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Diastereoselective Three-Component Vinylogous Mannich Reaction of Nitrogen Heterocycles, Acyl/Sulfonyl Chlorides, and Silyloxyfurans/pyrroles

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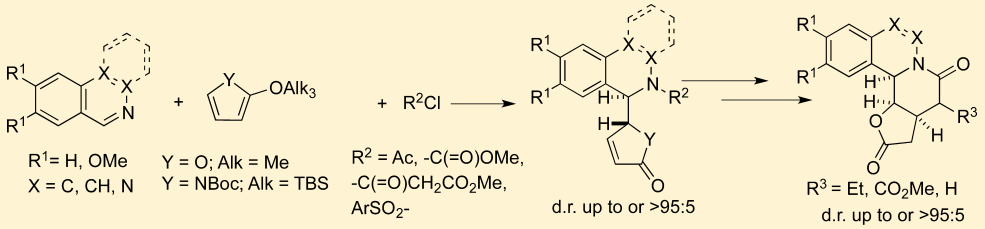
Supporting Information



ABSTRACT: A one-step, 3-component vinylogous Mannich reaction of trimethylsilyloxyfuran or *N*-protected *tert*-butyldimethylsilyloxypyrrole with a variety of nitrogen-containing heterocycles in the presence of diverse electrophiles is described. The reaction products were generally obtained in high yields and as a single diastereoisomer having the (*R**,*R**) relative configuration based on crystallographic studies of several derivatives. Several azaheterocycles were successfully used for this reaction, such as isoquinolines, quinoline, phenanthridine, quinazoline, phthalazine, and *β*-carboline, and electrophiles included acetyl chloride, methyl chloroformate, methyl chloromalonate, 2-bromobutanoyl chloride, and arylsulfonyl chlorides. The products of the vinylogous Mannich reactions were subjected to further transformations, leading to highly functionalized and stereochemically defined tetracyclic derivatives that are valuable building blocks for the preparation of natural products or medicinal agents.

INTRODUCTION

The Mannich reaction, including its vinylogous version, represents one of the most powerful and useful methodologies for the creation of carbon−carbon bonds. It has been successfully applied to imines and iminium salts for the synthesis of natural and medicinally relevant compounds, and recent efforts in the area have been aimed at the development of asymmetric methodologies for this reaction.[1−3] In particular, a large body of work concerning the vinylogous Mannich reaction of trialkylsilyloxyfurans to imines has developed in recent years. These reagents, pioneered by Casiraghi and co-workers,[4] have proven to be extremely useful and versatile for Mannich-type reactions, allowing introduction of two contiguous stereogenic centers with formation of functionalized *γ*-butenolides incorporating an amino group.[4,5] The asymmetric version of this reaction was pioneered by Martin using titanium complex catalysis.[6] Since then, important improvements have been made with respect to both yields and stereoselectivities. Notably, Snapper and Hoveyda have developed highly efficient procedures for asymmetric vinylogous Mannich reactions based on the use of catalytic AgOAc in the presence of chiral aniline-derived aldimines.[7b,h,i] Shi and co-workers have also used AgOAc catalysis for this reaction but in conjunction with chiral phosphine-oxazoline ligands,[7e,j−l] and Xu utilized chiral Ar-BINMOL-derived monophosphine ligands[7a] and Carretero employed $AgClO_4$ catalysis with copper(II) complexes of Fesulphos ligands.[7d] Akiyama has described the use of chiral binaphthyl-derived phosphoric acids for the same purpose.[7c] Finally, another successful approach to asymmetric vinylogous reactions of trialkylsilyloxyfurans and aldimines involves use of chiral auxiliairies, such as O-pivaloylated D-galactosylamine[7g] or sulfinimines.[7f]

Imines that are part of a heterocyclic system, such as isoquinolines and 3,4-dihydroisoquinolines, present a special challenge because the Mannich reaction is considered to be more difficult in these cases.[8] Nevertheless, a number of effective methodologies have been developed over the years for vinylogous Mannich additions of enol ethers to isoquinoline[8a,9] as well as to other heterocyclic substrates.[3b,10] Thus, the use of chiral auxiliaries has been exploited with success for asymmetric Mannich and vinylogous Mannich reactions to heterocyclic-derived imines,[9d,11] as have organocatalysts, particularly chiral thioureas for the addition of silyl enol ethers to *N*-acylisoquinolines.[12]

We were the first to report the vinylogous Mannich reaction of butyrolactone-derived silyl enol ethers to N-

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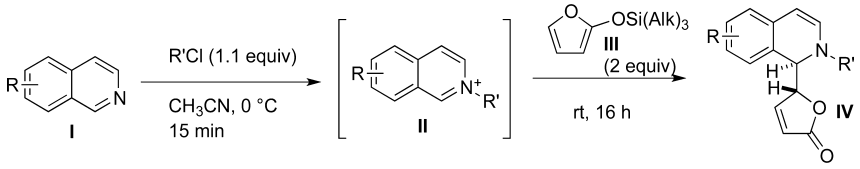
Scheme 1. Previous Stepwise Procedure for the Vinylogous Mannich Reaction of an Isoquinolium Salt with a Trialkylsilyloxyfuran



activated 3,4-dihydroisoquinolines to give the corresponding 1-(5-butyrolactone)-1,2,3,4-tetrahydroisoquinolines, which were subsequently shown to be potent ligands of the GABA-A receptor of the central nervous system.[13] Although the 3,4-dihydroisoquinoline substrates provided very little or no diastereoselectivity in the reaction with trialkylsilyloxyfurans **III**, the two-step procedure that we subsequently developed for the vinylogous Mannich reaction of **III** to preformed *N*-acyl- and *N*-arylsulfonylisoquinolinium salts **II** provided good to excellent yields of the corresponding isoquinolinobutyrolactones **IV** with high diastereoselectivities (dr > 95% in favor of the *R**,*R** diastereomer) (Scheme 1).[14]

A simplified one-step, 3-component version of this reaction, in which the electrophile is simply added to a solution of the isoquinoline and the trialkylsiloxyfuran to afford the targeted products, is now described. This procedure has been successfully extended to a variety of azaheterocycles as well as to a trialkylsiloxypyrrole as nucleophile to provide the corresponding vinylogous Mannich reaction products in good to high yields and, in many cases, with essentially complete diastereoselectivity.

