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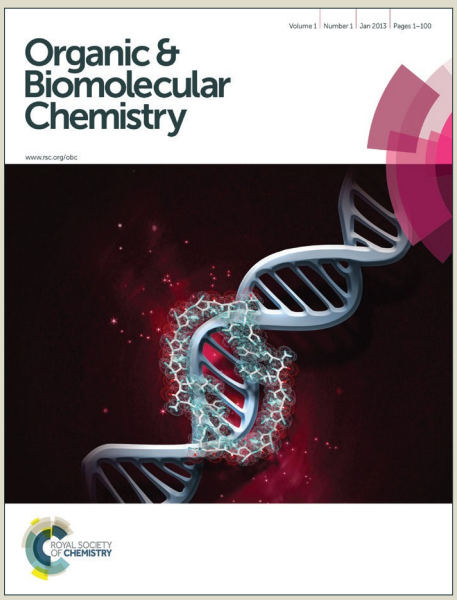

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Thermodynamically Driven, *syn*-Selective Vinylogous Aldol Reaction of Tetronamides

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Abstract: A stereoselective vinylogous aldol reaction of *N*-monosubstituted tetronamides with aldehydes is described. The procedure is simple and scalable, works well with both aromatic and aliphatic aldehydes, and affords mainly the corresponding *syn*-aldol adducts. In many cases, the latter are obtained essentially free of their *anti*-isomers (dr >99:1) in high yields (70-90%). Experimental and computational studies suggest that the observed diastereoselectivity arises through *anti*-*syn* isomer interconversion, enabled by an iterative retro-aldol/aldol reaction.

Keywords: β-aminobutenolides, vinylogous aldol reaction, *syn*-selectivity, retro-aldol reaction, GIAO NMR calculations.

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Introduction

Tetronamides are an important class of β–heterosubstituted butenolides that have attracted growing attention from synthetic and medicinal chemists alike.[1, 2] Although not nearly as common as their tetronate counterparts,[3] several tetronamides have been shown to display significant biological activities, as represented by the fungal antitumor antibiotic basidalin **1**,[4] the newly marketed systemic insecticide flupyradifurone (Sivanto®, **2**),[5] some potent antimitotic aza-lignans, e.g. **3**,[6] and broad-acting antibacterials[7] (**4**-**5**, Figure 1). Inspired by the structure of the tetronate *syn*-aldol adduct losigamone **6**, an experimental drug advanced to phase III clinical trials for the treatment of epilepsy,[3b, 8] we sought to prepare a library of new analogues in which the alkoxy group is replaced by an aromatic amine (cf. tetronamides **A**).[9]

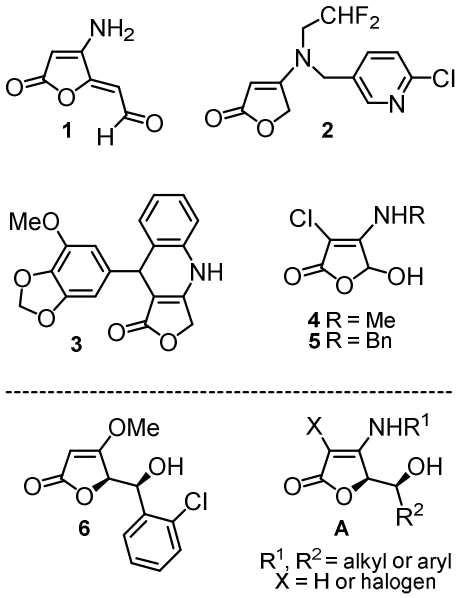

Figure 1 Bioactive tetronamides **1**-**5**, tetronate **6** and analogues **A**.

The vinylogous aldol reaction (VAR), carried our either directly from butenolides or, *via* conversion to the corresponding 2-silyloxyfurans (Mukaiyama variant; VMAR), represents one of the most widely explored avenues for installing a γ–carbon substituent (Scheme 1).[10] Much effort has been devoted in recent years in controlling the relative and absolute configuration of the newly formed stereogenic centers.[11, 12] Although

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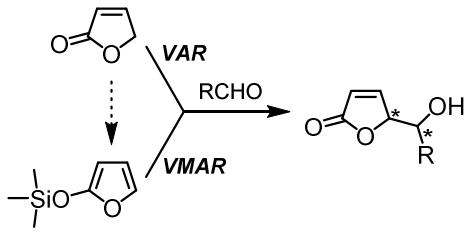
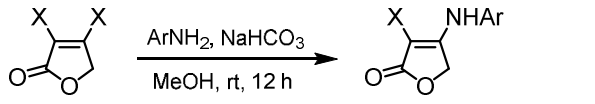
several heterosubstituted butenolides,[11e-h, 12c, d] including tetronates, have been utilized as substrates in VA reactions, surprisingly little is known concerning the serviceability of tetronamides.[8b, 13] The few pertinent examples invariably employ *N,N*-disubstituted tetronamides in conjuction with a strong base (*t*-BuLi, –78 °C), leading mainly to *anti*-aldolate adducts.[14] To date, only two *N*-substituted tetronamide-derived aldolates have been described in the literature; both were obtained as mixtures of diastereoisomers (dr ≈ 1:1 to 2:1) using a decarboxylative Knoevenagel-type reaction of γ–carboxymethyl tetronamides with aldehydes.[15] Reported herein is the hitherto unexplored VAR of unactivated *N*-substituted tetronamides along with the development of a simple, mild and scalable method enabling stereoselective access to *syn*-aldolate adducts.



Scheme 1 VA pathways to substituted butenolides.

Results and discussion

The starting tetronamides of the present work were prepared by utilizing a procedure reported by Cunha et al.[16] Thus, treatment of commercially available α,β–dihalobutenolides **7a-b** with aromatic amines in the presence of $NaHCO_3$ at room temperature readily accomplished an aza-Michael addition/elimination[17] to deliver the desired α–halotetronamides **8a-c** in high yields (Scheme 2).



7a X = Cl
7b X = Br

8a X = Cl, Ar = 4-Me-Ph (93%)
8b X = Cl, Ar = 4-Br-Ph (87%)
8c X = Br, Ar = 4-Me-Ph (82%)

Scheme 2 Preparation of α–halotetronamides from α,β-dihalofuran-2(*5H*)-ones **7a-b.**

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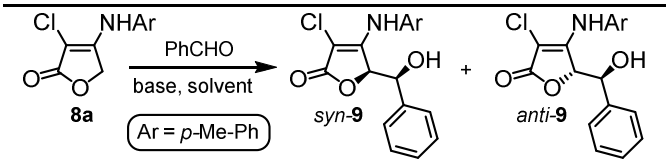
To assess the feasibility of the VAR, unprotected tetronamide **8a** and benzaldehyde were subjected to a range of base/solvent combinations, as outlined in Table 1. The assignment of *syn*/*anti* configuration to the tetronamide aldol adducts described herein (**9-26**) is discussed in a separate section (*vide infra*).

