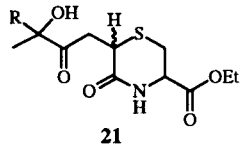
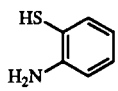
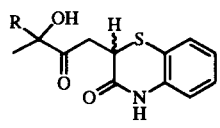


Table 1
Reaction of Binucleophiles with Lactone **4**



4

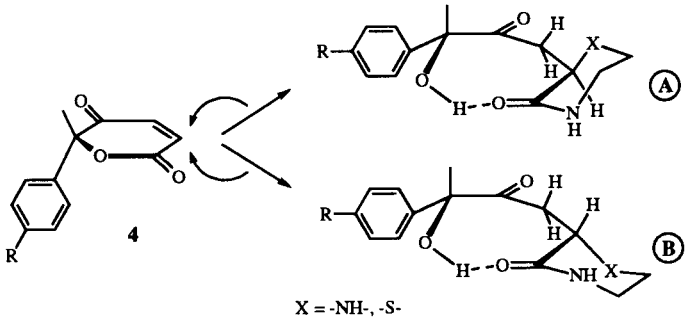
Binucleophile	Conditions	Product	Yield %	Ratio
 **6**	neat **6**, 60°, 3 days	No reaction	—	—
	neat **6**, Na_2CO_3, RT, 30 minutes	Decomposition	—	—
 **7**	CH_2Cl_2, RT, 5 minutes	 **15**	38	—
 **8**	CH_2Cl_2, RT, 15 minutes	 **16**	84	4:1
 **9**	CH_2Cl_2, RT, 15 minutes	 **17**	90	2:1
 **10**	CH_2Cl_2, RT, 48 hours	 **18**	93	2:1
 **11**	CH_2Cl_2, RT, 15 minutes	 **19**	80	-[a]
 **12**	CH_2Cl_2, RT, 3 minutes	 **20**	90	1:1
 **13**	CH_2Cl_2, RT, 20 minutes	 **21**	80	-[a]
 **14**	CH_2Cl_2, RT, 10 minutes	 **22**	88	4:1

[a] Undetermined.

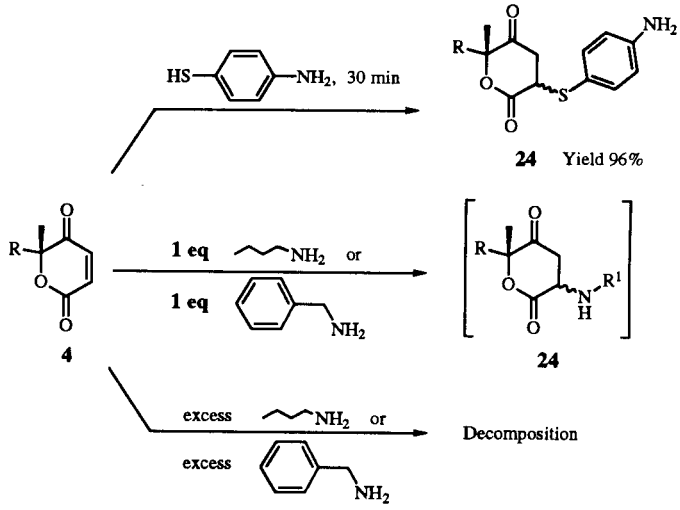
enough to give any reaction even when used as much as a solvent. The presence of base, even in catalytic amount, resulted in the decomposition of the starting material. In contrast, disulfide **7** was nucleophilic enough to yield a fast 1,4 type addition. However, since thiol could not attack the carboxylate moiety, the major isolated product was dimer **15**. When lactone **4** was treated with diamines, we were able to isolate in very good yield the desired heterocycles as a pair of diastereoisomers. Thus, 1,4-piperazinones **16** and **17** were synthesized in high yield using 1,2-diamines **8** and **9** respectively. Aromatic diamine **10** furnished quinoxalinone **18** almost quantitatively, even though longer reaction time was required and the reaction conditions and work up had to be slightly modified. It is noteworthy that similar results were obtained with 1,3-binucleophile **11**, and the desired 1,4-diazepinone **19** was obtained in satisfactory yield.