RESULTS AND DISCUSSION

We first investigated the possibility of effecting the vinylogous Mannich reaction among isoquinoline **1**, trimethylsilyloxyfuran **4**, and an electrophilic agent in a one-step, 3-component procedure rather than a stepwise fashion, as described previously. Thus, addition of acetyl chloride (1.2 equiv) in acetonitrile to a mixture of **1** (1 equiv) and **4** (1.5 equiv) at −15 °C provided, after 1 h at room temperature, the product of vinylogous Mannich addition **5** in quantitative yield (Table 1, entry 1). The d.r. was estimated as >95:5 by ^{1}H NMR spectroscopy of the product mixture. These results encouraged us to utilize this procedure for subsequent vinylogous Mannich reactions. Thus, use of acetic anhydride as the acylating agent provided the same compound **5**, but in lower yield (81%) and with a diminished d.r. (90:10) (entry 2). For purposes of subsequent transformations (see below), two other acyl chlorides were tested: methyl chloromalonate and 2-bromobutanoyl chloride. Reaction of these electrophiles with isoquinoline **1** under the same reaction conditions provided the expected products **6** and **7** in 97% and 96% yields, respectively, with again d.r.'s >95:5 (entries 3 and 4). Reaction of these four acylating agents with 6,7-dimethoxyisoquinoline **2** provided the expected products **8**−**10** in similar or slightly lower yields and d.r.'s (entries 5−8). Retro-Mannich reaction products were observed in the case of the preparation of compound **9**, accounting for its lower yield (61%, entry 7). Finally, reaction of phenanthridine **3** with **4** and acetyl chloride or 2-bromobutanoyl chloride gave 97% and 87% yields of Mannich products **11** and **12**, respectively, with formation of only one diastereomer in each case, as observed in the ^{1}H NMR spectra of the crude products (entries 9, 10). The relative configuration of the two contiguous stereogenic centers of crystalline compound **11** was shown by X-ray diffraction studies to be (*R**,*R**), as previously determined for analogous compounds prepared by the stepwise procedure.[14]

The origin of the high diastereoselectivities observed in the vinylogous Mannich reaction of trialkylsilyloxyfurans with *N*-tosylisoquinolinium salts was previously rationalized on the basis of modeling studies of the transition structures using RHF/AM1 semiempirical orbital calculations.[14] Analysis of the HOMO and LUMO coefficients for the favored transition states pointed to a key stabilizing orbital overlap of the silyloxyfuran with the π-system of the isoquinolinium species. The present results, in which high diastereoselectivities are also observed for this reaction using a variety of aromatic heterocycles other than isoquinolines, suggest that this rationalization is generally applicable (also, see below).

We next investigated the effectiveness of our one-step, 3-component procedure for the vinylogous Mannich reaction of azaheterocycles **1**-**3** with TMSO-furan **4** in the presence of a carbamoylating or sulfonylating agent. Thus, although isoquinoline **1** and methyl chloroformate provided an excellent yield (95%) and the usual high d.r. (>95:5) of the *N*-methylcarbamate derivative **13** (Table 2, entry 1), the result with tosyl chloride was disappointing: only 40% of the expected product **14** being obtained though the high d.r. was conserved (entry 2). Changing to the more electron-deficient nosyl chloride, however, improved the yield of *N*-sulfonyl product (**15**, 84%) with only a very minor loss in d.r. (93:7, entry 3). A similar trend was observed in the case of 6,7-dimethoxyisoquinoline **2**, the *N*-methylcarbamate **16** and the *N*-nosyl product **18** being obtained with 80% and 82% yields, respectively, and the *N*-tosyl analogue was obtained in only 45% yield (entries 4−6), high d.r.'s being conserved in all cases. Although methyl chloroformate reacted with phenanthridine **3** and TMSO-furan **4** to give **19** with a satisfactory 84% yield (although the d.r. was diminished somewhat to 90:10, entry 7), nosyl chloride provided, in the same reaction, only 28% of the expected addition product **20** (entry 8). Steric interference between the bulky arylsulfonyl group and the fused phenyl ring of phenanthridine is perhaps responsible for this low yield of **20**.

Several other nitrogen-containing heterocycles were then subjected to the vinylogous Mannich reaction using acetyl chloride and **4** as coreactants. Thus, although quinoline itself gave a mixture of products, presumably because of the possibility of addition to both the C2 and C4 positions, use of 4-methylquinoline (lepidine, **21**) as substrate provided exclusively the product of C2 addition of the furanone moiety (compound **22**) in 64% yield but with only a low d.r. of 60:40 (Scheme 2). Reaction of quinazoline **23** and phthalazine **25** under the same conditions provided the addition products **24** in 60% yield as a single diastereomer and **26** in 81% yield with a d.r. of 95:5. The structure of

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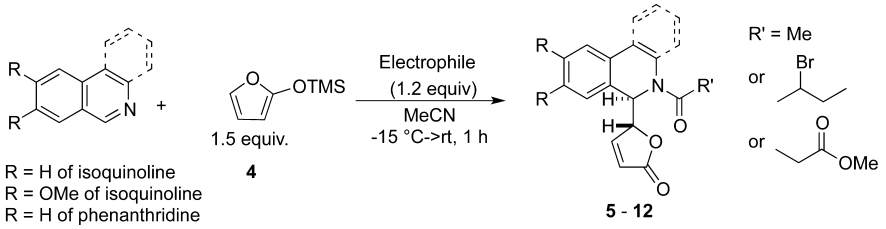
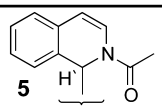
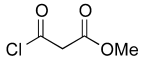
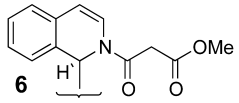
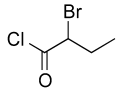
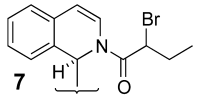
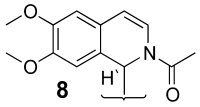
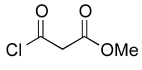
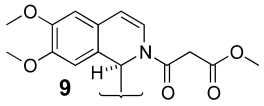
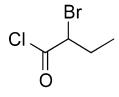
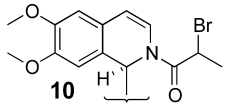
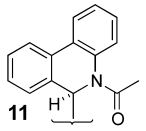
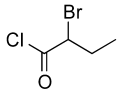
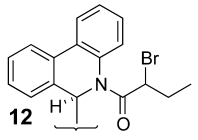
Table 1. 3-Component Vinylogous Mannich Reaction Using Various Electrophiles



1 : R = H of isoquinoline
2 : R = OMe of isoquinoline
3 : R = H of phenanthridine

Entry	Heterocycle	Electrophile	Product	Yield (%)	d.r.[c]
1	**1**	AcCl	 **5**	99[a]	>95:5
2	**1**	Ac_2O	**5**	81	90:10
3	**1**		 **6**	97[a]	>95:5
4	**1**		 **7**	96[a]	>95:5
5	**2**	AcCl	 **8**	84	>95:5
6	**2**	Ac_2O	**8**	75	85:15
7	**2**		 **9**	61	90:10
8	**2**		 **10**	97	>95:5
9	**3**	AcCl	 **11**	97	>95:5[b]
10	**3**		 **12**	87	>95:5

[a]Gram-scale. [b](*R**,*R**) configuration of the major diastereomer was confirmed by X-ray diffraction (see Supporting Information). [c]The d.r.'s were estimated by ^{1}H NMR spectroscopy of the crude product.

compound **26** was confirmed by X-ray crystallographic analysis. Finally, in view of the importance of the *β*-carboline nucleus in a wide variety of natural and biologically active compounds, the behavior of the *N*-methyl derivative **27** under these reaction conditions was studied. The product of C1 addition of the butyrolactone moiety to the *β*-carboline nucleus, that is, compound **28**, was thus obtained in 71% yield and as a single diastereomer observed by ^{1}H NMR spectroscopy.