Table 1 Optimization of the VA reaction of tetronamide **8a** with benzaldehyde



8a *syn*-**9** *anti*-**9**

Entry	Base	Solvent	Time[a] (h)	Yield[b] (%)	dr[c] (*syn:anti*)
1	Et_3N	MeOH	4	14	ND[d]
2	DBU	MeOH	12	11	ND[d]
3	DIPEA	MeOH	24	trace	ND[d]
4	$NaHCO_3$	MeOH	24	23	ND[d]
5	Na_2CO_3	MeOH	24	21	50:50
6	NaOH	MeOH	3	83	68:32
7	NaOH	CH_2Cl_2	12	36	60:40
8	NaOH	toluene	16	48	44:56
9	NaOH	THF	8	23	ND[d]
10	KOH	MeOH	3	65	63:37
11	*t*-BuOK	MeOH	4	78	50:50
12	NaOH	MeOH/H_2O[e]	3	91	>99:1
13	LiOH	MeOH/H_2O[e]	2	90	>99:1

[a] All reactions were run at room temperature and were quenched when **8a** was completely consumed according to TLC. [b] Yield of isolated product by column chromatography. [c] Determined by ^{1}H NMR analysis; all products are racemic. [d] ND = not determined. [e] Using a 2:1 MeOH/H_2O ratio (v/v).

Adaptation of the conditions of Zhang [11g] (cf. Et_3N/MeOH, rt), which had worked well for the VAR of α,β-dichlorobutenolide with benzaldehydes, were only modestly effective in providing the desired adducts **9** (14% yield, entry 1, Table 1). Replacing triethylamine with DBU or DIPEA did not improve matters either (entries 2-3). A slight improvement in the yield of **9** was observed when switching to mineral bases such as $NaHCO_3$ and Na_2CO_3 (entries 4-5). Pleasingly, the use of the stronger base NaOH led to a substantial increase in yield (83%) along with low selectivity in favour of the *syn*-adduct (68:32, entry 6). Next, the diastereoselectivity issue was addressed by assessing the effect of different solvents and mineral bases (entries 7-11). It is immediately seen

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from the results, that replacing MeOH by a less polar solvent, such as dichloromethane, toluene or THF, has a detrimental effect to product yield and/or diastereoselectivity (entry 6 vs entries 7-9). Accordingly, we decided to explore the effect of more polar solvents, such as the binary system methanol:water (2:1 v/v). Much to our delight, the use of NaOH or LiOH in this solvent delivered *syn*-**9** as the sole detectable isomer in excellent yield (entries 12-13).

Whilst water has been successfully employed as solvent/additive in aldol reactions,[18] most of the reported cases involve either pyrrole-mediated[19] or Mukaiyama variants.[20] A notable example pertains to the use of brine/MeOH in uncatalyzed VMA reactions of 2-silyoxyfurans and pyrroles with benzaldehydes, leading mainly to the corresponding *syn* and *anti* aldol-adducts, respectively.[21] It was suggested that water may serve as an H-bond donor to activate the aldehyde acceptor and control the arrangement of the reactants in the transition state.[21] Conceivably, the present VAR may also be speeded by intermolecular H-bonding, although, as will be discussed later, the observed diasteroselectivity is likely to arise by a thermodynamic process involving *syn*/*anti*-isomer equilibration.

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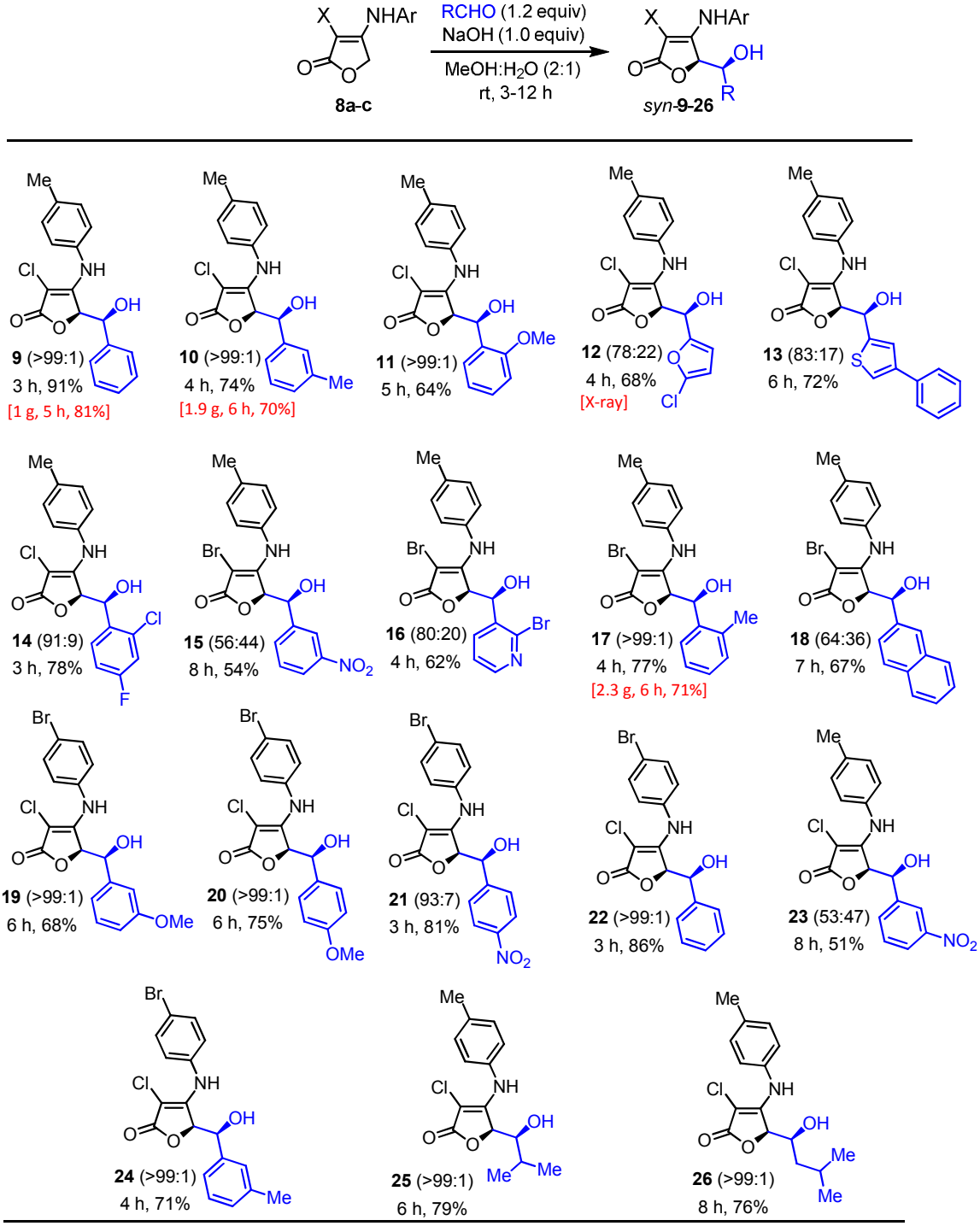
Table 2 Substrate scope in the VAR of tetronamides with aldehydes[a,b]



[a]For the sake of clarity only the *syn* (major) isomer is shown along with the *syn:anti* ratio (in brackets). [b]Similar yields and *syn*:*anti* ratios were obtained (cf. **9**, **12**, **15**, **17**, and **26**) by replacing NaOH by LiOH.

