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Novel Synthons from Mucochloric Acid: The First Use of α,β-Dichloro-γ-butenolides and γ-Butyrolactams for Direct Vinylogous Aldol Addition

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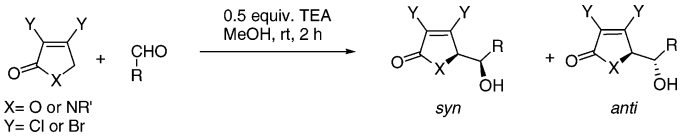

Novel 5-(1′-hydroxy)-γ-butyrolactone and γ-butyrolactam subunits were synthesized by direct vinylogous aldol addition of α,β-dichloro γ-butyrolactones and γ-butyrolactams with aldehydes under basic conditions. Different bases and solvents were screened in the context of generating γ-butyrolactones. Diastereoselectivity was observed and γ-butenolides and γ-butyrolactams showed opposite diastereoselectivity under the same reaction condition.

Introduction

The 5-(1′-hydroxy)-γ-butyrolactone and γ-butyrolactam subunits **1a** and **1b** are present in myriads of natural products with medicinal importance (Figure 1).[1] For example, stereoselective synthesis and evaluation of all the stereoisomers of μ-opioid analgesic viminol analogue Z4349 were reported.[2] Squamostolide and its related analogues were designed and prepared for anticancer activity studies.[3] Recently, the cytotoxic, antitumoral and bactericidal properties of 5-(1′-hydroxy)-3-methylidene-γ-butyrolactone (**2**) were presented,[4] and 4,5-disubstituted *cis*-pyrrolidinones **3** have been investigated as inhibitors of type II 17β-hydroxysteroid dehydrogenase.[5] These subunits, **1a** and **1b**, have also been employed as useful intermediates in organic synthesis.[6]

A variety of methods have been developed to synthesize 5-(1′-hydroxy)-γ-butyrolactone and γ-butyrolactam. For example, the γ-butyrolactone **1a** was synthesized from chiral sulfoxides,[7] lactonization of epoxides,[8] or osmium-catalyzed asymmetric dihydroxylation of γ,δ-unsaturated esters,[9] from D-mannitol[10] and from α-hydroxylated silyloxy-cyclobutanone derivatives.[11] A chemoenzymatic synthesis of L-factor has also been reported recently.[12] Among the reported syntheses of **1b**, notable are those from Juliá−Colona oxidation of chalcones,[13] radical hydroxylation of a *tert*-amide,[14] SmI_2-promoted, reductive coupling reactions of aromatic lactams,[15] and via oxidation of 5-alkylidene-2-pyrrolidinones to acyliminium ion precursors.[16] However, the most extensively exploited methodology is the vinylogous aldol[17] addition with suitable furan and pyrrole

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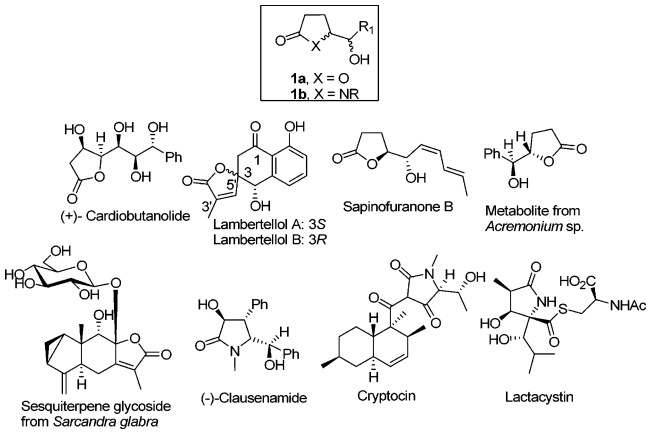


FIGURE 1. Naturally occurring 5-(1′-hydroxy)-γ-butyrolactone and γ-butyrolactam.

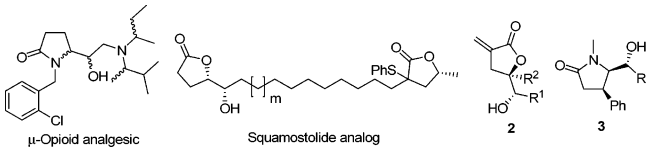
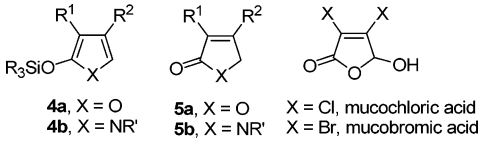


FIGURE 2. Synthetic analogues of 5-(1′-hydroxy)-γ-butyrolactone and γ-butyrolactam.

derivatives.[18] In the Mukaiyama aldol addition, 2-silyloxy furans **4a** or pyrroles **4b**, which could be prepared from **5a** or **5b**, are used in conjunction with Lewis acids or TBAF.[19] Alternatively, "direct" vinylogous aldol was performed on furan-2(5*H*)-ones **5a** and pyrrole-2(5*H*)-ones **5b** by strong base-induced generation of the enolates in the presence/absence of Lewis acids as additive,[20] which is relatively less explored compared to the Mukaiyama variation.



A common feature of those methodologies is the complexity in the synthesis that typically involves multistep, often tedious separation and the use of harmful reagents. In the Mukaiyama aldol approach, the reaction usually required more than a molar equivalent of Lewis acid as well as other additives and typically performed at −78 °C. The direct vinylogous aldol required the use of a strong base, such as LiHMDS, and operated at low temperature (−78 °C). As a result, these methodologies are often unsuitable for scale-up. This prompted us to explore a more simple methodology to synthesize novel synthons **1a** and **1b**.

Mucohalic acids are attractive and versatile building blocks in organic synthesis. Synthon **6** was prepared easily by reduction of mucohalic acid and was applied in the palladium-catalyzed Suzuki coupling reaction.[21] Synthon **7** was synthesized by reductive amination of mucohalic acids with use of sodium triacetoxyborohydride; however, its use in synthesis is limited.[22] Recently we reported[23] a simple and efficient synthesis of

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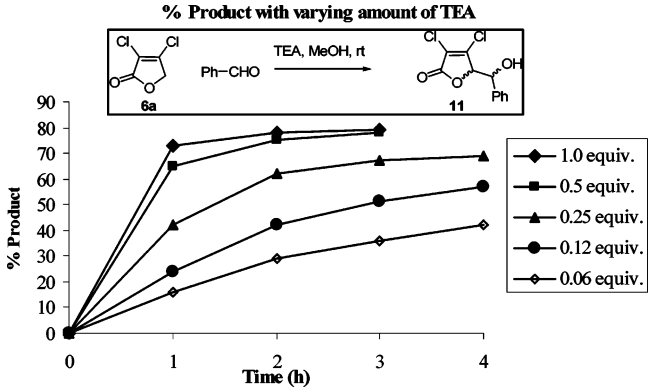


FIGURE 3. Percent product formation with varying amounts of Et_3N (TEA).