N-Boc-protected trialkylsiloxypyrroles have been shown to be useful nucleophiles for vinylogous Mannich reactions involving mainly aldimines.[15] As shown in Scheme 3, the

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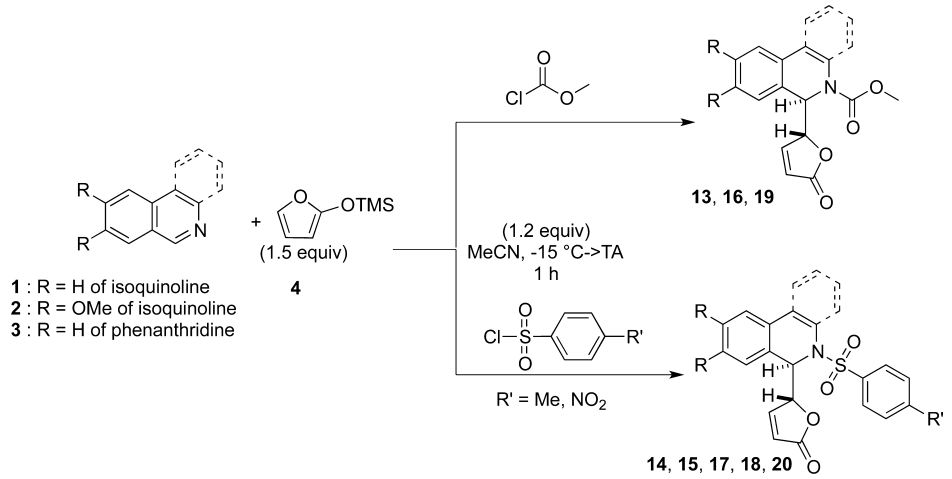
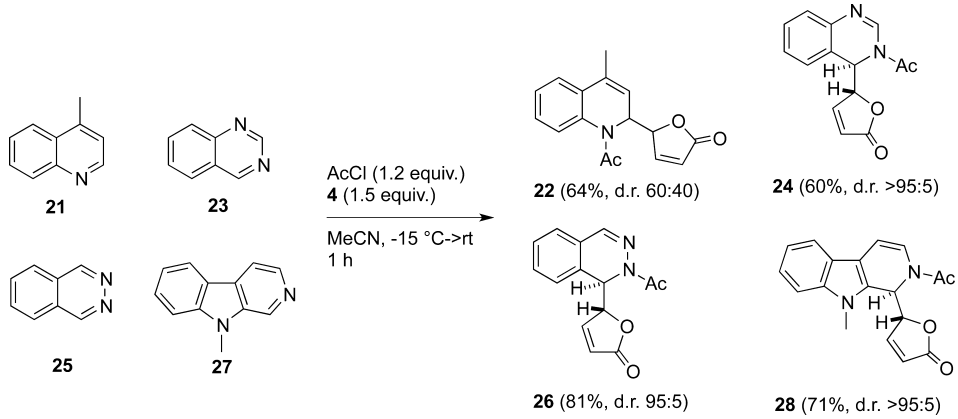
Table 2. 3-Component Vinylogous Mannich Reaction Using Methyl Chloroformate or Arylsulfonyl Chlorides as Electrophiles



entry	heterocycle	electrophile	product	yield (%)	d.r.[a]
1	**1**	MeOCOCl	**13**	95	>95:5
2	**1**	TsCl	**14**	40	>95:5
3	**1**	NsCl	**15**	84	93:7
4	**2**	MeOCOCl	**16**	80	>95:5
5	**2**	TsCl	**17**	45	94:6
6	**2**	NsCl	**18**	82	94:6
7	**3**	MeOCOCl	**19**	84	90:10[b]
8	**3**	NsCl	**20**	28	>95:5

[a]d.r.'s estimated by ^{1}H NMR spectroscopy of the crude product; [b](R^*,R^*) configuration of the major diastereomer was confirmed by X-ray diffraction (see Supporting Information)

Scheme 2. Vinylogous Mannich Reaction of Acetyl Chloride and TMSO-Furan with Various Azaheterocycles



TBSO-pyrrole derivative **29**, in the presence of acetyl chloride, also reacted very well with the different azaheterocycles employed above to give the expected addition products **30**–**36** in yields ranging from 48% to 97% and with high d.r.'s going from 80:20 (lepidine derivative **33**) to >95:5 (phenanthridine and β-carboline derivatives **32** and **36**, respectively). The structures and relative (R^*,R^*) configurations of compounds **31** and **32** were determined unambiguously by X-ray diffraction studies (see Supporting Information).

The synthetic utility of several of the compounds prepared by our methodology was also investigate as a preamble to the targeting of natural product synthesis. Thus, as illustrated in Scheme 4, treatment of the α-bromocarboxamide derivative **7** with *n*-butyllithium in THF at −78 °C provided compound **37**, the product of 1,4-addition to the unsaturated lactone ring, in 70% yield with conservation of the stereochemical integrity of the starting substrate (d.r. >95:5). The four contiguous stereogenic centers of compound **37** can thus be obtained in a controlled fashion.

The use of the malonamide derivatives **6** and **9** also allowed 1,4-addition of the methylene carbon atom to the α,β-unsaturated lactone system but under milder conditions. Thus, treatment of these compounds with 5 equiv of sodium methoxide in dichloromethane at room temperature provided cyclized products **38** and **39** in 87% and 78% yields, respectively (Scheme 5). Krapcho decarboxylation of the latter then furnished **40** and **41** in good yields and as single diastereomers. These can be considered as versatile functionalized building blocks for the preparation of natural or biologically active substances.