Finally, we have explored the reactivity of lactone **4** with mixed *S,N*-binucleophiles. Both saturated and aromatic substrates gave satisfactory results. Thus, 1,4-thiazinones **20, 21** and **22** were synthesized in high yields using the aminothiols **12, 13** and **14** respectively, as it is depicted in Table 1.

The stereochemical aspects of the above reaction are presented in Scheme 2. Two isomeric compounds (**A** and **B**) are observed in this reaction. Regarding the conformation of the side chain of the products, MM2 calculations [13] suggest that a hydrogen bond exists between the hydroxyl hydrogen and the amide oxygen. This expected hydrogen bond was evidented by the characteristic absorption, observed in their ir spectra. Since isomers **A** and **B** are structurally almost identical, especially in the case of unsubstituted heterocyclic rings, their ^{1}H nmr spectra were very similar and that is why, their full assignment was not attempted. However, the existence of the aforementioned hydrogen bond resulted in a characteristic distinct differentiation concerning the methylenic protons α to the carbonyl moiety and was observed in all products.



The order of the nucleophilic attacks was elucidated by a few more experiments. As it is depicted in Scheme 3, *p*-aminothiophenol furnished the expected thio-adduct **23** at almost quantitative yield, while primary amines like butylamine or benzylamine gave unstable products **24**. These aminoadducts, were in equilibrium with the starting materials and during work up were decomposed, presumably *via* a retro-Michael reaction (*i.e.* 1,4 adducts **24** were detectable only on tlc) [14]. Elaboration of large excess of the amines in order to force the reaction to completion, resulted in the decomposition of lactone **4**. Apparently, in the case of diamines, subsequent amide formation funnels the unstable intermediates like **24** towards the observed stable products **16-19** while the relatively slower reaction of *o*-aminoaniline **10**, in comparison with the saturated diamines (Table 1), is attributed to slower amide formation due to the lower nucleophilicity of **10**.



From the above experimental evidences we conclude that the presented ring chain transformation of γ-keto-δ-crotonolactones proceeds *via* a Michael attack of the softest nucleophile to the allylic double bond, followed by subsequent amidation of the lactone moiety. In the case of *S*-mononucleophiles the thioadduct is stable, while in the case of *N*-mononucleophiles the amino adduct is unstable.

Conclusion.

Lactone **4** is an ideal substrate for the synthesis of 6- and 7-membered diaza- (and thiaza-) heterocycles and can be used for the high yield synthesis of the pharmacologically interesting piperazinone, thiazinone and diazepinone ring systems. The transformation proceeds *via* a Michael attack and subsequent amidation of the lactone moiety.

EXPERIMENTAL

General Procedures.

All melting points, in degrees Centigrade, were determined in open capillary tubes with a Buchi melting point apparatus and

are uncorrected. Reaction progress was followed with analytical thin-layer chromatography (tlc) performed on 0.25 mm silica gel precoated plates with fluorescent indicator UV_{254} (Merck). All column chromatography was done by the flash chromatography technique using 32-63 μm silica gel packing (Merck). Proton magnetic resonance (^{1}H-nmr) spectra were recorded on a Brucker AM-500 (500 MHz) or on a Varian (200 MHz) spectrometers in the indicated solvents. Chemical shifts are reported in parts per million downfield from tetramethylsilane (δ scale). The two methylenic protons of the side chain are symbolized as H_α and H_β in the Experimental. Infrared (ir) spectra were obtained on a Perkin Elmer Model 283 B (4,000-200 cm^{-1}) spectrophotometer from samples prepared in accordance with the potassium bromide disk technique. Peaks are reported in cm^{-1}. Microanalytical data were provided by the University of Thessaloniki, Greece. Reagents were purchased at analytical reagent grade. All solvents were used as received.

Starting Materials.

6-(*p*-Methoxyphenyl)-6-methyl-5,6-dihydro-2*H*-pyran-2,5-dione (**4**) has been prepared according to the literature [9] and characterized by melting point, ir and ^{1}H nmr data.