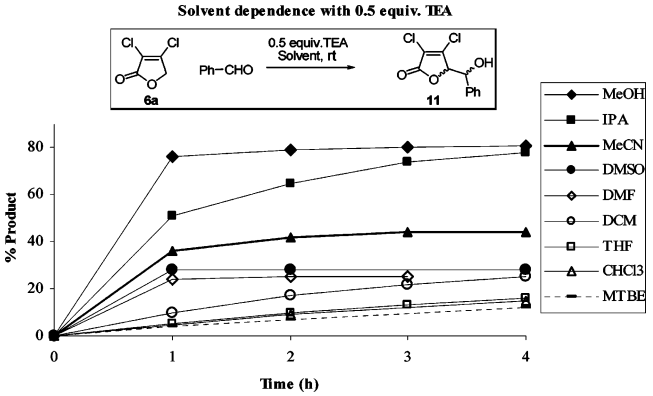
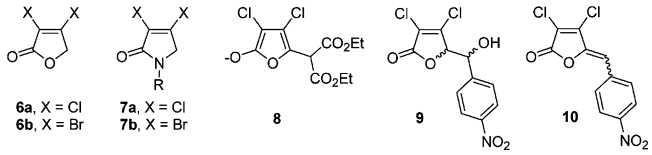


FIGURE 4. Percent product formation in different solvents.

γ-alkylidenebutenolide by base-induced selective dehalogenation of Knoevenagel aldol adducts which were obtained from mucohalic acids.[24] The mechanistic investigation indicated formation of the furan intermediate **8**, which encouraged us to explore the applicability of **6** and **7** toward direct vinylogous aldol addition under mild conditions.



Results and Discussion

We initiated our study with α,β-dichloro-γ-butenolide **6a**. When an activated aldehyde, 4-nitrobenzaldehyde, was used, the corresponding aldol product **9** was isolated in 63% yield by using one molar equivalent of Et_3N (TEA) in MTBE at room temperature.[25] Unfortunately, under this reaction condition the dehydration product **10** was also found to form along with the desired aldol product **9**.[26] Thus, we decided to optimize the reaction condition. In an attempt to reduce the use of TEA, the transformation was carried out with various molar equivalents of TEA.[27] As seen in Figure 3, both 1 and 0.5 molar equiv of TEA were found to be equally efficient. However, the yield of the aldol reaction was very low when benzaldehyde was used.[28] With a more electron-rich aldehyde like 3-methoxybenzaldehyde, hardly any conversion was observed. In the benzaldehyde case, the retro-aldol was also observed by HPLC and LC-MS analysis; this prompted us to further investigate the effect of different solvents on this transformation.

For this solvent screen benzaldehyde was reacted with **6a** in eight different solvents (Figure 4). Interestingly, the best transformation was observed in MeOH and ^{i}PrOH, two proton-exchangeable solvents, where almost no trace of the dehydration product was found. We rationalized that the alcoholic solvents stabilize the intermediates **I** and **II** by solvation or hydrogen bonding[29] and thereby assist the transformation (Figure 5). Notably, CH_2Cl_2 and THF, the commonly used solvents in direct vinylogous aldol reactions, failed to give product in good yield.

Next, we studied the effect of basicity on the aldol reaction, where bases with pK_a values ranging from 7.4 to 12 were chosen for this investigation (Figure 6). Five monodentate organic amine bases (NMM, DABCO, TEA, DIEA, DBU) and one bidentate base (TMEDA) were screened. A half molar equivalent was used for monodentate bases and 0.25 molar equiv was used for TMEDA.[30] The product formation was very low when NMM and DABCO were used, only 24% and 7% of product, respectively, after 4 h. However, the product formation in TMEDA and TEA was fast, slightly better compared with results in DIEA. The transformation in DBU remained at 48% between 1 to 4 h.

After these important screenings, we found that the alcoholic solvent, MeOH, and 0.5 molar equiv of Et_3N provided the best result for direct vinylogous aldol addition. The reaction was rapid, and achieved satisfactory conversion in 1 to 4 h without significant side reaction; thus, we decided to apply this optimized condition (MeOH, Et_3N, 3 h) in the coming study.

The *syn*/*anti* ratio was assigned by analyzing ^{1}H NMR spectra of **11**. Bella and co-workers reported that the *syn* diastereomer of the aldol product **12** has a larger $J_{1'-5}$ (after D_2O exchange) compared to the *anti* diastereomer, whereas C-1′ and C-3 have lower chemical shifts for the *syn* isomer as compared with the corresponding *anti* isomer.[31] Similar trends were observed for the reduction product **13** and its acetyl derivative **14**. For **11** we observed a clear doublet formation for C_5-H and a broad peak for $C_{1'}-H$. However, upon D_2O exchange, the signal corresponding to C_5-H and $C_{1'}-H$ of one of the isomers tends to coalesce. A higher $J_{1'-5}$ of 6.64 Hz indicated this to be the *syn* isomer, which is the major product in this transformation. To establish the identity of the major isomer unambiguously, **11** was converted to the acyl derivative **14** (Scheme 1). ^{1}H NMR of the crude product shows the C*H*OAc proton at 5.97 ppm for the *anti* (J = 3.51 Hz) product and at 5.81 ppm for the *syn* (J

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(25) Abbreviations used for bases; TEA, triethylamine; NMM, *N*-methyl morpholine; DABCO, 1,4-diazabicyclo[2.2.2]octane; DIEA, diisopropylethylamine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine.

(26) The identity of the dehydration product **10** was established by LCMS.

(27) The reactions were monitored by HPLC. Percent product formed was calculated based on the peak area corresponding to the aldol product **9** as compared with the combined peak areas of **6a**, **10**, and **9**. All the reactions monitored by HPLC were done in duplicate.

(28) No significant amount of dehydration product was observed by HPLC.

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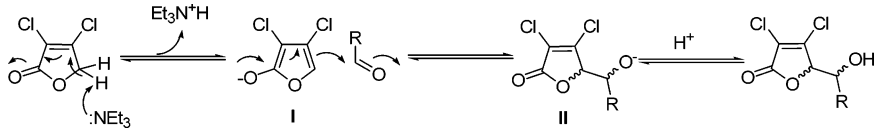


FIGURE 5. Proposed mechanism of aldol addition.