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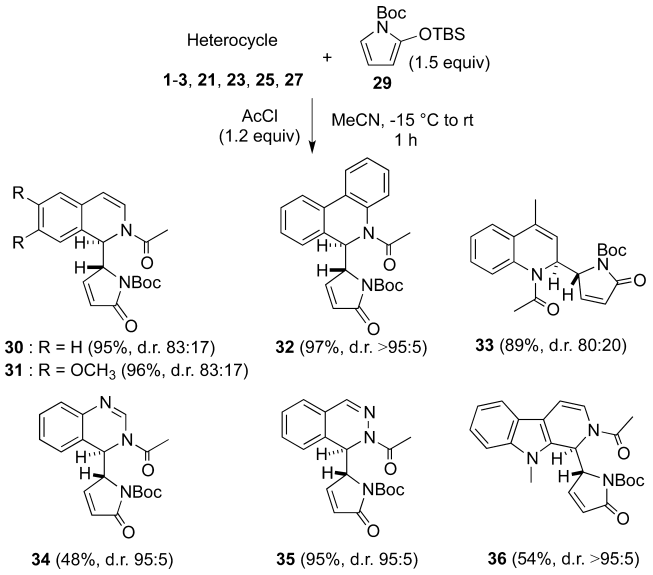
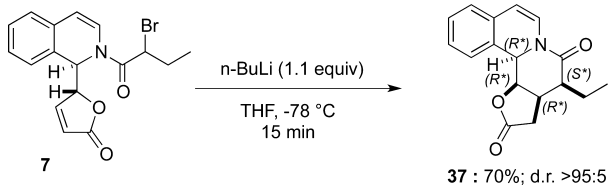
Scheme 3. Vinylogous Mannich Reaction of Trialkylsilyloxy-*N*-Boc-pyrrole and Acetyl Chloride with Various Azaheterocycles



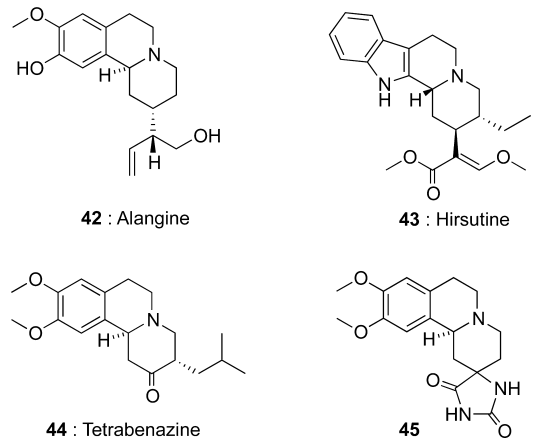
Scheme 4. Formation of a Tetracycle from the Bromo Derivative 7



CONCLUSION

We have previously shown that the vinylogous Mannich reaction of trialkylsilyloxyfurans with isoquinolinium salts prepared in situ from isoquinoline and diverse electrophiles was very efficient, providing the C1−C5 coupled products in a highly diastereoselective fashion.[14] The original stepwise procedure has now been replaced by an improved one-step, three-component approach that simply requires addition of the electrophile to a solution of isoquinoline and the silyl enol ether, allowing formation of the desired products with high yields and diastereoselectivities. We also demonstrated that the vinylogous Mannich reaction can be extended to a wide variety of nitrogen-based heterocycles, including quinoline, phenanthridine, quinazoline, phthalazine, and β-carboline with high yields and diastereoselectivities. Furthermore, the use of the *N*-Boc-protected TBSO-pyrrole **29** instead of the furan-based silyl enol ether **4** for these vinylogous Mannich reactions was also successful. Depending on the electrophile used in the reaction, various transformations can subsequently be performed with the generation of new heterocyclic systems, as illustrated by conversion of the α-bromocarboxamide (**7**) and malonamide derivatives (**6**, **9**) into the highly functionalized and stereochemically defined tetracycles **37**, **40**, and **41**. A novel synthetic route to such natural products as alangine (**42**)[16] and hirsutine (**43**)[17] or to analogues of biologically active compounds such as tetrabenazine **44**,[18] used for the treatment of hyperkinetic disorders and Huntington's disease, or the antihypertensive agent **45**[19] can be envisaged (Chart 1). These objectives are presently being pursued in our laboratory.

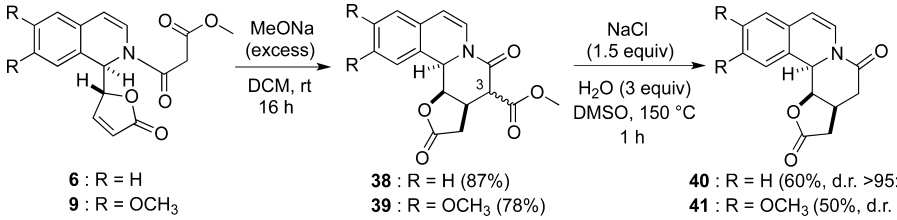
Chart 1. Targeted Natural and Medicinal Products



EXPERIMENTAL SECTION

General Methods. Melting points, measured in capillary tubes, are uncorrected. IR spectra were recorded without solvent. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a 300 MHz spectrometer (QNP—^{13}C, ^{31}P, ^{19}F—probe or dual ^{13}C probe). Unless otherwise mentioned, spectra were recorded at 293 K in $CDCl_3$ unless otherwise indicated. Chemical shifts (δ) are reported in parts per million (ppm) with reference to $CDCl_3$ (^{1}H, 7.27; ^{13}C, 77.16). The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, qu: quintuplet, sept: septuplet, m: multiplet, br: broad. Coupling constants (J) are reported in Hertz (Hz). Carbon multiplicities were determined using 2D spectra (HMQC and HMBC). Quaternary carbons were determined using HMBC couplings. Thin-layer chromatography was performed on silica gel 60 F254 on aluminum plates and visualized under a UV lamp (254 nm) and with ninhydrin in ethanol. Preparative TLC was performed on silica gel glass plates. Flash column chromatography was performed according to the literature[20] using silica gel at medium pressure (300 mbar). In some indicated cases, purification of compounds was performed on an automatic fraction collector using prepacked silica gel columns with a solvent gradient from apolar to polar over 20

Scheme 5. Formation of Tetracycles from the Malonamide Derivatives 6 and 9



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column volumes (isocratic elution was used when a UV signal (254 or 300 nm) was detected). Mass spectra were obtained by using electrospray ionization and time-of-flight analyzer (ESI-MS) for high-resolution mass spectra (HRMS). All solvents were freshly distilled when required or dried over activated basic alumina.[21] All reagents were obtained from commercial suppliers unless otherwise stated.

General Procedure for the Vinylogous Mannich Reaction. Under argon, the nucleophile (1.16 mmol, 1.5 equiv) was added to a cooled solution (−15 °C, ice/acetone bath) of azaheterocycle (0.77 mmol) in MeCN (8 mL). The electrophile (0.93 mmol, 1.2 equiv) in MeCN (1 mL) was then slowly added. After stirring for 15 min, the reaction mixture was allowed to reach room temperature over 45 min before being evaporated under reduced pressure without heating. The crude product was purified on a silica gel cartridge (heptane/AcOEt or DCM/MeOH 100/0−95/5). In cases that the product was contaminated by 2(5*H*)-furanone, trituration in Et_2O or dichloromethane/pentane afforded pure solid compound.