1,2-Bis[6'-(*p*-methoxyphenyl)-6'-methyl-2',5'-dioxo-3',4',5',6'-tetrahydro-2'*H*-3'-pyranylthio]ethane (**15**).

To an ice cold stirred solution of **4** (0.50 g, 2.15 mmoles) in 20 ml of methylene chloride, ethanedithiol (0.22 g, 2.3 mmoles) was added dropwise. Within 5 minutes the reaction was completed (tlc). The reaction mixture was extracted with methylene chloride (2 x 50 ml), washed with brine, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. Flash column chromatography (ethyl acetate-hexane 1:3) of the resulted slurry, afforded, as major product, the title compound, which was recrystallized from ethyl acetate-ethyl ether-hexane to give 0.23 g (38%) of pure product as white crystals, mp 147-149°; R_f = 0.28 (ethyl acetate-hexane, 1:2); ir: ν max 1740 (lactone CO), 1720 (CO); ^{1}H nmr (500 MHz, deuteriochloroform): δ 7.20 and 6.85 (2d, 4H, aromatic), 3.74 (s, 3H, CH_3O), 3.73 (dd, 1H, H_3), 3.05 (dd, 1H, H_{4eq}, $J_{3,4eq}$ = 6 and J_{gem} = 17.5 Hz), 2.86-2.77 (m, 4H, SCH_2CH_2S), 2.61 (dd, 1H, H_{4ax}, $J_{3,4ax}$ = 9 Hz), 1.73 (s, 3H, CH_3); hrms: Calcd. for $C_{28}H_{30}O_8S_2H^+$: 559.1460. Found: 559.1460.

Anal. Calcd. for $C_{28}H_{30}O_8S_2$ (558.66): C, 60.20; H, 5.41. Found: C, 60.29; H, 5.48.

3-[3'-Hydroxy-3'-(*p*-methoxyphenyl)-2'-oxobutyl]-piperazin-2-one (**16**).

To an ice cold stirred solution of lactone **4** (0.50 g, 2.15 mmoles) in methylene chloride (20 ml), 1,2-ethylenodiamine (0.3 g, 5 mmoles) was added dropwise. The reaction mixture was allowed to reach the room temperature and the stirring was continued for an additional 15 minutes (tlc), then extracted with methylene chloride (2 x 50 ml), washed with brine, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The resulted residue was crystallized from ethyl acetate-hexane to give 0.53 g (84%) of a mixture of isomers (4:1 by nmr). After several recrystallizations pure isomer **16a** was obtained as white crystals, mp 86-88°; ir: ν max 3300 and 3270 (NH and amide NH), 3200 br (OH), 1710 (CO), 1655 (amide CO) cm^{-1}; ^{1}H nmr (500 MHz, deuteriochloroform): δ 7.29 and 6.80 (2d, 4H, aromatic), 6.53 (s, 1H, amide NH), 4.65 (s, 1H, OH), 3.72 (s, 3H, CH_3O), 3.64 (dd, 1H, H_3, $J_{3,\alpha}$ = 4.5 and $J_{3,\beta}$ = 7 Hz), 3.33 (m, 1H, H_{6eq}), 3.15 (m, 1H, H_{6ax}), 3.09 (dd, 1H, H_α, J_{gem} = 17.5 Hz), 3.00 (m, 1H, H_{5eq}), 2.87 (m, 1H, H_{5ax}), 2.65 (dd, 1H, H_β), 2.03 (s, 1H, NH), 1.65 (s, 3H, CH_3); hrms: Calcd. for $C_{15}H_{20}N_2O_4H^+$: 293.1501. Found: 293.1498.

Anal. Calcd. for $C_{15}H_{20}N_2O_4$ (292.33): C, 61.63; H, 6.90; N, 9.58. Found: C, 61.49; H, 6.81; N, 9.67.

3-[3'-Hydroxy-3'-(*p*-methoxyphenyl)-2'-oxobutyl]perhydroquinoxalin-2-one (**17**).