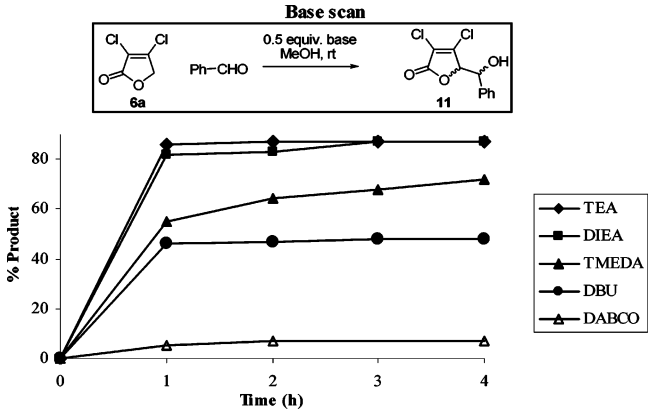
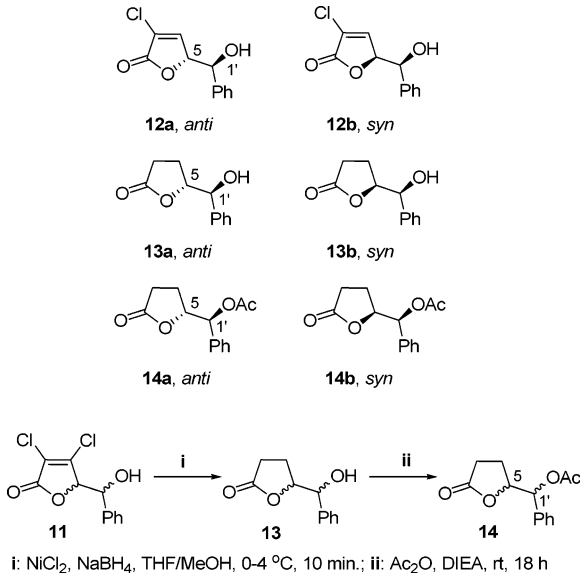


FIGURE 6. Percent product formation with different bases.

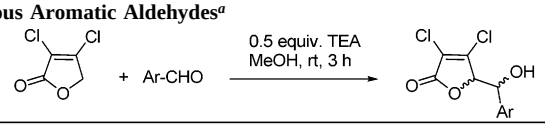
SCHEME 1. Aldol Products and Their Reduction and Derivatization[31]

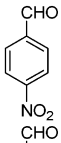
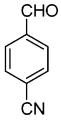
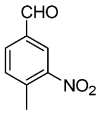
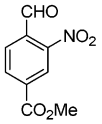
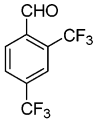
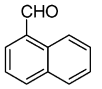
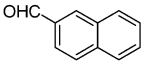
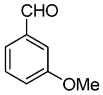
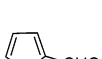


= 6.63 Hz) product in 1:2 ratio. The "*J*" values match closely with the reported values.[31] This proves that these aldol reactions show *syn* selectivity when α,β-dichloro-γ-butenolide **6a** is used.

Next, the generality of this reaction was studied. Various aromatic aldehydes and the effects of ring substitution on the diastereomeric ratio were ascertained (Table 1). These reactions were performed with 0.5 molar equiv of TEA in MeOH at room temperature. Typically the reactions were complete within 3 h with moderate to good yield. For para- and meta-substituted benzaldehydes, the *syn*/*anti* ratio was similar to that observed in benzaldehyde at 2/1 (entries 2, 3, 4, and 9) while the *syn*/*anti* ratio was enhanced by ortho-substituents on the aromatic ring. For example, methyl 4-formyl-3-nitrobenzoate (entry 5) gave a 5/1 *syn*/*anti* ratio and, for a more sterically demanding trifluoromethyl group as ortho-substituent, the *syn*/*anti* ratio increased to 10/1 (entry 6). 1-Napthaldehyde (entry 7) provided a slight improvement in the *syn*/*anti* ratio over that observed in benzaldehyde (3/1 ratio) due to nonbonding, steric interactions with the C-8 hydrogen, similar to the described ortho-substitution effect. 2-Napthaldehyde mimicked the *syn*/*anti* ratio (2/1) observed for benzaldehyde. For 2-furaldehyde, where the furan ring is spatially less demanding than the phenyl ring, the *syn*/*anti* ratio eroded to 1.4/1. The transformation was also successful on a 12 mmol scale and the yield of the aldol product **11** was increased to 79% from 70% as observed on a smaller scale.

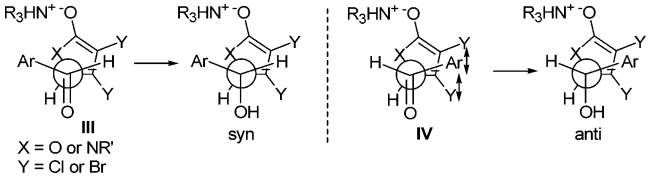
TABLE 1. TEA-Promoted Aldol Reaction of Butenolide 6a with Various Aromatic Aldehydes[a]



Entry	Ar-CHO	Product	%Yield	*syn*/*anti*
1	Ph-CHO	**11**	79	2/1
2		**9**	68	2/1
3		**15**	60	2/1
4		**16**	52	2/1
5		**17**	64	5/1
6		**18**	66	10/1
7		**19**	50	3/1
8		**20**	50	2/1
9		**21**	47	2/1
10		**22**	70	1.4/1

[a] Reaction conditions: 0.5 equiv of TEA was added to a mixture of 3.3 mmol of **6a** and ArCHO (1.1 equiv) in 10 mL of MeOH. [b] Products were isolated and purified by silica gel chromatography and characterized.

SCHEME 2. The Newman Projection of Possible Transition State Conformers III and IV



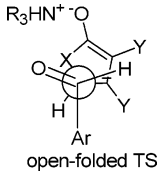
This indicated that this methodology is easily operated and should be easily scaled-up.

There has been significant exploration into the diastereoselective control in vinylogous aldol reactions by changing the Lewis acids or additives.[19,20] Unfortunately, no clear trend has emerged from these studies and predicting the *syn*/*anti* ratio of the product is at times difficult. Using the present methodology, one can predict the diastereomeric outcome with relative ease. Interestingly, Lewis acids like $ZnCl_2$ or $BF_3{\cdot}OEt_2$ failed to influence the *syn*/*anti* ratio in these reactions.[32] In fact the rate of product formation slowed down considerably in both cases, and negligible amounts of product were seen with $BF_3{\cdot}OEt_2$ even after 24 h. To study the effect of temperature on the *syn*/*anti* ratio, the transformation with benzaldehyde was performed at −20 and −40 °C. Interestingly, though the reaction slowed down with lowering of the temperature, there was no effect whatsoever on the *syn*/*anti* ratio.