(*R,*R**)-5-(-2-Acetyl-1,2-dihydroisoquinolin-1-yl)furan-2(5*H*)-one (5).** Using acetyl chloride: Following the general procedure using AcCl (304 μL, 4.26 mmol) as the electrophile, isoquinoline (459 μL, 3.87 mmol) as the azaheterocycle and **4** (976 μL, 5.80 mmol) as the nucleophile in MeCN (39 mL) afforded compound **5** as a white solid (980 mg, 3.84 mmol, 99%). ^{1}H NMR showed only one diastereomer.

Using acetic anhydride: Following the general procedure using Ac_2O (88 μL, 0.93 mmol) as the electrophile, isoquinoline (92 μL, 0.77 mmol) as the azaheterocycle and **4** (195 μL, 1.16 mmol) as the nucleophile in MeCN (8 mL) afforded **5** as a white solid (160 mg, 0.93 mmol, 81%). ^{1}H NMR showed two diastereomers (d.r. A/B 90:10).

Compound **5** was in both cases identical to that previously prepared by the stepwise procedure.[14]

Methyl (*R,*R**)-3-Oxo-3-(1-(-5-oxo-2,5-dihydrofuran-2-yl)-isoquinolin-2(1*H*)-yl)propanoate (6).** Following the general procedure using **4** (976 μL, 5.80 mmol) as the nucleophile, methyl malonyl chloride (635 μL, 4.64 mmol) as the electrophile and isoquinoline **1** (100 mg, 0.77 mmol) as the azaheterocycle afforded compound **6** as a pink solid (1.18 g, 3.79 mmol, 97%). The ^{1}H NMR spectrum showed the presence of only one diastereomer. mp 120−122 °C; IR υ 2958, 1745, 1668, 1628 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 7.56 (dd, J = 5.8, 1.5 Hz, 1H), 7.32−7.23 (m, 3H), 7.21−7.15 (m, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.07 (dd, J = 5.9, 1.9 Hz, 1H), 6.04 (d, J = 7.8 Hz, 1H), 6.01 (d, J = 4.4 Hz, 1H), 5.22 (ddd, J = 4.4, 1.9, 1.7 Hz, 1H), 3.88 (d, J = 16.2 Hz, 1H), 3.78 (d, J = 16.2 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 172.2 (C), 167.4 (C), 165.2 (C), 153.5 (CH), 130.5 (C), 128.6 (CH), 127.7 (CH), 127.0 (CH), 126.7 (C), 125.6 (CH), 124.6 (CH), 121.2 (CH), 110.0 (CH), 84.1 (CH), 53.6 (CH), 52.1 (CH_3), 40.5 (CH_2); HRESMS m/z calcd for $[C_{17}H_{15}NO_5Na]^+$ 336.0848, found 336.0859.

(*R,*R**)-5-(2-(2-Bromobutanoyl)-1,2-dihydroisoquinolin-1-yl)furan-2(5*H*)-one (7).** Following the general procedure using 2-bromobutanoyl chloride (113 μL, 0.93 mmol) as the electrophile, isoquinoline **1** (92 μL, 0.77 mmol) as the azaheterocycle and **4** (182 μL, 1.16 mmol) as the nucleophile in MeCN (5 mL) afforded compound **7** as two separable diastereomers. Diastereomer 1 (140 mg, 0.39 mmol, 50%). mp 135−137 °C; IR υ 3097, 1977, 1781, 1754, 1665, 1626 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, J = 5.7, 1.6 Hz, 1H), 7.25−7.11 (m, 3H), 7.06−7.00 (m, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.02−5.94 (m, 2H), 5.84 (dd, J = 5.7, 1.9 Hz, 1H), 5.13 (ddd, J = 3.9, 1.9, 1.9 Hz, 1H), 4.23 (t, J = 7.1 Hz, 1H), 2.14−1.93 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 167.2 (C), 151.3 (CH), 130.2 (C), 129.0 (CH), 128.0 (CH), 127.6 (CH), 127.0 (C), 125.3 (CH), 123.8 (CH), 122.5 (CH), 112.3 (CH), 84.4 (CH), 54.3 (CH), 44.6 (CH), 27.5 (CH_2), 12.1 (CH_3); HRESMS m/z calcd for $[C_{17}H_{16}NO_3NaBr^{79}]^+$ 384.0211, found 384.0210; m/z calcd for $[C_{17}H_{16}NO_3NaBr^{81}]^+$ 386.0191, found 386.0199. Diastereomer 2 (130 mg, 0.36 mmol, 46%): mp 135−137 °C; IR υ 2983, 2941, 1740, 1668, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, J = 5.7, 1.6 Hz, 1H), 7.25−7.09 (m, 3H), 7.08−7.02 (m, 1H), 6.72 (d, J = 7.9 Hz, 1H), 6.00−5.92 (m, 2H), 5.86 (dd, J = 5.7, 1.9 Hz, 1H), 5.06 (ddd, J = 4.9, 1.9, 1.6 Hz, 1H), 4.43 (t, J = 7.1 Hz, 1H), 2.15 (ddq, J = 14.2, 7.3, 7.1 Hz, 1H), 2.01 (ddq, J = 14.2, 7.3, 7.1 Hz, 1H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 167.4 (C), 152.0 (CH), 130.3 (C), 129.0 (CH), 127.8 (CH), 127.4 (CH), 127.1 (C), 125.4 (CH), 123.6 (CH), 122.3 (CH), 111.3 (CH), 84.4 (CH), 55.1 (CH), 44.6 (CH), 28.1 (CH_2), 12.2 (CH_3); HRESMS m/z calcd for $[C_{17}H_{16}NO_3NaBr^{79}]^+$ 384.0211, found 384.0197; m/z calcd for $[C_{17}H_{16}NO_3NaBr^{81}]^+$ 386.0191, found 386.0191.

(*R,*R**)-5-(2-Acetyl-6,7-dimethoxy-1,2-dihydroisoquinolin-1-yl)furan-2(5*H*)-one (8).** Following the general procedure using acetyl chloride (15 μL, 0.63 mmol) as the electrophile, **2** (100 mg, 0.53 mmol) as the azaheterocycle and **4** (133 μL, 0.79 mmol) as the nucleophile in MeCN (5 mL) afforded compound **8** as an off-white solid (140 mg, 0.44 mmol, 84%). The ^{1}H NMR spectrum showed only one diastereomer. Alternatively, following the general procedure using Ac_2O (60 μL, 0.63 mmol) as the electrophile, **2** (100 mg, 0.53 mmol) as the azaheterocycle, and **4** (133 μL, 0.79 mmol) as the nucleophile in MeCN (5 mL) afforded **8** as a white solid (125 mg, 0.40 mmol, 75%). The ^{1}H NMR spectrum showed two diastereomers (A/B 85:15). mp 188−190 °C; IR υ 2943, 1788, 1745, 1672, 1633, 1519 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) of major diastereomer δ 7.42 (dd, J = 5.8, 1.5 Hz, 1H), 6.71 (s, 1H), 6.63 (dd, J = 7.8, 1.0 Hz, 1H), 6.60 (s, 1H), 6.07 (d, J = 4.5 Hz, 1H), 5.90−5.86 (m, 2H), 5.14 (dt, J = 4.5, 1.7 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) of major diastereomer δ 172.3 (C), 168.9 (C), 151.9 (CH), 149.1 (C), 148.4 (C), 123.4 (C), 123.1 (CH), 122.4 (CH), 118.4 (C), 111.1 (CH), 110.5 (CH), 108.1 (CH), 83.7 (CH), 56.3 (CH_3), 56.0 (CH_3), 54.1 (CH), 21.5 (CH_3); HRESMS m/z calcd for $[C_{17}H_{17}NO_5Na]^+$ 338.1004, found 338.1009.