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Having established a simple and efficient method enabling stereoselective access to *syn*-**9**, the next task was to investigate the substrate scope. Thus, tetronamides **8a-c** were screened with several aldehydes using NaOH in methanol:water (2:1 v/v) at room temperature (Table 2). The results show that product yields are generally good to excellent (51-91%), and in most cases, the *syn:anti* ratio is at least 90:10. The three tetronamides tried behaved similarly in terms of yield and diastereoselectivity. However, the nature of the aldehyde did impact selectivity in some cases. Benzaldehydes bearing electron-donating substituents performed remarkably well, leading uniquely to *syn*-adducts (**10**, **11**, **17**, **19**, **20** and **24**), as did benzaldehyde itself (**9** and **22**). High *syn*-selectivities (>90:10) were also observed with *p*-nitrobenzaldahyde and 2-chloro-4-fluorobenzaldahyde (cf. **14** and **21**). The lowest selectivities, but still in favour of the *syn*-isomer, were observed with *meta*-nitrobenzaldehyde (cf. **15** and **23**[22]), 2-naphtalenecarbaldehyde (**18**), and some heteroaromatic aldehydes (**12**, **13** and **16**). Importantly, excellent results were obtained with the two aliphatic aldehydes tried, providing solely the *syn*-adducts in high yield (**25** and **26**). As indicated in Table 2, we have also demonstrated the preparative value of this method by the gram-scale synthesis of *syn*-adducts **9**, **10** and **17**. Indeed, the scale-up did not affect diastereoselectivity, and yields were fairly close to those obtained from the 1 mmol scale experiments (e.g. 71 vs 77% for **17**).

In general, these reactions were fairly clean. Also, no by-products arising from dehydration of the aldol adducts could be observed within 3-12 h. However, we found that the yield of the desired adducts was time dependent. Careful monitoring of the progress of these reactions by TLC, further revealed that the *syn*/*anti* ratios improved in favour of the *syn* isomer. At this point, a more detailed study of the VAR reaction of **8a** with benzaldahyde was performed using our optimized conditions, where the aldol adducts *syn*-**9**/*anti*-**9** were isolated at different time intervals (Figure 2). Thus, compound **9** was obtained in 54% yield after 0.5 h with a *syn:anti* ratio of 45:55. When the reaction time increased to 2 hours, the yield reached a maximum (94%) while the *syn:anti* ratio had improved to 90:10. Further increase in the reaction time to 3 hours led to virtually complete control of diastereoselectivity (*syn:anti* >99:1) but a slightly lower yield (91%).

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After 6 hours the product yield decreased to 82% although the selectivity was still excellent. From the preparative standpoint, these findings show that quenching the VAR at the right time, in this case 3 hours, is critical to ensure an optimal balance between diastereoselectivity and yield.

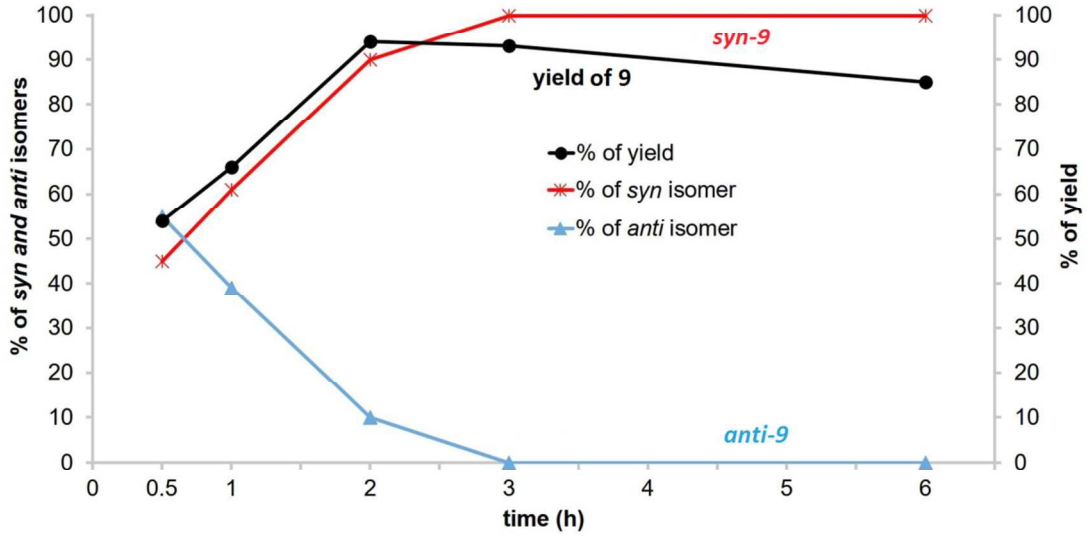

Figure 2 Yield and *syn*/*anti* composition (%) of aldol **9** versus time for the VAR of **8a** with benzaldehyde using the procedure outlined in Table 2.

The variation of diastereoselectivity over time can best be explained by a dynamic resolution process, whereby diastereomeric equilibration ultimately affords the most stable isomer. We considered two pathways by which *anti*-*syn* interconversion may occur. The first involves an iterative retro-aldol/aldol reaction (path **A**, Scheme 3). Alternatively, the butenolide stereogenic center may epimerize via intervention of furanolate **F2** (path **B**). Given the high thermodynamic acidity of butenolides (pK_a ca. 12-15),[23] direct abstraction of the C5-H is possible, especially under basic conditions. Indeed, furanolate formation has been invoked to explain the racemization of a formal VAR-adduct, namely, γ–hydroxymethylbutenolide.[24] Moreover, a γ–benzyltetronate was shown to epimerize in the presence of Hünig's base, but not pyridine.[25]

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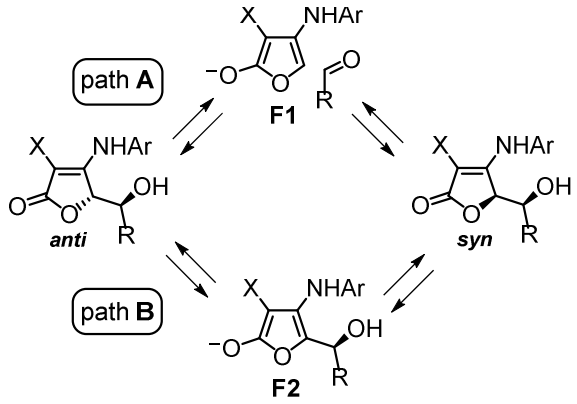

Scheme 3 Plausible pathways for isomer interconversion.

Whilst some classical retro-aldol/aldol reactions have been previously investigated, notably in the context of catalytic kinetic resolution[26] and total synthesis,[27] to the best of our knowledge, there have been no such studies on vinylogous variants involving butenolides. With this in mind, we sought to test the feasibility of path **A** by conducting "transfer-aldol" experiments, such as that shown in Scheme 4.