The observed diastereoselectivity can be explained by examining possible transition states from the Newman projections **III** and **IV** (Scheme 2).[33] It is clear that if X is an oxygen atom, or when the butenolide system was used as starting material, the transition state (TS) for conformer **III** has fewer steric interactions than that of the TS for conformer **IV**, giving predominantly the *syn* product instead of the *anti* product *(syn*/*anti* is 2/1 in entries 1, 2, 3, 4, 8, and 9 of Table 1). Nonbonding, steric interactions between the two Y (Cl or Br) atoms and substituted aromatic ring would increase in proposed TS conformer **IV**, when the aromatic ring is ortho-substituted, showing increased preference for the *syn* adduct. For example, when NO_2 or CF_3 are present as the ortho-substituent on the phenyl ring (entries 5 and 6 of Table 1), the ratio is increased to 5/1 and 10/1, respectively, sterically disfavoring the TS leading to the *anti* adduct. Thus the general rule governing the *syn*/*anti* ratio by the substituted functional group is ortho > meta > para. Interestingly, a phenyl ring fused to the aromatic ring has little effect on the *syn*/*anti* ratio (entries 7 and 8 of Table 1), likely due to the plane orientation or the favorable $\pi-\pi$ interaction. This model also provided an easy explanation for the outcome of the aldol adduct derived from reaction of α,*β*-dibromo-*γ*-butenolide, **6b,** with benzaldehyde where the *syn*/*anti* ratio is 5:1 (Scheme 3, in α,*β*-dichloro-*γ*-butenolide, the *syn*/*anti* ratio is 2:1). The increase in *syn*-selectivity is presumably due to the Br atom being larger than the Cl atom. We then expect that when X = NR′, or in the case of α,*β*-dichloro-*γ*-butyrolactams used as starting material, that the *anti* aldol adduct derived from TS conformer **IV** would be preferred, since NR′ is much larger than the oxygen atom (vide infra).

(32) The reaction with $ZnCl_2$ was run in MTBE as solvent. With $BF_3{\cdot}OEt_2$, the reaction was run without adding other solvent.

(33) (a) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563−1572. (b) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027−3037. (c) An alternative TS suggested by a referee that would give rise to the anti product is an open-folded TS.



SCHEME 3. Aldol Addition of α,*β*-dibromo-*γ*-butenolide, 6b, with Aromatic Aldehyde

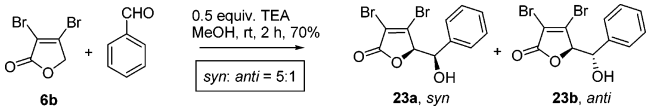
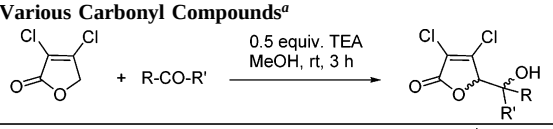


TABLE 2. TEA-Promoted Aldol Reaction of Butyrolactone 6a with Various Carbonyl Compounds[a]



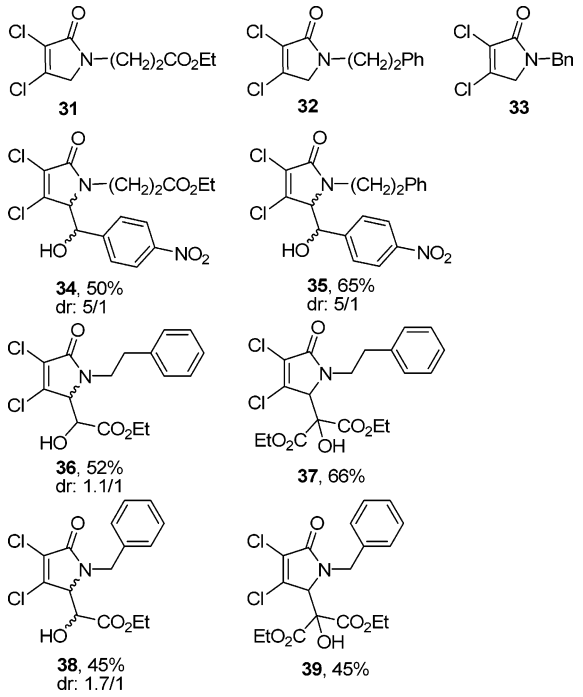
Entry	R-CO-R'	Product	%Yield[b]	*syn*/*anti*
1	Ph—≡—CHO	**24**	35	1/1
2	CHO	**25**	52	2/1
3	CHO	**26**	35	2/1
4	OHC−CO_2Et	**27**	52	4/1
5	CO_2Et	**28**	60	1/1
6	EtO$_2$C CO_2Et	**29**	86	--
7	OPh	**30**	30	1/1

[a] Reaction conditions: 0.5 equiv of TEA was added to a mixture of 3.3 mmol of **6a** and RCOR′ (1.1 equiv) in 10 mL of MeOH [b] Products were isolated and purified by silica gel chromatography and characterized.

We then extended this methodology toward nonaromatic aldehydes and ketones (Table 2). The diastereoselectivity reduced as the phenyl ring moved further away from the aldehyde functionality (entry 1). However, the preference of *syn* over *anti* was conserved in the vinylogue system (entries 2 and 3). For ethyl glyoxalate (entry 4), the *syn* preference is probably due to the increased bulk associated with the −CO_2-Et functionality. For ethyl pyruvate (entry 5) this selectivity is lost due to the presence of the Me− group, as in both transition states, nonbonding steric interactions are comparable. The transformation was also successful (entry 6) with an activated ketone such as diethyl ketomalonate resulting in higher yield of products. For 1-phenoxypropan-2-one (entry 7) no diastereoselectivity was observed as both proposed transition states will encounter steric interactions.

We extended the aldol methodology to α,*β*-dichloro-*γ*-butyrolactams (Scheme 4). The initial attempt reacted *γ*-

SCHEME 4. α,β-Dichloro-γ-butyrolactam Substrates and Corresponding Aldol Products



butyrolactam **31** with 4-NO_2-benzaldehyde in the presence of 0.5 molar equiv of TEA and resulted in the formation of aldol adducts in a 5/1 diastereomeric ratio with an isolated yield of 35%. The yield could be increased to 50% by using 1 molar equiv of TEA. The diastereomers were assigned based on ^{1}H NMR and the *anti* isomer was found to be the major diastereomer in this case.[34] A similar trend was observed in the aldol with **32** and a 5/1 diastereomeric ratio was observed favoring the *trans* aldol adduct. In general these transformations were found to propagate better with nonaromatic aldehydes and ketones. Thus yields were moderate to good with ethyl glyoxalate (**36**, **38**) and diethyl ketomalonate (**37**, **39**). However, the diastereomers could not be assigned for aldol adducts **36** and **38** by ^{1}H NMR.[35] We are currently investigating the effects of substitution on N, solvents, bases, and additives on these transformations.