Methyl (*R,*R**)-3-(6,7-Dimethoxy-1-(5-oxo-2,5-dihydrofuran-2-yl)isoquinolin-2(1*H*)-yl)-3-oxopropanoate (9).** Following the general procedure using **4** (666 μL, 3.96 mmol) as the nucleophile, methyl malonyl chloride (340 μL, 3.71 mmol) as the electrophile and **2** (500 mg, 2.64 mmol) as the azaheterocycle afforded compound **9** as an amorphous yellow solid (600 mg, 1.6 mmol, 61%) and as a mixture of two diastereomers (A/B 90:10) that were not separated: IR υ 2954, 1748, 1668, 1634, 1517 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, J = 5.6, 1.7 Hz, 0.1H, dia B), 7.36 (dd, J = 5.7, 1.6 Hz, 0.9H, dia A), 6.64 (s, 0.9H, dia A), 6.63 (s, 0.1H, dia B), 6.59 (s, 0.1H, dia B), 6.51 (s, 0.9H, dia A), 6.47 (d, J = 7.7 Hz, 0.9H, dia A), 5.98 (d, J = 4.6 Hz, 1H), 5.84 (d, J = 7.7 Hz, 1H), 5.8 (dd, J = 5.7, 1.9 Hz, 1H), 5.10 (ddd, J = 4.4, 1.8, 1.7 Hz, 0.9H, dia A), 5.04 (ddd, J = 6.4, 1.8, 1.8 Hz, 0.1H, dia B), 3.82−3.77 (m, 6H), 3.71 (s, 0.3H, dia B), 3.70 (s, 2.7H, dia A), 3.62 (d, J = 15.8 Hz, 1H), 3.48 (d, J = 15.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer only) δ 172.2 (C), 167.1 (C), 164.5 (C), 151.7 (CH), 149.2 (C), 148.7 (C), 123.0 (C), 122.5 (CH), 122.0 (CH), 118.8 (C), 111.9 (CH), 111.1 (CH), 108.3 (CH), 83.5 (CH), 56.3 (CH_3), 55.9 (CH_3), 54.5 (CH), 52.8 (CH_3), 40.8 (CH_2); HRESMS m/z calcd for $[C_{19}H_{19}NO_7Na]^+$ 396.1059, found 396.1059.

(*R,*R**)-5-(2-(2-Bromobutanoyl)-6,7-dimethoxy-1,2-dihydroisoquinolin-1-yl)furan-2(5*H*)-one (10).** Following the general procedure using 2-bromobutanoyl chloride (77 μL, 0.63 mmol) as the electrophile, **2** (100 mg, 0.53 mmol) as the azaheterocycle and **4** (133 μL, 0.79 mmol) as the nucleophile in MeCN (5 mL) afforded compound **10** as an off-white solid (217 mg, 0.51 mmol, 97%). The ^{1}H NMR spectrum showed the presence of two diastereomers (A/B 75:25) that were not separated. mp 126−128 °C; IR υ 2933, 1748, 1665, 1633, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, J = 5.7, 1.5 Hz, 0.75H), 7.41 (dd, J = 5.7, 1.5 Hz, 0.25H), 6.84−6.69 (m, 2H), 6.65−6.59 (m, 1H), 6.04−5.95 (m, 2H), 5.93 (dd, J = 5.7, 1.7 Hz, 0.25H), 5.90 (dd, J = 5.7, 1.7, 0.75H), 5.23−5.19 (m, 0.75H), 5.16−5.12 (m, 0.25H), 4.53−4.45 (m, 0.25H), 4.35−4.28 (m, 0.75H), 3.90 (s, 3H), 3.88 (s, 3H), 2.26−2.04 (m, 2H), 1.08 (t, J = 7.3 Hz, 0.75H), 1.02 (t, J = 7.3 Hz, 2.25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 167.2 (C), 151.8 (CH, dia B), 151.2 (CH, dia

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A), 149.3 (C), 148.8 (C), 123.2 (C, dia B), 123.1 (C, dia A), 122.6 (CH, dia A), 122.5 (CH, dia B), 122.0 (CH, dia A), 121.8 (CH, dia B), 119.1 (C), 112.2 (CH), 111.3 (CH, dia B), 111.0 (CH, dia A), 108.4 (CH, dia B), 108,3 (CH, dia A), 84.0 (CH, dia B), 83.6 (CH, dia A), 56.3 (CH_3), 56.0 (CH_3), 54.9 (CH, dia B), 54.2 (CH, dia A), 44.7 (CH, dia A), 44.6 (CH, dia B), 28.0 (CH_2, dia B), 27.5 (CH_2, dia A), 12.2 (CH_3, dia B), 12.08 (CH_3, dia A); HRESMS m/z calcd for $[C_{19}H_{20}NO_5{}^{79}BrNa]^+$ 444.0423, found 444.0423; m/z calcd for $[C_{19}H_{20}NO_5{}^{81}BrNa]^+$ 446.0402, found 446.0425.

(*R,*R**)-5-(5-Acetyl-5,6-dihydrophenanthridin-6-yl)furan-2(5*H*)-one (11).** Following the general procedure using AcCl (48 μL, 0.67 mmol) as the electrophile, phenanthridine **3** (100 mg, 0.56 mmol) as the azaheterocycle and **4** (141 μL, 0.84 mmol) as the nucleophile in MeCN (6 mL) afforded compound **11** as a white solid (166 mg, 0.54 mmol, 97%). The ^{1}H NMR showed the presence of only one diastereomer. mp 170−171 °C; IR υ 3090, 1767, 1752, 1653 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.80 (m, 2H), 7.50−7.42 (m, 1H), 7.41−7.29 (m, 4H), 7.25 (bs, 1H), 7.11 (d, J = 5.4 Hz, 1H), 6.18 (bs, 1H), 5.98 (d, J = 5.8 Hz, 1H), 5.03 (d, J = 6.4 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 169.8 (C), 152.7 (CH), 132.2 (C), 131.5 (C), 129.2 (CH), 128.5 (2 CH), 128.3 (2 CH), 127.6 (CH), 126.66 (CH), 125.2 (C), 124.5 (C), 123.6 (CH), 122.6 (CH), 83.7 (CH), 55.0 (CH), 22.6 (CH_3); HRESMS m/z calcd for $[C_{19}H_{16}NO_3]^+$ 306.1130, found 306.1133.