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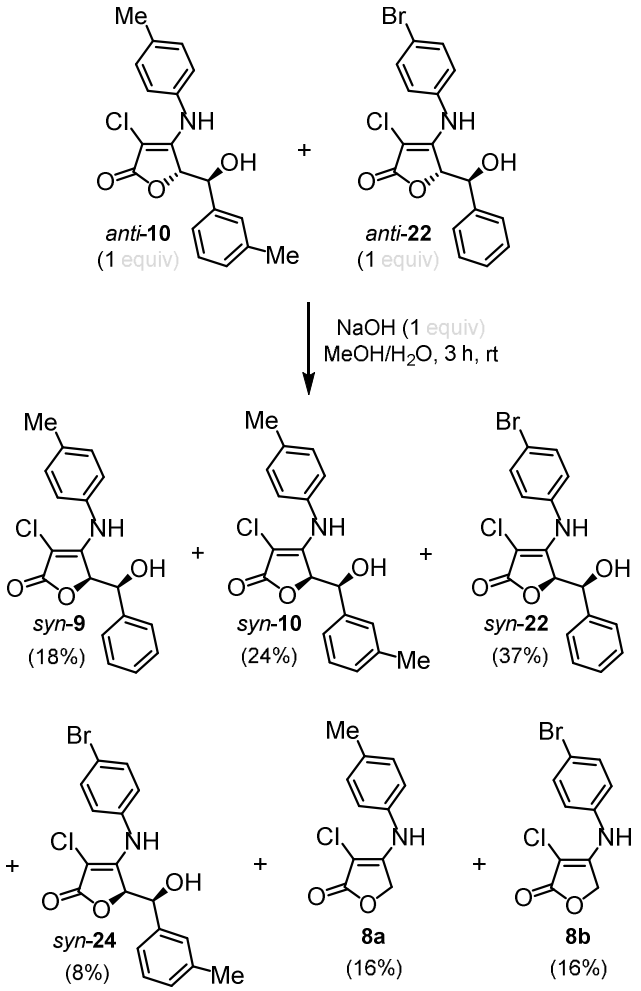

Scheme 4 Base-catalysed transfer-aldol reaction.

Thus, a 1:1 mixture of *anti*-**10** and *anti*-**22** were subjected to our optimized procedure and the reaction was quenched after 3 hours. Flash column chromatography afforded three mixtures, each consisting of only two compounds: (i) tetronamides **8a** and **8b** (1:1), (ii) *syn*-**9** and *syn*-**22** (1:2), and (iii) a 3:1 ratio of *syn*-**10** and *syn*-**24** (Figures S71-73). ^{1}H NMR analysis of these mixtures, and comparison with those of authentic compound samples, permitted both the identity and yield of each product to be determined. The crude reaction mixture also revealed signals for the expected aldehydes, but no signals corresponding to the starting *anti* compounds (Figure S70). These findings demonstrate that the reto-aldol/aldol sequence (path **A**) is indeed involved and capable of accomplishing complete *anti*-to-*syn* conversion. However, paths **A** and **B** are not mutually exclusive.

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To explore the possibility of direct C5-H (path **B**), the following experiment was performed. Pure *anti*-**9** was dissolved in CD_3OD/D_2O and a ^1H NMR spectrum was taken immediately and after one hour. Both spectra showed that only the NH and OH protons underwent deuterium exchange (Figure S74). The doublets at 4.85 ppm (H-6, J = 5.5 Hz) and 5.60 ppm (H-5, J = 5.5 Hz) were used as diagnostic signals to monitor the isomerization process. To this solution, NaOH was added and the ^1H NMR spectrum was taken after 10 minutes. In this spectrum (Figure S75) the signals corresponding to H-5 and H-6 for the *anti*-**9** isomer had disappeared and new signals at 4.88 ppm (H-6, broad singlet for *syn*-**9**) and 5.40 ppm (H-5, broad singlet for *syn*-**9**) were observed. The 1:1 integral ratio of the new signals clearly indicates that no deuterium exchange took place at C5. In addition, new signals corresponding to tetronamide **8a** and benzaldehyde could be seen. Therefore, *anti*-**9** is converted into the *syn*-**9** isomer *via* a retro-aldol process and not *via* C5-H abstraction. Only after 30 minutes the C5-H signal of *syn*-**9** disappeared, revealing that complete deuterium exchange had taken place (Figure S76). Whether this occurs by direct abstraction of the C5-H in *syn*-**9** (cf. Path **B**, Scheme 3) or indirectly via deuteration of furanolate **F2** (Path **A**) is an open question. It is fairly clear though, that C5-deuteration is substantially slower than the iterative retro-aldol/aldol reaction.

Taken together, the experiments just described leave little doubt that (i) a retro-aldol/aldol sequence is involved, and (ii) that the latter readily accomplishes conversion of the *anti* to the presumably more stable *syn*-isomer.

To verify that this is indeed the case, we computed the stability of the *syn* and *anti* isomers for the simplified model compound **27** using the increasingly popular meta hybrid exchange-correlation functional M06-2X developed by Truhlar and co-workers, coupled with the high 6-311+G** basis set. This functional has been shown to perform well in main-group thermochemistry, and to describe non-covalent interactions.[28] The enthalpies and Gibbs free energies differences (ΔH and ΔG, respectively) between *syn/anti* aldol adducts were computed to provide computational support to the proposed thermadynamic equilibration. As shown in Figure 3, the *syn*-**27** aldol was found to be more stable than its *anti*-**27** isomer (ΔH = 0.5 kcal/mol; ΔG = 0.7 kcal/mol), in line with our expectation. Interestingly, when similar calculations were carried out for compound **9**, the preference towards the *syn* aldol was increased (ΔH = 1.5 kcal/mol; ΔG = 1.9

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kcal/mol). Under equilibration conditions at room temperature, such energy differences predict a *syn/anti* ratio of 93/7 and 96/4 (based on formation enthalpies and Gibbs free energies, respectively), which are in good agreement with the experimental findings. Similar calculations were carried out for compounds **13** and **18** (their *syn* and *anti* isomers). The ratios computed from the ΔG values (90:10 and 70:30 respectively) are close to those found experimentally (83:17 and 64:36).