In conclusion, we have developed a simple approach to access novel 5-(1′-hydroxy)-γ-butenolide and γ-butyrolactam subunits by direct vinylogous aldol addition of α,β-dichloro γ-butenolide and γ-butyrolactam to aldehydes under basic conditions. The reaction was carried out under mild conditions and the operation is simple and practical. The effects of bases and solvents were studied carefully in context of aldols with γ-butyrolactones for the first time. γ-Butyrolactones and γ-butyrolactams showed opposite diastereoselectivity under the same reaction conditions. We are studying the applications of these highly functionalized synthons in organic synthesis and results will be reported in due course.

Experimental Section

All reactions were carried out under nitrogen atmosphere unless otherwise noted. Synthesis of the starting materials **6a**, **6b**, **31**, and **33** was previously reported.[36] The synthesis of **32** was accomplished by using the standard reductive amination procedure.[22]

General Procedure for Aldols. TEA (0.5 equiv for reactions with γ-butyrolactones and 1 equiv for γ-butyrolactams) was added dropwise to a mixture of the γ-butyrolactone (or γ-butyrolactam) and the carbonyl compound (1.1 equiv) in MeOH (10 mL for a 3 mmol scale reaction) with continuous stirring at room temperature. The progress of the reaction was monitored by HPLC and the reactions were found to be complete within 3 h in most of the cases. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 2 N HCl solution. The ethyl acetate layer was separated, washed with 2 N HCl and brine, and dried over anhydrous Na_2SO_4. The crude product obtained upon solvent removal was purified by silica gel column chromatography, using ethyl acetate/hexane as eluent.

3,4-Dichloro-5-(hydroxy(4-nitrophenyl)methyl)furan-2(5H)-one (9, dr = 66:33). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.26 (m, 2H), 7.76 (m, 2H), 6.64 (d, J = 5.26 Hz, 0.33H), 6.41 (d, J = 5.65 Hz, 0.66H), 5.75 (d, J = 2.92 Hz, 0.33H), 5.66 (d, J = 1.75 Hz, 0.66H), 5.38 (dd, J = 5.17, 3.02 Hz, 0.33H), 5.29 (dd, J = 5.85, 1.95 Hz, 0.66H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.2, 164.9, 151.1, 150.1, 147.9, 147.1, 147.0, 146.1, 127.8, 123.2, 120.7, 120.2, 84.9 (2 peaks), 70.3, 68.4. Anal. Calcd for $C_{11}H_7Cl_2NO_5$: C, 43.45; H, 2.32; N, 4.61; Cl, 23.32. Found: C, 43.46; H, 2.23; N, 4.49; Cl, 23.20.

3,4-Dichloro-5-(hydroxy(phenyl)methyl)furan-2(5*H*)-one (11, dr = 66:33). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49−7.36 (m, 5H), 5.33 (d, J = 3.12 Hz, 0.33H), 5.27 (br s, 0.33H), 5.14 (br s, 0.66H), 5.12 (d, J = 4.0 Hz, 0.66H), 2.48 (br m, 0.33H), 2.16 (br m, 0.66H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 165.2, 150.0, 138.0, 135.8, 129.3, 129.2, 129.0, 128.8, 126.9, 126.7, 122.4, 84.9, 84.6, 73.6, 72.0. Anal. Calcd for $C_{11}H_8Cl_2O_3$: C, 50.99; H, 3.11; Cl, 27.37. Found: C, 50.97; H, 3.08; Cl, 27.05.

4-((3,4-Dichloro-5-oxo-2,5-dihydrofuran-2-yl)(hydroxy)methyl)benzonitrile (15, dr = 66:33). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.77−7.63 (m, 4H), 5.54 (d, J = 2.92 Hz, 0.33H), 5.40 (d, J = 1.95 Hz, 0.66H), 5.32 (d, J = 2.73 Hz, 0.33H), 5.25 (d, J = 1.75 Hz, 0.66H). ^{13}C NMR (100 MHz, CD_3OH) δ: 167.0, 166.7, 152.0, 151.0, 146.9, 144.9, 133.4, 133.2, 129.0, 128.9, 123.3, 122.8, 119.7, 119.6, 113.2, 112.9, 86.6, 86.5, 73.0, 71.0. Anal. Calcd for $C_{12}H_7Cl_2NO_3$: C, 50.73; H, 2.48; N, 4.93; Cl, 24.96. Found: C, 50.72; H, 2.38; N, 4.91; Cl, 24.70.

3,4-Dichloro-5-(hydroxy(4-methyl-3-nitrophenyl)methyl)furan-2(5*H*)-one (16, dr = 66:33). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J = 1.8 Hz, 0.66H), 8.02 (d, J = 1.8 Hz, 0.33H), 7.65 (dd, J = 7.9, 1.8 Hz, 0.66), 7.56 (dd, J = 7.9, 1.8 Hz, 0.33 H), 7.42 (d, J = 8.0 Hz, 0.66H), 7.39 (d, J = 8.0 Hz, 0.33H), 5.35 (m, 0.33H), 5.31 (d, J = 3.12 Hz, 0.33H), 5.22 (m, 0.66H), 5.12 (d, J = 2.34 Hz, 0.66H), 2.84 (d, J = 5.07 Hz, 0.33H), 2.63 and 2.62 (s, 3H), 2.46 (d, J = 5.85 Hz, 0.66H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 149.2, 149.1, 142.9, 141.5, 137.3, 135.4, 134.4, 133.5, 133.2, 131.2, 130.8, 122.9, 122.8, 122.7, 122.0, 84.2, 84.0, 72.1, 70.5. 21.9, 20.3. Anal. Calcd for $C_{12}H_9Cl_2NO_5$: C, 45.31; H, 2.85; N, 4.40; Cl, 22.29. Found: C, 45.37; H, 2.88; N, 4.33; Cl, 22.14.

Methyl 4-((3,4-Dichloro-5-oxo-2,5-dihydrofuran-2-yl)(hydroxy)methyl)-3-nitrobenzoate (17, dr = 83:17). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (d, J = 1.56 Hz, 0.17H), 8.74 (d, J = 1.75 Hz, 0.83H), 8.37 (m, 1H), 8.14 (d, J = 8.19 Hz, 0.17H), 8.10 (d, J = 8.19 Hz, 0.83H), 6.08 (m, 0.17H), 5.92 (dd, J = 5.17, 0.68 Hz, 0.83H), 5.43 (m, 0.83H), 5.28 (m, 0.17H), 4.01 (s, 3H), 3.02 (d, J = 5.26 Hz, 0.17H), 2.46 (d, J = 5.46 Hz, 0.83H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1, 164.5, 149.2, 147.1, 138.6, 136.8, 134.5, 134.2, 131.9, 130.8, 126.4, 125.9, 122.6, 83.1, 83.0, 70.0, 66.2, 53.0. Anal. Calcd for $C_{13}H_9Cl_2NO_7$: C, 43.12; H, 2.51; N, 3.87; Cl, 19.58. Found: C, 43.17; H, 2.53; N, 3.82; Cl, 19.81.