To an ice cold stirred solution of **4** (0.20 g, 0.86 mmole) in methylene chloride (10 ml), *trans*-1,2-diaminocyclohexane (0.22 g, 1.93 mmoles) was added dropwise. The reaction mixture was allowed to reach room temperature and stirring was continued for an additional 15 minutes (tlc), then extracted with methylene chloride (2 x 50 ml), washed with brine, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The remaining slurry was chromatographed to give **17a** and **17b** in 91% total yield.

Isomer **17a** was obtained in 30% (0.09 g) as white crystals, mp 153-155°; R_f = 0.17 (ethyl acetate/hexane 3:1 two passes); ir: ν max 3280 and 3200 br (NH, amide NH and OH), 1730 (CO), 1690 (amide CO); ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.40 and 6.90 (2d, 4H, aromatic), 5.65 (s, 1H, amide NH), 4.50 (br, 1H, OH), 3.80 (m, 4H, CH_3O and H_3), 3.15 (m, 1H, H_α, $J_{3,\alpha}$ = 4.3 and J_{gem} = 17.5 Hz), 3.10 (m, 1H, H_{1a}), 2.80 (dd, 1H, H_β, J_β = 7.5 Hz), 2.55 (t, 1H, H_{4a}), 1.85-1.65 (m, 12H, CH_3, NH and $4CH_2$).

Anal. Calcd. for $C_{19}H_{26}N_2O_4$ (346.43): C, 65.88; H, 7.56; N, 8.09. Found: C, 65.72; H, 7.49; N, 8.00.

Isomer **17b** was obtained in 60% yield (0.18 g) as white crystals, mp 158-159.5°; R_f = 0.12 (ethyl acetate/hexane 3:1 two passes); ir: ν max 3315 and 3280 (NH and amide NH), 3205 br (OH), 1720 (CO), 1660 (amide CO); ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.40 and 6.90 (2d, 4H, aromatic), 5.70 (s, 1H, amide NH), 4.65 (br, 1H, OH), 4.00 (dd, 1H, H_3, $J_{3,\alpha}$ = 4.8 and $J_{3,\beta}$ = 8.5 Hz), 3.80 (s, 3H, CH_3O), 3.15-2.75 (m, 3H, H_{1a}, H_α and H_β), 2.40 (t, 1H, H_{4a}), 1.80-1.60 (m, 12H, CH_3, NH and $4CH_2$).

Anal. Calcd. for $C_{19}H_{26}N_2O_4$ (346.43): C, 65.88; H, 7.56; N, 8.09. Found: C, 65.65; H, 7.42; N, 8.17.

3-[3'-Hydroxy-3'-(*p*-methoxyphenyl)-2'-oxobutyl]-1,2,3,4-tetrahydroquinoxalin-2-one (**18**).

A solution of **4** (0.2 g, 0.86 mmole) and *o*-aminoaniline **10** (0.37 g, 3.4 mmoles) in methylene chloride (15 ml) was stirred for 48 hours in an open flask, yielding a residue which was diluted with ethyl acetate and repeatedly washed with water. Evaporation of the organic layer under reduced pressure and crystallization from ethyl acetate-hexane afforded compound **18** (0.27 g, 92%) as mixture of two isomers (2:1 by nmr); ir: ν max 3340 and 3310 (NH and amide NH), 3160 br (OH), 1710 (CO), 1670 (amide CO); ^{1}H nmr (200 MHz, deuteriochloroform, major isomer): δ 8.5 (s, 1H, NHCO), 7.5-6.5 (m, 8H, aromatic), 4.4 (s, 1H, OH), 4.2 (dd, 1H, H_3), 3.8 (s, 3H, CH_3O), 3.4 (s, 1H, NH), 3.1 (dd, 1H, H_α, J_{gem} = 15 Hz), 2.9 (dd, 1H, H_β), 1.7 (s, 3H, CH_3); ms: Calcd. for $C_{19}H_{20}N_2O_4H^+$ 341.15. Found 341.1.