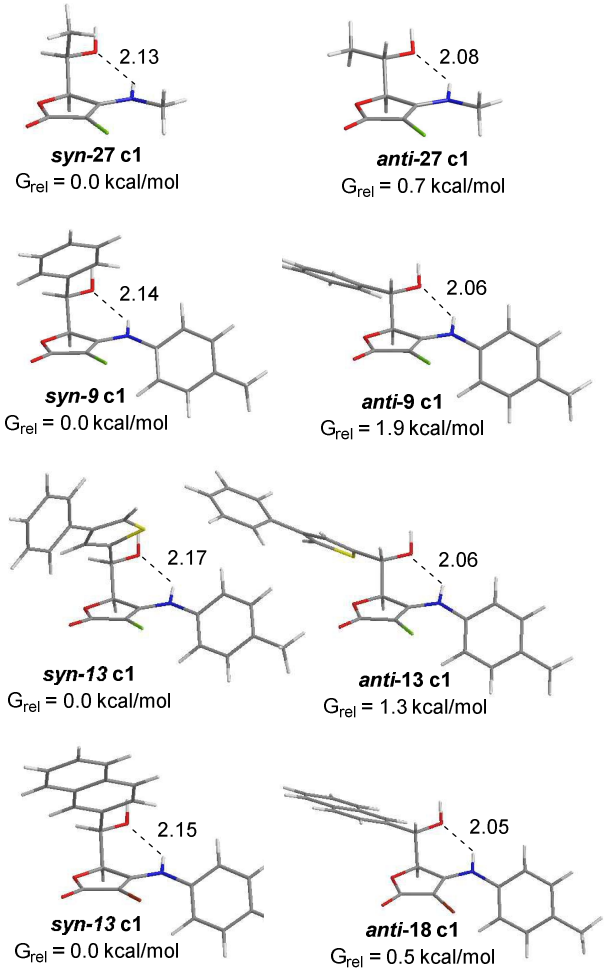

Figure 3 M06-2X/6-311+G** optimized geometries (global minima) found for *syn* and *anti* aldol adducts **27** (model compounds) **9, 13** and **18**, with selected distances in Å.

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Computational and NMR studies on the relative configuration of aldol adducts

All the discussion up to this point was made considering that the relative configuration of the major and minor isomers were assigned based on the ^{1}H-NMR data. Here, we take a representative example of the ^{1}H-NMR of both isomers of compound **9** (Figure 4) for the detailed discussion on this assignment.

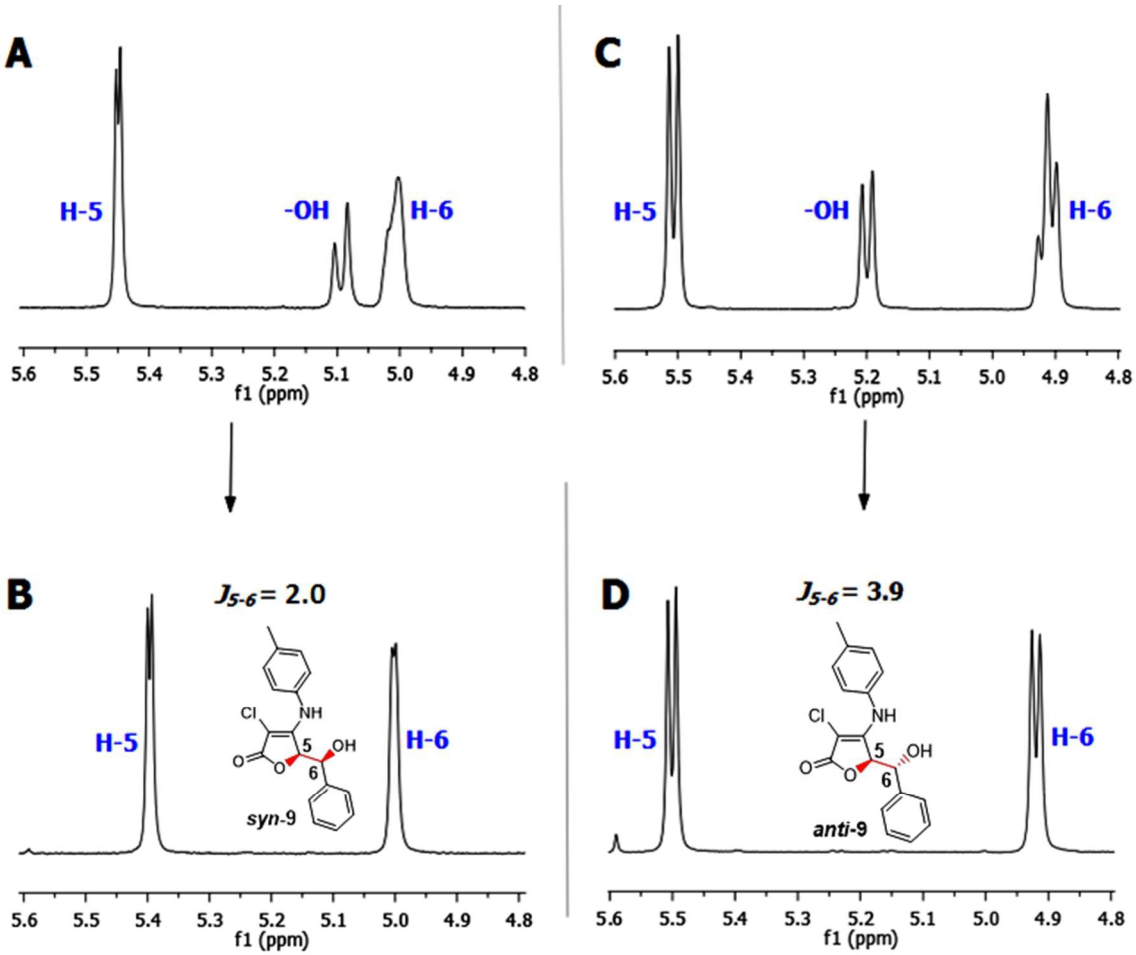

Figure 4 Expansion (4.8-5.6 ppm) of the ^{1}H-NMR (300 MHz, acetone-d_6) spectra of *syn*-**9** (4A) and *anti*-**9** (4C) isomers. The corresponding D_2O exchange spectra are shown in 4B (*syn*-**9**) and 4D (*anti*-**9**)

The major difference in the spectra of both isomers is the value of ^{3}J between H-5 and H-6. In the spectra rum in acetone-d_6 the signal for H-5 is a doublet with $J_{5\text{-}6}$ = 2.0 Hz for the major isomer (Figure 4A) and a doublet with $J_{5\text{-}6}$ = 3.9 Hz for the minor

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isomer (Figure 4C). The signals for H-6 around δ = 4.9-5.1 is a multiplet due to a further coupling between H-6 and OH (Figure 4A, 4C). So, doing a D_2O exchange a clear doublet is observed in both cases (Figure 4B and 4D), confirming the coupling reported for H-5. Since no one has prepared these types of aldol-tetronamides before, we need a reliable way to secure a correct assignment of the stereochemistry of the synthesized compounds. To accomplish this, we undertook a DFT study using Gaussian 09.[29]

Since the coupling constant $J_{5\text{-}6}$ strongly depends on the conformational preference of the aldols, we first performed an extensive conformational search of a simplified system (compounds *syn*-**27** and *anti*-**27,** Figure 5) at the B3LYP/6-31G* level of theory.[30]

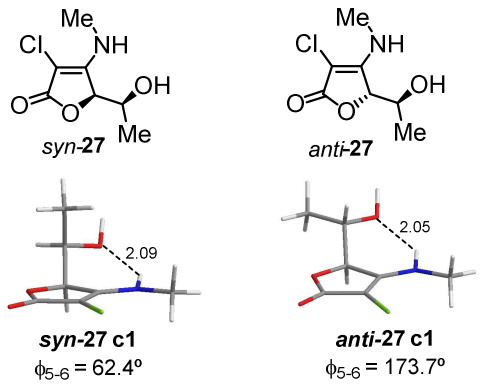

Figure 5 B3LYP/6-31G* optimized geometries (global minima) found for compounds **27**, with selected distances in Å.