5-((2,4-Bis(trifluoromethyl)phenyl)(hydroxy)methyl)-3,4-dichlorofuran-2(5*H*)-one (18, dr = 91:9). ^{1}H NMR (400 MHz, $CDCl_3$)

(34) Bigi, F.; Casnati, G.; Sartori, G.; Ardaldi, G. *Gazz. Chem. Ital.* **1990**, *120*, 413−419.

(35) The major product seemed to be *anti* based on chemical shift of the C-1′ proton. However, the J1′-5 did not show the expected trend.

(36) Reference 21 for **6a** and **6b**; ref 22b for **31**; and ref 22a for **33**.

δ: 8.33 (d, J = 8.19 Hz, 0.1H), 8.12 (d, J = 8.19 Hz, 0.9H), 7.96−7.91 (m, 2H), 5.83 (d, J = 3.90 Hz, 0.1H), 5.65 (d, J = 5.07 Hz, 0.9H), 5.23 (d, J = 3.90 Hz, 0.1H), 5.02 (d, J = 1.17 Hz, 0.9H), 2.84 (d, J = 4.68 Hz, 0.1H), 2.39 (d, J = 5.07 Hz, 0.9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −58.67, −63.51. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.0, 148.8, 140.9, 131.7, 131.4, 130.9, 129.4, 128.1, 127.8, 127.5, 127.2, 124.9, 123.0, 122.7, 122.1, 121.7, 83.3, 65.9. Anal. Calcd for $C_{13}H_6Cl_2F_6O_3$: C, 39.52; H, 1.53; Cl, 17.95; F, 28.85. Found: C, 39.43; H, 1.36; Cl, 17.71; F, 28.49.

3,4-Dichloro-5-(hydroxy(naphthalen-1-yl)methyl)furan-2(5*H*)-one (19, dr = 75:25). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.58 Hz, 0.75H), 7.97−7.93 (m, 2.5H), 7.80 (d, J = 7.21 Hz, 0.75H), 7.63−7.51 (m, 3H), 6.06 (br s, 0.25H), 5.97 (br s, 0.75H), 5.48 (d, J = 2.73 Hz, 0.25H), 5.31 (d, J = 1.95 Hz, 0.75H), 2.70 (br s, 0.25H), 2.30 (br s, 0.75H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.3, 149.8, 133.8, 133.2, 130.0, 129.6, 129.5, 129.4, 127.0, 126.0, 125.9, 125.5, 125.3, 125.2, 124.9, 122.2, 121.8, 83.9, 83.5, 70.1, 67.5. Anal. Calcd for $C_{15}H_{10}Cl_2O_3$: C, 58.28; H, 3.26; Cl, 22.94. Found: C, 58.18; H, 3.42; Cl, 22.65.

3,4-Dichloro-5-(hydroxy(naphthalen-2-yl)methyl)furan-2(5*H*)-one (20, dr = 66:33). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (s, 0.66H), 7.91 (s, 0.33H), 7.87 (m, 3H), 7.58−7.45 (m, 3H), 5.42 (d, J = 2.8 Hz, 0.33H), 5.39 (d, J = 2.8 Hz, 0.33H), 5.29 (br d, J = 2 Hz, 0.66H), 5.19 (d, J = 2 Hz, 0.66H), 2.70 (br s, 0.33H), 2.37 (br s, 0.66H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.3, 164.9, 149.7, 149.0, 135.2, 133.5, 133.0, 128.8, 127.8, 126.7, 126.7, 126.6, 126.1 (2 peaks), 124.0, 123.6, 122.3, 84.6, 84.4, 73.5, 72.0. Anal. Calcd for $C_{15}H_{10}Cl_2O_3$: C, 58.28; H, 3.26; Cl, 22.94. Found: C, 57.91; H, 3.11; Cl, 22.68.

3,4-Dichloro-5-(hydroxy(3-methoxyphenyl)methyl)furan-2(5*H*)-one (21, dr = 66:33). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39−7.24 (m, 1H), 7.02−6.86 (m, 3H), 5.30 (m, 0.66H), 5.22 (m, 0.33H), 5.10 (m, 1H), 3.82 and 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.3, 165.0, 159.9, 149.8, 149.1, 139.4, 137.3, 129.9, 129.6, 122.6, 122.2, 118.8, 118.7, 114.6, 114.5, 112.3, 112.0, 84.7, 84.4, 73.2, 71.6, 55.4, 55.3. LRMS (APCI): m/z 253.1 [(M − HCl)H$^+$], 255.1 [({M + 2} − HCl)H$^+$].

3,4-Dichloro-5-(furan-2-yl(hydroxy)methyl)furan-2(5*H*)-one (22, dr = 59:41). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (dd, J = 1.95, 0.78 Hz, 0.6H), 7.41 (dd, J = 1.75, 0.97 Hz, 0.4H), 6.52 (m, 0.6H), 6.42 (dd, J = 3.51, 1.95 Hz, 0.6H), 6.40 (m, 0.4H), 6.38 (m, 0.4H), 5.39 (d, J = 3.12 Hz, 0.4H), 5.28 (d, J = 2.34 Hz, 0.6H), 5.27 (m, 0.4H), 5.15 (m, 0.6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 164.9, 150.7, 149.4, 149.1, 143.0, 142.9, 122.5, 122.4, 110.8, 110.7, 108.9, 108.8, 83.3, 82.7, 68.0, 66.0. Anal. Calcd for $C_9H_6Cl_2O_4$: C, 43.40; H, 2.43; Cl, 28.47. Found: C, 43.13; H, 2.34; Cl, 28.22.

3,4-dibromo-5-(hydroxy(phenyl)methyl)furan-2(5*H*)-one (23, dr = 83:17). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46−7.33 (m, 5 H), 5.30 (m, 0.17H), 5.25 (m, 0.17H), 5.14 (br d, J = 1.56 Hz, 0.83H), 5.09 (m, 0.83H), 2.99 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5., 165.9, 151.7, 145.7, 145.2, 138.3, 135.8, 133.9, 130.4, 129.2, 129.0, 128.7, 127.0, 126.9, 116.1, 87.4, 83.8, 72.2. Anal. Calcd for $C_{11}H_8Br_2O_3$: C, 37.97; H, 2.32. Found: C, 38.57; H, 2.35.