3-[3'-Hydroxy-3'-(*p*-methoxyphenyl)-2'-oxobutyl]perhydro-1,4-diazepin-2-one (**19**).

To an ice cold stirred solution of **4** (0.13 g, 0.56 mmole) in methylene chloride (20 ml), 1,3-propylenediamine (0.083 g,

1.12 mmoles) was added dropwise. The reaction mixture was allowed to reach room temperature and stirring was continued for an additional 15 minutes (tlc), then extracted with methylene chloride (2 x 50 ml), washed with brine, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The remaining slurry was chromatographed to give 0.138 g (81%) of the pure product as white crystals, mp 138-140°; ir: ν max 3430 and 3280 (NH and amide NH), 3200 br (OH), 1710 (CO), 1665 (amide CO); ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.40 and 6.90 (2d, 4H, aromatic), 4.15 (s, 2H, amide NH, OH), 3.75 (m, 4H, CH_3O, H_3), 3.50-3.30 (m, 4H, H_7, H_{5eq}, H_α), 2.90 (t, 1H, H_{5ax}), 2.45 (dd, 1H, H_β, $J_{3,\beta}$ = 5.5, J_{gem} = 16.3 Hz), 1.70 (m, 6H, CH_3, NH, H_6).

Anal. Calcd. for $C_{16}H_{22}N_2O_4$ (306.36): C, 62.73; H, 7.24; N, 9.14. Found: C, 62.98; H, 7.22; N, 9.27.

2-[3'-Hydroxy-3'-(*p*-methoxyphenyl)-2'-oxobutyl]-2,3,5,6-tetrahydro-4*H*-1,4-thiazine-2-one (**20**).

To an ice cold stirred solution of **4** (0.20 g, 0.86 mmole) and 2-aminoethylmercaptan hydrochloride (0.12 g, 1.06 mmoles) in methylene chloride (10 ml), triethylamine (0.10 g, 1.00 mmole) was added dropwise. The reaction mixture was allowed to reach room temperature and stirring was continued for an additional 3 minutes (tlc), then extracted with methylene chloride (2 x 50 ml), washed with brine, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The remaining slurry was chromatographed to give **20a** and **20b** in 90% total yield.

Isomer **20a** was obtained in 45% yield (0.12 g) as white crystals, mp 110.5-112°; R_f = 0.33 (ethyl acetate/hexane 3:1); ir: ν max 3520 (amide NH), 3300 br (OH), 1720 (CO), 1660 (amide CO); ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.45 and 6.95 (2d, 4H, aromatic), 6.30 (s, 1H, amide NH), 4.95 (s, 1H, OH), 4.10 (dd, 1H, H3, $J_{3,\alpha}$ = 9.1 and $J_{3,\beta}$ = 5.7 Hz), 3.80 (s, 3H, CH_3O) 3.65 (m, 2H, H_6), 3.35 (dd, 1H, H_α, J_{gem} = 16.2 Hz), 2.95 (m, 2H, H_5), 2.20 (dd, 1H, H_β), 1.85 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{19}NO_4S$ (309.38): C, 58.23; H, 6.19; N, 4.53. Found: C, 58.10; H, 6.29; N, 4.66.

Isomer **20b** was obtained in 45% yield (0.12 g) as white crystals, mp 79-81°; R_f = 0.23 (ethyl acetate/hexane 3:1); ir: ν max 3450 (amide NH), 3225 br (OH), 1720 (CO), 1660 (amide CO); ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.40 and 6.90 (2d, 4H, aromatic), 6.00 (s, 1H, amide NH), 4.55 (s, 1H, OH), 4.05 (t, 1H, H_3, J = 6.7 Hz), 3.80 (s, 3H, CH_3O), 3.60 (m, 2H, H_6), 3.20 (dd, 1H, H_α, J_{gem} = 17.5 Hz), 2.85 (m, 2H, H_5), 2.50 (dd, 1H, H_β), 1.85 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{19}NO_4S$ (309.38): C, 58.23; H, 6.19; N, 4.53. Found: C, 58.39; H, 6.26; N, 4.44.