In both cases, we found a clear preference towards the conformer characterized by an intramolecular N-H---OH hydrogen bond. In such conformation, a *gauche* relationship between H-5 and H-6 was found for the *syn* isomer (ϕ 62.4°), and an *anti* relationship between both hydrogen atoms in the case of the *anti* isomer (ϕ 173.7°), indicating that the lower $J_{5\text{-}6}$ value should be expected for the former. This was further confirmed after Boltzmann-averaged *J*-coupling calculations of all significantly populated conformers at the B3LYP/6-31G**//B3LYP/6-31G* level: the computed $J_{5\text{-}6}$ was 4.1 Hz (*syn*-**27**) and 7.4 Hz (*anti*-**27**).[30] To validate our assignment, we next performed a full conformational search over three selected aldol pairs synthesized in this work: compounds **9**, **12** and **13** (Figure 6).

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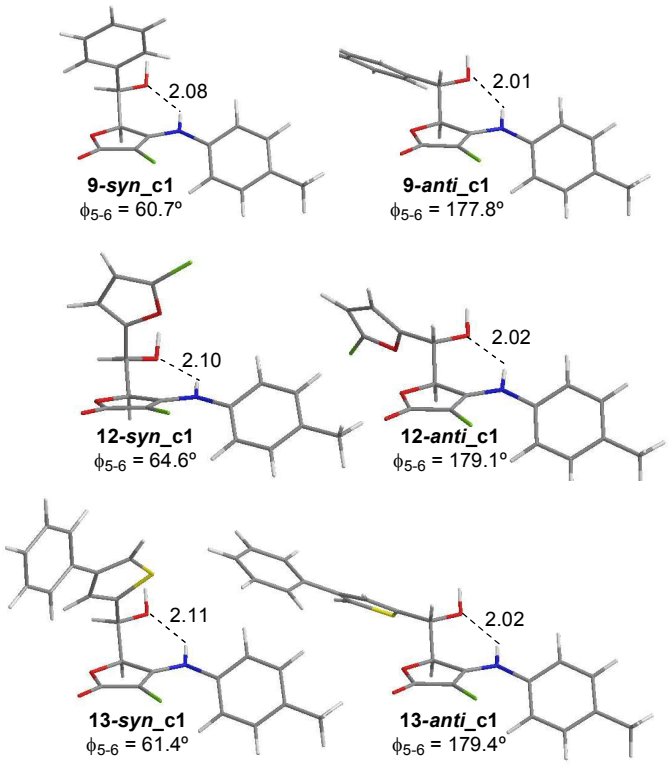

Figure 6 B3LYP/6-31G* optimized geometries (global minima) found for compounds **9**, **12** and **13,** with selected distances in Å.

Interestingly, despite the degree of conformational freedom was higher than that of the simplified model, in all cases the rotational preference towards the conformers showing intramolecular N-H---OH hydrogen bond was found.[30] This result suggested that the major isolated adducts, showing smaller $J_{5\text{-}6}$ coupling values, should display a *syn* stereochemistry. In an additional supporting of our findings, we next performed GIAO ^{13}C-NMR calculations, which represent a valuable and indisputable tool in modern structural elucidation.[31] The magnetic shielding tensors of all significantly populated conformers were computed at the mPW1PW91/6-31+G**//B3LYP/6-31G* level of theory in solution (PCM, $CHCl_3$), using the multi-standard approach to extract the chemical shifts.[30, 32] Next, we computed the Goodman's CP3 parameter to address the question of assigning two sets of experimental data to two plausible candidates.[33] In all cases, positive CP3 values were computed for the "matched" cases (major-*syn*/minor-*anti*), while negative CP3 values were found for the "mismatched" cases (major-

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anti/minor-*syn*).[30] It is important to recall that positive values indicate good agreement (assignment likely to be correct), whereas negative values indicate poor agreement (assignment likely to be incorrect).[33]

Finally, the *in silico* stereochemical assignments were validated by X-ray diffraction analysis on single crystals of both diastereoisomers of compound **12** (Figure 7).

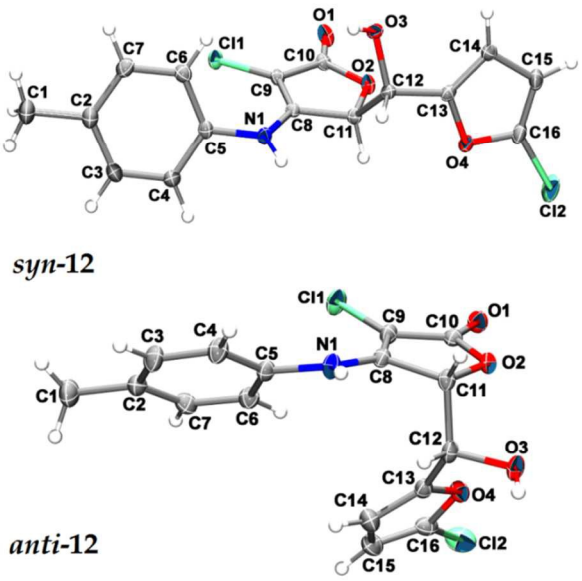

Figure 7 X-ray structures for both diastereomers of compound **12.**

As seen from Figure 7, the major aldol adduct of compound **12** is the *syn* isomer, while the minor is the *anti,* as predicted by the computational studies. In the particular case of compound **12**, it is also clear that in the solid crystalline form no intramolecular N-H---OH hydrogen bond is observed, as predicted by calculations in the gas phase and in solution.

Conclusions

The foregoing inaugural study of the vinylogous aldol reaction (VAR) of *N*-monosubstituted tetronamides has enabled the development of a viable new method for

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constructing medicinally relevant aldols. Of great practicality, the method employs NaOH in aq. MeOH at ambient temperature and works well with both aromatic and aliphatic aldehydes. Importantly, most of the VA reactions tried afforded single diastereoisomers (*syn/anti* > 99:1) in good to excellent yields. Several lines of evidence suggest that the observed selectivity arises from *anti*-to-*syn* isomer interconversion via an iterative retro-aldol/aldol reaction sequence. Studies on the wider scope of this chemistry are in progress, and the results will be reported in due course.