(*R,*R**)-5-(5-(2-Bromobutanoyl)-5,6-dihydrophenanthridin-6-yl)furan-2(5*H*)-one (12).** Following the general procedure using 2-bromobutanoyl chloride (81 μL, 0.67 mmol) as the electrophile, phenanthridine **3** (100 mg, 0.56 mmol) as the azaheterocycle and **4** (141 μL, 0.84 mmol) as the nucleophile in MeCN (6 mL) afforded compound **12** as an off-white amorphous solid (200 mg, 0.48 mmol, 87%) and as a mixture of two diastereomers (A/B 55:45) that were not separated. IR υ 2970, 1752, 1661 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.79 (m, 2H), 7.52−7.06 (m, 7H), 6.23−5.81 (m, 2H), 5.20−5.05 (m, 0.55H, dia A), 5.03−4.95 (m, 0.45H, dia B), 4.92−4.83 (m, 0.45H, dia B), 4.64−4.53 (m, 0.55H, dia A), 2.33−2.01 (m, 1.1H, dia A), 2.00−1.87 (m, 0.9H, dia B), 1.07 (t, J = 7.3 Hz, 1.55H, A), 0.64 (t, J = 7.5 Hz, 1.35H, dia B); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C, dia B), 171.7 (C, dia A), 169.7 (C, dia B), 169.2 (C, dia A), 152.8 (CH, dia A), 152.3 (CH, dia B), 134, 5 (C, dia B), 134.2 (C, dia A), 132.0 (C, dia A), 131.7 (C, dia B), 131.3 (C, dia A), 131.2 (C, dia B), 129.4 (CH), 128.9 (C), 128.6 (2 CH, dia A), 128.5 (2 CH, dia B), 127.65 (2 CH, dia B), 127.6 (CH), 127.4 (2 CH, dia A), 125.1 (CH, dia A), 125.0 (CH, dia B), 123.7 (CH, dia B), 123.65 (CH, dia B), 127.58 (CH, dia A), 122.7 (CH, dia A), 84.2 (CH, dia A), 83.2 (CH, dia B), 56.7 (CH, dia B), 55.4 (CH, dia A), 46.6 (CH, dia A), 45.4 (CH, dia B), 29.8 (CH_2, dia B), 27.9 (CH_2, dia A), 12.3 (CH_3, dia A), 11.7 (CH_3, dia B); HRESMS m/z calcd for $[C_{21}H_{19}NO_3Br^{79}]^+$ 412.0548, found 412.0557; m/z calcd for $[C_{21}H_{19}NO_3Br^{81}]^+$ 414.0528, found 414.0552.

Methyl (*R,*R**)-1-(5-Oxo-2,5-dihydrofuran-2-yl)isoquinoline-2(1*H*)-carboxylate (13).** Following the general procedure using **4** (195 μL, 1.16 mmol) as the nucleophile, isoquinoline **1** (92 μL, 0.77 mmol) as the azaheterocycle and methyl chloroformate (70 μL, 0.93 mmmol) as the electrophile in MeCN (8 mL) afforded compound **13** as a light yellow solid (230 mg, 0.73 mmol, 95%). The ^{1}H NMR spectrum showed the presence of two conformers in a 6:4 ratio that coalesced to a single diastereomer when the ^{1}H NMR sample in DMSO-d_6 was heated at 313 K. Compound **13** prepared in this manner was identical in all respects to that prepared by the stepwise procedure.[14]

(*R,*R**)-5-(2-(4-Methylphenylsulfonyl)-1,2-dihydroisoquinolin-1-yl)furan-2(5*H*)-one (14).** Following the general procedure using tosyl chloride (177 mg, 0.93 mmol) as the electrophile, isoquinoline **1** (92 μL, 0.77 mmol) as the azaheterocycle and **4** (195 μL, 1.16 mmol) as nucleophile in MeCN (8 mL) afforded compound **14** as an off-white solid (115 mg, 0.31 mmol, 40%) contaminated by 10% of 2-(5*H*)-furanone (attempted further purification led to degradation). The ^{1}H NMR spectrum showed the presence of only one diastereomer. This compound was identical in all respects to that prepared by the stepwise procedure.[14]

(*R,*R**)-5-(2-(4-Nitrophenylsulfonyl)-1,2-dihydroisoquinolin-1-yl)furan-2(5*H*)-one (15).** Following the general procedure using nosyl chloride (206 mg, 0.93 mmol) as the electrophile, isoquinoline **1** (92 μL, 0.77 mmol) as the azaheterocycle and **4** (195 μL, 1.16 mmol) as the nucleophile in MeCN (8 mL) afforded compound **15** as a white amorphous solid (260 mg, 0.65 mmol, 84%). The ^{1}H NMR spectrum showed the presence of two diastereomers (A/B 93:7) that were not separated. IR υ 3105, 2255, 1755, 1745, 1530, 1348 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) (major diastereomer only) δ 8.27 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 9.0 Hz, 2H), 7.45 (dd, J = 5.8, 1.6 Hz, 1H), 7.26−7.15 (m, 2H), 7.07−6.97 (m, 2H), 6.84 (dd, J = 7.6, 1.4 Hz, 1H), 6.14 (d, J = 7.6 Hz, 1H), 5.94 (dd, J = 5.9, 1.9 Hz, 1H), 5.53 (d, J = 5.3 Hz, 1H), 5.24 (ddd, J = 5.3, 1.9, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) (major diastereomer only) δ 171.5 (C), 151.3 (CH), 150.4 (C), 143.9 (C), 129.5 (CH), 129.2 (C), 128.4 (CH), 128.0 (2 CH), 127.6 (CH), 125.5 (CH), 124.5 (2 CH), 123.7 (C), 123.35 (CH), 123.29 (CH) 114.3 (CH), 84.0 (CH), 58.4 (CH); HREIMS m/z calcd for $[C_{19}H_{13}N_2O_6S]^+$ 397.0494, found 397.0493.