3,4-Dichloro-5-(1-hydroxy-3-phenylprop-2-ynyl)furan-2(5*H*)-one (24, dr = 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (dd, J = 7.99, 1.56 Hz, 1H), 7.33−7.22 (m, 4H), 5.19 (d, J = 2.73 Hz, 0.5H), 5.09 (d, J = 2.34 Hz, 0.5H), 5.05 (d, J = 2.53 Hz, 0.5H), 4.99 (d, J = 2.53 Hz, 0.5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 149.0, 148.4, 131.9, 131.8, 129.3, 129.2, 128.4, 122.7, 121.1, 120.9, 89.3, 87.9, 83.6, 83.3, 81.4, 63.3, 61.5. LRMS (APCI): m/z 283.1 (M$^-$).

3,4-Dichloro-5-((2*E*,4*E*)-1-hydroxyhexa-2,4-dienyl)furan-2(5*H*)-one (25, dr = 66:33, starting material ~83% *trans*, *trans*). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.76−6.64 (m, 0.33H), 6.40−6.28 (m, 0.66H), 6.10−6.01 (m, 1H), 5.87−5.76 (m, 1H), 5.67 (dd, J = 15.40, 7.41 Hz, 0.66H), 5.45 (dd, J = 15.3, 7.12 Hz, 0.33H), 5.12 and 5.11 (d, J = 2.73 Hz, 0.33H total), 4.95 (d, J = 2.34 Hz) and 4.92 (d, J = 2.14 Hz, 0.66H), 4.66 (m, 0.33H), 4.55 (m, 0.66H), 2.58 (m, 0.33H), 2.14 (m, 0.66H), 1.78 (overlapping d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 165.3, 149.8, 149.3, 135.3, 135.2, 132.9, 132.7, 129.9, 129.9, 129.6, 127.7, 125.4, 122.8, 121.8, 84.6, 84.3, 72.1, 70.4, 18.1, 13.5. Anal. Calcd for $C_{10}H_{10}Cl_2O_3$: C, 48.22; H, 4.05. Found: C, 47.72; H, 4.06.

(*E*)-3,4-Dichloro-5-(1-hydroxy-3-phenylallyl)furan-2(5*H*)-one (26, dr = 66:33). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44−7.28 (m, 5H), 6.81 (d, J = 15.79 Hz, 0.66H), 6.76 (dd, J = 15.20, 1.17 Hz, 0.33H), 6.37 (dd, J = 15.99, 7.41 Hz, 0.66H), 6.15 (dd, J = 15.79, 6.82 Hz, 0.33H), 5.18 (d, J = 2.92 Hz, 0.33H), 5.02 (d, J = 2.14 Hz, 0.66H), 4.85 (m, 0.33H), 4.74 (m, 0.66H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.3, 162.0, 149.6, 147.6, 135.4, 135.0, 134.9, 128.9, 128.7, 128.6, 128.4, 126.8, 124.9, 122.6, 119.99, 119.8, 84.4, 84.1, 72.4, 70.7. HRMS (ESI) calcd for $C_{13}H_{10}Cl_2O_3$ [{M − HCl} − H]$^-$ 247.0162, found 247.0152.

Ethyl 2-(3,4-Dichloro-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyacetate (27, dr = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.37 (d, J = 2.14 Hz, 0.2H), 5.31 (d, J = 1.75 Hz, 0.8H), 4.72 (br d, J = 1.95 Hz, 0.2H), 4.58 (br s, 0.8H), 4.41−4.28 (m, 2H), 1.34 and 1.29 (t, J = 7.12 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 169.0, 164.8, 164.5, 148.5, 147.9, 122.6, 122.3. 82.6, 81.9, 69.4, 67.9, 63.4, 63.1, 14.0, 13.9. Anal. Calcd for $C_8H_8Cl_2O_5$: C, 37.67; H, 3.16; Cl, 27.80. Found: C, 37.76; H, 3.25; Cl, 27.73.

Ethyl 2-(3,4-Dichloro-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxypropanoate (28, dr = 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.23 (s, 0.5H), 5.16 (s, 0.5H), 4.41−4.26 (m, 2H), 3.69 (m, 0.5H), 3.32 (br s, 0.5H), 1.68 and 1.65 (s, 3H), 1.38−1.31 (overlapping t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.7, 172.5, 164.5, 164.4, 148.3, 148.1, 123.3, 122.9, 84.6, 84.2, 74.6, 74.1, 63.4, 63.2, 23.6, 22.3, 14.0 (2 peaks). Anal. Calcd for $C_9H_{10}Cl_2O_5$: C, 40.17; H, 3.75; Cl, 26.35. Found: C, 40.11; H, 3.86; Cl, 26.10.

Diethyl 2-(3,4-Dichloro-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxymalonate (29). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.93 (d, J = 0.97 Hz, 1H), 4.45−4.33 (m, 4H), 4.03 (d, J = 0.97 Hz, 1H), 1.36 (t, J = 7.12 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 166.0, 164.2, 147.2, 123.6, 82.4, 78.0, 64.5, 63.7, 13.9. Anal. Calcd for $C_{11}H_{12}Cl_2O_7$: C, 40.39; H, 3.70; Cl, 21.68. Found: C, 40.42; H, 3.67; Cl, 21.40.

3,4-Dichloro-5-(2-hydroxy-1-phenoxypropan-2-yl)furan-2(5*H*)-one (30, dr = 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (m, 2H), 6.99 (m, 1H), 6.91−6.84 (m, 2H), 5.20 (s, 0.5H), 5.08 (s, 0.5H), 3.95 (m, 2H), 3.04 (br s, 1H), 1.48 and 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9, 157.6, 157.4, 151.0, 150.7, 129.6, 122.3, 121.9, 121.8, 114.6, 114.4, 84.2, 83.0, 74.0, 73.5, 71.9, 70.7, 22.0, 18.8. LRMS (APCI): m/z 301.8 ([M − H]$^-$).

3,4-Dichloro-1-phenethyl-1*H*-pyrrol-2(5*H*)-one (32). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (appt, J = 7.5 Hz, 2H), 7.24 (m, 1 H), 7.20 (d, J = 7.5 Hz, 2H), 3.78 (s, 2 H), 3.74 (t, J = 7.12 Hz, 2H), 2.93 (t, J = 7.12 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 139.3, 138.1, 128.6, 126.8, 125.7, 54.0, 44.7, 34.7. Anal. Calcd for $C_{12}H_{11}Cl_2NO$: C, 56.27; H, 4.33; Cl, 27.68; N, 5.47. Found: C, 56.20; H, 4.30; Cl, 27.39; N, 5.41.