Experimental section

General experimental

All reactions were performed using analytical grade solvents without further purifications, unless otherwise stated. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 instrument (300 MHz and 75 MHz, respectively), using deuterated chloroform, acetone or DMSO as a solvent and tetramethylsilane (TMS) as internal standard (δ = 0). The experiments were performed at controlled probe temperature of 25 °C, using a number of scans (nt) of 16, a number of points in the FID of 43686 (np); 90° pulse width; spectral width of 4800.8 Hz; acquisition time (at) of 4.550 s; delay time (D1) of 1.00 s. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm. All coupling constants (*J* values) were expressed in Hertz (Hz). Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), multiplet (m) and broad (br). Infrared spectra were recorded on a Varian 660-IR, equipped with GladiATR scanning from 4000 to 500 cm^{-1}. Melting points are uncorrected and were obtained from MQAPF-301 melting point apparatus (Microquimica, Brazil). High resolution mass spectra were recorded on a Bruker MicroTof (resolution = 10,000 FWHM) under electrospray ionization (ESI) and are given to four decimal places. XRD was recorded on Bruker D8 focus X-ray Diffraction spectrometer. Analytical thin layer chromatography analysis was conducted on aluminum packed precoated silica gel plates. Column chromatography was performed over silica gel (230-400 mesh).

General procedure for the preparation of compound 8a-c

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3-chloro-4-(p-tolylamino)furan-2(5H)-one (**8a**). To a 100 mL round bottomed flask, were added **7a** (2 g, 13.08 mmol), MeOH (20 mL for a 13.08 mmol scale reaction), $NaHCO_3$ (550 mg, 6.54 mmol) and *p*-toluidine (1.4 g, 13.08 mmol). The reaction mixture was stirred at room temperature for 12 h. After the consumption of the starting butenolide **7a**, the reaction mixture was quenched by addition of aqueous HCl solution (1M, 10 mL). The methanol was then removed under reduced pressure and the aqueous mixture was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and the solvent evaporated. The crude residue was purified by silica gel column chromatography, eluted with hexane/ethyl acetate (70:30 v/v) to afford compound **8a** as white solid in 93% yield (2.7 g, 12.16 mmol). Mp: 213.8-215.1 ºC. R_f = 0.4 (hexane: ethyl acetate, 1:1, v/v). FTIR (KBr) ν_{max} 3234, 3068, 1741, 1629, 1052, 982, 899, 741, 531 cm^{-1}. ^1H NMR (300 MHz, Acetone-d_6:DMSO-d_6; 9:1) δ 9.06 (s, 1H, -NH), 7.19 (apparent singlet, 4H, H-3′, H-4′, H-6′ and H-7′), 4.99 (s, 2H, H-5), 2.31 (s, 3H, H-8′). ^{13}C NMR (75 MHz, Acetone-d_6:DMSO-d_6; 9:1) δ: 168.76 (C-2), 158.51 (C-4), 135.95 (C-2′), 134.85 (C-5′), 129.78 (2C, C-4′ and C-6′), 122.48(2C, C-3′ and C-7′), 87.21 (C-3), 66.07 (C-5), 20.01 (C-8′). HRMS (ESI) $[M-H]^-$ calculated for $C_{11}H_9ClNO_2$, 222.0322; found, 222.0326

4-[(4-bromophenyl)amino]-3-chlorofuran-2(5H)-one (**8b**). Compound **8b** was synthesized using a method similar to that of **8a** and was isolated as white solid in 87% yield (3.3 g, 11.38 mmol); purified by column chromatography, eluent hexane/ethyl acetate (68:32 v/v). Mp: 221.3-222.6 ºC. R_f = 0.4 (hexane: ethyl acetate, 1:1, v/v). FTIR (KBr) ν_{max} 3235, 3061, 1749, 1632, 1054, 977, 891, 739, 515 cm^{-1}. ^1H NMR (300 MHz, Acetone-d_6) δ: 8.80 (s, 1H, -NH), 7.56 (d, J= 8.9 Hz, 2H, H-4′ and H-6′), 7.27 (d, J= 8.9 Hz, 2H, H-3′ and H-7′), 5.12 (s, 2H, H-5) . ^{13}C NMR (75 MHz, Acetone-d_6) δ: 168.38 (C-2), 157.65 (C-4), 137.90 (C-2′), 132.31 (2C, C-4′ and C-6′), 123.69 (C-3′), 123.58 (C-7′), 117.36 (C-5′), 89.13 (C-3), 66.15 (C-5). HRMS (ESI) $[M-H]^-$ calculated for $C_{10}H_6BrClNO_2$, 285.9270; found, 285.9273

3-bromo-4-(p-tolylamino)furan-2(5H)-one (**8c**). Compound **8c** was synthesized using a method similar to that of **8a** and was isolated as orange solid in 82% yield (1.8 g, 6.78

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mmol); purified by column chromatography, eluent hexane/ethyl acetate (70:30 v/v). Mp: 225.2-226.8 ºC. R_f = 0.4 (hexane: ethyl acetate, 1:1, v/v). FTIR (KBr) ν_{max} 3230, 3074, 1729, 1628, 1050, 985, 896, 740, 520 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 9.45 (s, 1H, -NH), 7.15 (apparent singlet, 4H, H-3′, H-4′, H-6′ and H-7′), 4.99 (s, 2H, H-5), 2.27 (s, 3H, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.09 (C-2), 162.19 (C-4), 135.91 (C-2′), 135.05 (C-5′), 130.09 (2C, C-4′ and C-6′), 123.21 (2C, C-3′ and C-7′), 73.82 (C-3), 67.66 (C-5), 20.87 (C-8′). HRMS (ESI) $[M-H]^-$ calculated for $C_{11}H_9BrNO_2$, 265.9817; found, 265.9832

Typical procedure for the VAR of tetronamides (9–26)

3-Chloro-5-[hydroxy(phenyl)methyl]-4-(p-tolylamino)furan-2(5H)-one (*syn*-**9**). To a 25 mL one neck round bottomed flask were added tetronamide **8a** (200 mg, 0.89 mmol), a mixture of MeOH and H_2O (4 and 2 mL, v/v), followed by NaOH (36 mg, 0.89 mmol). After stirring the reaction mixture for 5 min at room temperature, benzaldehyde (114 mg, 1.07 mmol) was added slowly. The reaction mixture was stirred at room temperature until TLC analysis revealed total consumption of **8a**. The reaction was then quenched by addition of an aqueous solution of HCl (1M, 10 mL). The methanol was removed under reduced pressure and the aqueous mixture was extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and the solvent evaporated. The crude residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (80:20 v/v) to afford pure *syn*-**9** as white solid in 91% yield (267 mg, 0.81 mmol). Mp: 192.3-194.6 °C. R_f = 0.35 (hexane: ethyl acetate, 80:20, v/v). FTIR (KBr) ν_{max} 3386, 3282, 3228, 3070, 3037, 3002, 2971, 1754, 1635, 1197, 1029, 647 cm^{-1}. ^1H NMR (300 MHz, Acetone-d_6) δ: 8.54 (s, 1H, -NH), 7.40-7.25 (m, 5H, H-8 to H-12), 7.25 (d, J = 8.7 Hz, 2H, H-4′ and H-6′), 7.21 (d, J = 8.7 Hz, 2H, H-3′ and H-7′), 5.45 (d, J = 2.0 Hz, 1H, H-5), 5.09 (d, J = 6.0 Hz, 1H, -OH), 5.00 (m, 1H, H-6), 2.35 (s, 3H, H-8′). ^1H NMR (300 MHz, D_2O Exchange) δ: 7.23-7.39 (m, 5H, H-8 to H-12), 7.21 (d, J = 8.6 Hz, 2H, H-4′ and H-6′), 7.16 (d, J = 8.6 Hz, 2H, H-3′ and H-7′), 5.40 (d, J = 2.0 Hz, 1H, H-5), 5.00 (d, J = 2.0 Hz, 1H, H-6), 2.32 (s, 1H, H-8′). ^1H NMR (300 MHz, $CDCl_3$: DMSO-d_6; 9:1) δ: 7.83(s, 1H, -NH), 7.32-7.18 (m, 5H, H-8 to H-12), 7.07 (d, J =