Ethyl 2-[3'-Hydroxy-3'-(*p*-methoxyphenyl)-2'-oxobutyl]3-oxo-2,3,5,6-tetrahydro-4*H*-1,4-thiazin-5-carboxylate (**21**).

To a methanolic solution of **4** (1.16 g, 5 mmoles) and L-cysteine ethyl ester hydrochloride (1.15 g, 6.2 mmoles), was added triethylamine (0.63 g, 6.2 mmoles). After stirring for 20 minutes (tlc), methanol was removed *in vacuo* and the residue was extracted with ethyl acetate (2 x 100 ml), washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure yielding a yellowish oil. Flash column chromatography (ethyl acetate-hexane, 1:1) afforded as major products isomers **21a** and **21b** in 80% total yield.

Isomer **21a** was obtained in 40% yield (0.76 g), R_f = 0.30 (ethyl acetate/hexane, 1:1, two passes); $[a]_D$ = -40° (methanol, c = 0.5 mg/ml), mp 86-88°; ir: ν max 3340 (OH and amide NH), 1750 (ester CO), 1715 (CO), 1650 (amide CO); ^{1}H nmr (500 MHz, deuteriochloroform): δ 7.37 and 6.87 (2d, 4H, aromatic), 6.46 (s, 1H, amide NH), 4.51 (s, 1H, OH), 4.40 (dq, 1H, H_5, J = 2, $J_{5,6eq}$ = 4 and $J_{5,6ax}$ = 9.5 Hz), 4.25 (q, 2H, CH_2O), 3.97 (dd, 1H, H_3, $J_{3,\alpha}$ = 7.5 and $J_{3,\beta}$ = 6 Hz), 3.79 (s, 3H, CH_3O), 3.25 (dd, 1H, H_α, J_{gem} = 16 Hz), 3.13 (dd, 1H, H_{6eq}, J_{gem} = 14 Hz), 2.99 (dd, 1H, H_{6ax}, J_{gem} = 14 Hz), 2.46 (dd, 1H, Hβ, J_{gem} = 16 Hz), 1.71 (s, 3H, CH_3), 1.30 (t, 3H, CH_3CH_2O); hrms: Calcd. for $C_{18}H_{23}NO_6SH^+$ 382.1324. Found: 382.1324.

Anal. Calcd. for $C_{18}H_{23}NO_6S$ (381.44): C, 56.68; H, 6.08; N, 3.67. Found: C, 56.48; H, 6.28; N, 3.71.

Isomer **21b** was obtained in 40% yield (0.75 g), R_f = 0.23 (ethyl acetate-hexane, 1:1, two passes), $[a]_D$ = -133° (methanol, C = 0.5 mg/ml), mp 90-92°; ir: ν max 3440 (amide NH), 3370 br (OH), 1740 (ester CO), 1720 (CO), 1645 (amide CO); ^{1}H nmr (500 MHz, deuteriochloroform): δ 7.28 and 6.83 (2d, 4H, aromatic), 6.29 (s, 1H, amide NH), 4.38 (s, 1H, OH), 4.28 (octet, 1H, H_5, J = 2.5, $J_{5,6eq}$ = 4.5 and $J_{5,6ax}$ = 8.5 Hz), 4.18 (q, 2H, CH_2O), 3.89 (dd, 1H, H_3, $J_{3,\alpha}$ = 5 and $J_{3,\beta}$ = 7.5 Hz), 3.74 (s, 3H, CH_3O), 3.11 (dd, 1H, H_α, J_{gem} = 18 Hz), 2.94 (dd, 1H, H_{6eq}, J_{gem} = 13.5 Hz), 2.89 (dd, 1H, H_{6ax}, $J_{5,6ax}$ = 8.5 Hz), 2.69 (dd, 1H, H_β, J_{gem} = 18 Hz), 1.70 (s, 3H, CH_3), 1.23 (t, 3H, CH_3CH_2O); hrms: Calcd. for $C_{18}H_{23}NO_6SH^+$: 382.1324. Found: 382.1333.