Ethyl 3-(3,4-Dichloro-2-(hydroxy(4-nitrophenyl)methyl)-5-oxo-2*H*-pyrrol-1(5H)-yl)propanoate (34, dr = 83:17). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.23 (d, J = 8.97 Hz, 1.66H), 8.17 (d, J = 8.97 Hz, 0.34H), 7.75 (d, J = 8.38 Hz, 0.34H), 7.67 (d, J = 8.38 Hz, 1.66H), 6.44 (d, J = 4.87 Hz, 0.83H), 6.36 (d, J = 5.65 Hz, 0.17H), 5.44 (dd, J = 4.78, 2.44 Hz, 0.83H), 5.33 (dd, J = 5.07, 3.12 Hz, 0.17H), 4.95 (d, J = 2.53 Hz, 0.17H), 4.91 (d, J = 2.34 Hz, 0.83H), 4.08 (q, J = 4.21 Hz, 2H), 4.11−3.93 (m, 2H), 3.71 (m, 0.83H), 3.62 (m, 0.17H), 2.79−2.59 (m, 1H), 1.18 and 1.08 (t, J = 7.12 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 171.9, 163.9, 147.6, 142.0, 132.9, 130.6, 128.2, 123.6, 87.8, 68.0, 60.8, 38.1, 32.9, 14.7. Anal. Calcd for $C_{16}H_{16}Cl_2N_2O_6$: C, 47.66; H, 4.00; N, 6.95. Found: C, 47.12; H, 3.85; N, 6.75.

3,4-Dichloro-5-(hydroxy(4-nitrophenyl)methyl)-1-phenethyl-1*H*-pyrrol-2(5*H*)-one (35, dr, 83:17). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.26 (d, J = 8.78 Hz, 0.34H), 8.21 (d, J = 8.98 Hz, 1.66H),

7.78 (d, $J = 8.59$ Hz, 0.34H), 7.59 (d, $J = 8.59$ Hz, 1.66H), 7.35−7.16 (m, 5H), 6.86 (d, $J = 7.81$ Hz, 0.17H), 6.47 (br s, 0.83H), 5.41 (br s, 0.83H), 5.33 (br s, 0.17H), 4.90 (d, $J = 2.34$ Hz, 0.17H), 4.74 (d, $J = 2.34$ Hz, 0.83H), 4.04−3.97 (m, 1H), 3.7 (m, 1H), 2.90−2.85 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 147.7, 147.6, 141.6, 139.5, 129.4, 129.3, 129.2, 128.2, 127.1, 126.2, 123.6, 70.4, 67.9, 43.4, 34.3. HRMS (ESI) calcd for $C_{19}H_{17}Cl_2N_2O_4$ 407.0560 (MH^+), found 407.0555.

Ethyl 2-(3,4-Dichloro-5-oxo-1-phenethyl-2,5-dihydro-1*H*-pyrrol-2-yl)-2-hydroxyacetate (36, dr = 53:47). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.15 (m, 5H), 4.60 (br s, 0.5H), 4.56 (br s, 0.5H), 4.38−4.25 (m, 2.5H), 4.21−4.08 (m, 1.5H), 4.05−3.99 (m, 0.5H), 3.51−3.40 (m, 1.5H), 3.10−2.73 (m, 2H), 1.33 and 1.24 (t, $J = 7.12$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 170.4, 164.8, 164.3, 141.2, 140.0, 138.0, 137.7, 128.8, 128.7, 128.6, 128.5, 127.0, 126.9, 126.8, 126.7, 69.1, 67.8, 65.2, 64.9, 43.5, 43.4, 34.3, 34.1, 14.0, 13.9. HRMS (ESI) calcd for $C_{16}H_{18}Cl_2NO_4$ 358.0607 (MH^+), found 358.0604.

Diethyl 2-(3,4-Dichloro-5-oxo-1-phenethyl-2,5-dihydro-1*H*-pyrrol-2-yl)-2-hydroxymalonate (37). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (m, 2H), 7.27 (m, 3H), 5.04 (s, 1H), 4.42−4.31 (m, 5H), 4.14 (m, 1H), 3.38 (m, 1H), 3.07 (m, 1H), 2.82 (m, 1H), 1.36 (overlapping t, $J = 7.2$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 167.2, 164.8, 140.1, 137.8, 128.5, 128.4, 126.5, 78.9, 65.2, 63.6, 63.3, 44.7, 34.0, 13.6. HRMS (ESI) calcd for $C_{19}H_{22}Cl_2NO_6$ 430.0819 (MH^+), found 430.0821.

Ethyl 2-(1-Benzyl-3,4-dichloro-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)-2-hydroxyacetate (38, dr = 63:37). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 − 7.24 (m, 4H), 7.09 (br d, $J = 6.63$ Hz, 1H), 5.25 (d, $J = 16$ Hz, 0.4H), 5.16 (d, $J = 15.2$ Hz, 0.6H), 4.65 (d, $J = 2.14$ Hz, 0.6H), 4.54 (d, $J = 1.56$ Hz, 0.4H), 4.42 (d, $J = 1.56$ Hz, 0.4H), 4.36 (m, 0.6H), 4.30−4.01 (m, 2.6H), 3.92 (d, $J = 16$ Hz, 0.4H), 1.21 and 1.11 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 170.4, 165.1, 164.6, 141.8, 140.7, 135.9, 135.6, 128.9, 128.4, 128.0, 127.9, 127.2, 126.9, 69.3, 67.6, 64.1, 63.8, 63.0, 62.8, 45.6, 45.0, 13.9, 13.7. HRMS (ESI) calcd for $C_{15}H_{16}Cl_2NO_4$ 344.0451 (MH^+), found 344.0464.

Diethyl 2-(1-Benzyl-3,4-dichloro-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)-2-hydroxymalonate (39). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (m, 3H), 7.21 (d, $J = 6.82$ Hz, 2H), 5.11 (d, $J = 15.60$ Hz, 1H), 4.99 (s, 1H), 4.35 (d, $J = 15.79$ Hz, 1H), 4.29 (q, $J = 7.08$ Hz, 2H), 4.15 (q, $J = 7.15$ Hz, 2H), 4.09 (br s, 1H), 1.28 (t, $J = 7.21$ Hz, 3H), 1.22 (t, $J = 7.12$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 166.9, 165.6, 141.0, 136.3, 128.7, 128.2, 127.6, 79.2, 65.0, 63.8, 63.3, 47.1, 13.7, 13.6. HRMS (ESI) calcd for $C_{18}H_{20}Cl_2NO_6$ 416.0662 (MH^+), found 416.0659.

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Supporting Information Available: ^{1}H and ^{13}C NMR data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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