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8.3 Hz, 2H, H-4′ and H-6′), 6.89 (d, *J*= 8.3 Hz, 2H, H-3′ and H-7′), 5.15 (d, *J* = 3.6 Hz, 1H, H-5), 5.03 (d, *J* = 3.6 Hz, 1H, H-6), 2.27 (s, 3H, H-8′). ^{13}C NMR (75 MHz, $CDCl_3$: DMSO-d_6; 9:1) *δ*: 169.74 (C-2), 156.24 (C-4), 138.85 (C-7), 135.28 (C-2′), 134.24 (C-5′), 129.10 (2C, C-4′ and C-6′), 127.89 (2C, C-8 and C-12), 127.78 (C-10), 126.40 (2C, C-8 and C-12), 123.96 (2C, C-3′ and C-7′), 88.62 (C-3), 79.40 (C-5), 71.26 (C-6), 20.80 (C-8′). HRMS (ESI) $[M-H]^-$ calculated for $C_{18}H_{15}ClNO_3$, 328.0740; found, 328.0732

Compounds **10-26** were synthesized using a method similar to that described for compound *syn*-**9**. Characterization data of all synthesized products and copies of ^{1}H and ^{13}C NMR spectra are available on supporting information.

3-chloro-5-[hydroxy(phenyl)methyl]-4-(p-tolylamino)furan-2(5H)-one (*anti*-**9**). To a dry 25 mL one neck round bottomed flask were added tetronamide **8a** (200 mg, 0.89 mmol), anhydrous MeOH (5 mL), followed by *t*-BuOK (99 mg, 0.89 mmol). After stirring the reaction mixture for 5 min at room temperature, benzaldehyde (114 mg, 1.07 mmol) was added slowly. The reaction mixture was stirred at room temperature under nitrogen atmosphere until TLC analysis revealed total consumption of **8a**. The reaction was then quenched by addition of an aqueous solution of HCl (1M, 10 mL). The methanol was removed under reduced pressure and the aqueous mixture was extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and the solvent evaporated. The crude residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (80:20 v/v) to afford the *syn*-**9** (117 mg, 0.36 mmol) as white solid in 40% yield and eluting with hexane/ethyl acetate (79.5:20.5 v/v) to afford *anti*-**9** as light yellow solid in 39% yield (114 mg, 0.35 mmol). Data for *anti*-**9**: Mp: 190.1-191.2 °C. R_f = 0.33 (hexane: ethyl acetate, 3:2, v/v). FTIR (KBr) ν_{max} 3309, 3278, 3191, 3081, 3068, 3029, 1743, 1631, 1583, 1195, 1008, 734 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6) *δ*: 8.44 (s, 1H, -NH), 7.43-7.26 (m, 5H, H-8 to H-12), 7.24 (d, *J* = 8.5 Hz, 2H, H-4′ and H-6′), 7.18 (d, *J* = 8.5 Hz, 2H, H-3′ and H-7′), 5.51 (d, *J* = 4.3 Hz, 1H, H-5), 5.20 (d, *J* = 4.8 Hz, 1H, -OH), 4.91 (m, 1H, H-6), 2.34 (s, 3H, H-8′). ^{1}H NMR (300 MHz, D_2O Exchange) *δ*: 7.24-7.40 (m, 5H, H-8 to H-12), 7.20 (d, *J* = 8.4 Hz, 2H, H-4′ and H-6′), 7.12 (d, *J* = 8.4 Hz, 2H, H-3′ and H-7′), 5.50 (d, *J* = 3.9 Hz, 1H,

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H-5), 4.92 (d, J = 3.9, 1H, H-6), 2.31 (s, 3H, H-8′). ^{1}H NMR (300 MHz; $CDCl_3$:DMSO-d_6; 9:1) δ: 8.04 (s, 1H, -NH), 7.31-7.10 (m, 5H, H-8 to H-12), 7.05-6.94 (m, 2H, H-4′ and H-6′), 6.91-6.81 (m, 2H, H-3′ and H-7′), 4.97 (dd, J = 6.0, 4.3 Hz, 1H, H-5), 4.70 (dd, J = 6.0, 4.3 Hz, 1H, H-6), 2.22 (s, 3H, H-8′). ^{13}C NMR (75 MHz, $CDCl_3$: DMSO-d_6 9:1) δ: 169.62 (C-2), 156.80 (C-4), 139.21 (C-7), 135.34 (C-2′), 134.11 (C-5′), 129.18 (2C, C-4′ and C-6′), 128.48 (C-10), 128.26 (2C, C-8 and C-12), 127.16 (2C, C-8 and C-12), 123.76 (2C, C-3′ and C-7′), 88.86 (C-3), 79.36 (C-5), 74.49 (C-6), 20.89 (C-8′). HRMS (ESI) $[M-H]^-$ calculated for $C_{18}H_{15}ClNO_3$, 328.0740; found, 328.0678

Compound *anti*-**10** and *anti*-**22** were synthesized using a method similar to that described for compound *anti*-**9.** Characterization data of synthesized products and copies of ^{1}H and ^{13}C NMR spectra are available on supporting information.

Procedure for the retro-aldol reaction

To a solution of aldol compound *anti*-**10** (87 mg, 0.25 mmol) and *anti*-**22** (100 mg, 0.25 mmol) in MeOH/H_2O (2:1 mL, v/v), NaOH (10 mg, 0.25 mmol) was added with continuous stirring at room temperature. The reaction mixture was then stirred at room temperature for 3 h and quenched by addition of aqueous HCl solution (1M, 5 mL). The methanol was then removed under reduced pressure and the aqueous mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and the solvent evaporated. The crude residue was subjected to silica gel column chromatography, eluting with hexane/ethyl acetate (82:18 v/v) and isolated three different fractions as a mixture of tetronamides **8a**/**8b** (21 mg) *syn*-**9**/**22**(52 mg and *syn*-**10**/**24** (28 mg) respectively. Characterization data of retro-aldol products and copies of ^{1}H NMR spectra are available on supporting information.

Experimental procedure for the 'D' incorporation vs. isomerization

A solution of *anti*-**9** (25 mg, 0.08 mmol) in CD_3OD:D_2O (0.7 mL, 4:1 v/v) was transferred to a NMR tube and the ^{1}H NMR spectrum was obtained. Then anhydrous NaOH (3 mg, 0.08 mmol) was added to the solution and the NMR was obtained after 10,

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20, 40 and 180 minutes. The spectra obtained are presented in the supporting information.

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