Anal. Calcd. for $C_{18}H_{23}NO_6S$ (381.44): C, 56.68; H, 6.08; N, 3.67. Found: C, 56.48; H, 6.23; N, 3.41.

2-[3'-Hydroxy-3'-(*p*-methoxyphenyl)-2'-oxobutyl]-2,3-dihydro-4*H*-1,4-benzothiazin-3-one (**22**).

To an ice cold stirred solution of lactone **4** (0.20 g, 0.86 mmole) in methylene chloride (10 ml), 2-aminothiophenol (0.13 g, 1.04 mmoles) was added. The reaction mixture was allowed to reach room temperature and stirring was continued for an additional 10 minutes (tlc), then extracted with methylene chloride (2 x 50 ml), washed with brine, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The remaining slurry was chromatographed to give isomer **22a** and isomer **22b** in 88% total yield.

Isomer **22a** was obtained in 72% yield (0.22g), as white crystals, mp 152-153.5°; R_f = 0.60 (ethyl acetate/hexane 3:1); ir: ν max 3430 (amide NH), 3250 br (OH), 1720 (CO), 1660 (amide CO); ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.05 (s, 1H, amide NH), 7.30-6.70 (m, 8H, aromatic), 4.45 (s, 1H, OH), 4.10 (t, 1H, H_3, J = 7.3 Hz), 3.80 (s, 3H, CH_3O), 3.30 (dd, 1H, H_α, J_{gem} = 16.5 Hz), 2.45 (dd, 1H, H_β), 1.75 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{19}NO_4S$ (357.42): C, 63.85; H, 5.36; N, 3.92. Found: C, 64.01; H, 5.20; N, 4.03.

Isomer **22b** was obtained in 16% yield (0.06 g) as white crystals, mp 143-145°; R_f = 0.56 (ethyl acetate/hexane 3:1); ir: ν max 3450 (amide NH), 3250 br (OH), 1715 (CO), 1665 (amide CO); ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.55 (s, 1H, amide NH), 7.40-6.70 (m, 8H, aromatic), 4.45 (s, 1H, OH), 4.05 (t, 1H, H_3, J = 7.2 Hz), 3.80 (s, 3H, CH_3O), 3.20 (dd, 1H, H_α, J_{gem} = 16.4 Hz), 2.50 (dd, 1H, H_β), 1.60 (s, 3H, CH_3).

3-(*p*-Aminophenylthio)-6-(*p*-methoxyphenyl)-6-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2,5-dione (**23**).

To 10 ml methylene chloride, compound **4** (1.16 g, 5 mmoles) and *p*-aminothiophenol (0.70 g, 5.6 mmoles) were dissolved. The reaction mixture was stirred for 30 minutes (tlc), then extracted with methylene chloride (2 x 50 ml), washed with brine, dried over magnesium sulfate and the solvent was evapo-

rated under reduced pressure. The remaining residue was crystallized (white crystals) from methylene chloride-hexane to give 1.71 g (96% total yield) of a mixture of two isomers (ratio 4:1 based on ^{1}H nmr). Further purification was not achieved due to a retro-Michael reaction during column chromatography. Pure major product R_f = 0.21 (ethyl ether-hexane 1:2), was obtained after several recrystallizations: mp 142-144°; ir: ν max 3480 and 3370 (NH_2), 1735 (lactone CO), 1720 (ketone CO); ^{1}H nmr (500 MHz, dimethyl sulfoxide-d_6): δ 7.36 and 7.07 (2d, 4H, aromatic), 7.24 and 6.62 (2d, 4H, aromatic), 5.61 (s, 2H, NH_2), 4.05 (dd, 1H, H_3, $J_{3,4eq}$ = 5.6 and $J_{3,4ax}$ = 8.5 Hz), 3.84 (s, 3H CH_3O), 3.33 (dd, 1H, H_{4eq}, J_{gem} = 17.1 Hz), 2.59 (dd, 1H, H_{4ax}), 1.71 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{19}NO_4S$ (357.42): C, 63.85; H, 5.36; N, 3.92. Found: C, 63.81; H, 5.41; N, 4.00.

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