Methyl (*R,*R**)-6,7-Dimethoxy-1-(5-oxo-2,5-dihydrofuran-2-yl)isoquinoline-2(1*H*)-carboxylate (16.).** Following the general procedure using **4** (133 μL, 0.79 mmol) as the nucleophile, **2** (100 mg, 0.53 mmol) as the azaheterocycle and methyl chloroformate (48 μL, 0.63 mmmol) as the electrophile in MeCN (5 mL) afforded compound **16** as a light yellow solid (140 mg, 0.42 mmol, 80%). The ^{1}H NMR spectrum showed the presence of two conformers in a 6:4 ratio that coalesced to a single diastereomer when the ^{1}H NMR sample in DMSO-d_6 was heated at 313 K. mp 183−185 °C; IR υ 2954, 1747, 1711, 1518, 1437, 1260, 1103 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 6.0 Hz, 0.6H), 7.40 (d, J = 5.6 Hz, 0.4H), 7.01 (d, J = 7.8 Hz, 0.4H), 6.83 (d, J = 7.7 Hz, 0.6H), (m, 1H), 6.69 (s, 0.6H), 6.64 (s, 0.4H), 6.58 (s, 1H), 5.89−5.79 (m, 2H), 5.78 (d, J = 3.0 Hz, 0.6H), 5.65 (d, J = 5.18 Hz, 0.4H), 5.20−5.14 (m, 0.6H), 5.14−5.08 (m, 0.4H), 3.96−3.84 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (6:4 mixture of conformers A, B) δ 172.4 (C), 153.0 (C), 151.8 (CH), 148.2 (C), 148.0 (C), 123.4 (CH, conf B), 122.9 (C), 122.7 (CH + CH, conf A), 117.7 (C), 111.13 (CH, conf B), 111.08 (CH, conf A), 109.1 (CH, conf B), 108.9 (CH, conf A), 108.1 (CH), 83.3 (CH, conf A), 82.8 (CH, conf B), 56.8 (CH, B), 56.3 (CH_3), 56.1 (CH, conf A), 55.9 (CH_3), 53.85 (CH, conf B), 55.80 (CH, conf A); HRESMS m/z calcd for $[C_{17}H_{21}N_2O_6]^+$ 349.1400, found 349.1407.

(*R,*R**)-5-(6,7-Dimethoxy-2-(4-methylphenylsulfonyl)-1,2-dihydroisoquinolin-1-yl)furan-2(5*H*)-one (17).** Following the general procedure using tosyl chloride (121 mg, 0.63 mmol) as electrophile, **2** (100 mg, 0.53 mmol) as the azaheterocycle and **4** (133 μL, 0.79 mmol) as nucleophile in MeCN (5 mL) afforded compound **17** as a bright yellow solid (100 mg, 0.24 mmol, 45%) and as a mixture of two diastereomers (A/B 94:6), as determined from the ^{1}H NMR spectrum. This compound was identical in all respects to that prepared by the stepwise procedure.[14]

(*R,*R**)-5-(6,7-Dimethoxy-2-(4-nitrophenylsulfonyl)-1,2-dihydroisoquinolin-1-yl)furan-2(5*H*)-one (18).** Following the general procedure using nosyl chloride (141 mg, 0.63 mmol) as electrophile, **2** (100 mg, 0.53 mmol) as the azaheterocycle and **4** (133 μL, 0.79 mmol) as nucleophile in MeCN (5 mL) afforded compound **18** as a bright yellow amorphous solid (200 mg, 0.43 mmol, 82%). The ^{1}H NMR spectrum showed the presence of two diastereomers (A/B 94:6) that were not separated. IR υ 3106, 1783, 1754, 1530, 1516, 1347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer only) δ 8.30 (d, J = 9.0, 2H), 7.97 (d, J = 9.0, 2H), 7.44 (dd, J = 5.8, J = 1.5, 1H), 6.75 (dd, J = 7.5, J = 1.3, 1H), 6.55 (s, 1H), 6.48 (s, 1H), 6.04 (d, J = 7.5, 1H), 5.90 (dd, J = 5.8, J = 1.9, 1H), 5.50 (d, J = 4.9, 1H), 5.23 (dt, J = 5.1, J = 1.7, 1H), 3.85 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer only) δ 171.6 (C), 151.2 (CH), 150.4 (C), 149.5 (C), 148.8 (C), 144.0 (C), 127.9 (2 CH), 124.5 (2 CH), 123.3 (CH), 122.1 (C), 121.4 (CH), 116.0 (C), 114.1 (CH), 110.8 (CH), 108.4

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(CH), 84.5 (CH), 58.0 (CH), 55.3 (CH_3), 55.9 (CH_3); HRESMS m/z calcd for $[C_{21}H_{22}N_3O_8S]^+$ 476.1128, found 476.1148.

Methyl (*R,*R**)-6-(5-Oxo-2,5-dihydrofuran-2-yl)-phenanthridine-5(6*H*)-carboxylate (19).** Following the general procedure using **4** (141 μL, 0.84 mmol) as the nucleophile, phenanthridine **3** (100 mg, 0.56 mmol) as the azaheterocycle and methyl chloroformate (51 μL, 0.67 mmmol) as the electrophile in MeCN (6 mL) afforded compound **19** as a light yellow solid (150 mg, 0.47 mmol, 84%) slightly contaminated by furanone. The ^{1}H NMR spectrum showed the presence of two diastereomers (A/B 90:10) that were not separated. mp 145−147 °C; IR υ 3098, 2953, 1768, 1753, 1711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.78 (m, 2H), 7.71 (bs, 1H), 7.55−7.20 (m, 5H), 7.09 (d, J = 5.9 Hz, 0.1H, dia B), 7.00 (dd, J = 5.8, 1.6 Hz, 0.9H, dia A), 5.99 (dd, J = 5.8, 1.9 Hz, 0.9H, dia A), 5.94 (dd, J = 5.9, 2.0 Hz, 0.1H, dia B), 5.87 (d, J = 7.0 Hz, 0.1H, dia B), 5.79 (d, J = 6.8 Hz, 0.9H, dia A), 5.02 (ddd, J = 7.0, 1.9, 1.6 Hz, 1H), 3.85 (s, 2.7H, dia A), 2.84 (s, 0.3H, dia B); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer A only) δ 172.0 (C), 152.6 (C), 152.4 (CH), 134.4 (C), 131.6 (C), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.5 (CH), 127.3 (C), 125.8 (C), 125.6 (CH), 125.5 (CH), 123.9 (CH), 123.7 (CH), 122.8 (CH), 82.8 (CH), 58.1 (CH), 53.6 (CH_3); HRESMS m/z calcd for $[C_{19}H_{16}NO_4]^+$ 322.1079, found 322.1088.

(*R,*R**)-5-(5-(4-Nitrophenylsulfonyl)-5,6-dihydrophenanthridin-6-yl)furan-2(5*H*)-one (20).** Following the general procedure using nosyl chloride (148 mg, 0.67 mmol) as the electrophile, phenanthridine **3** (100 mg, 0.56 mmol) as the azaheterocycle and **4** (141 μL, 0.84 mmol) as the nucleophile in MeCN (6 mL) afforded compound **20** as a white solid (70 mg, 0.16 mmol, 28%). The ^{1}H NMR spectrum showed the presence of only one diastereomer complexed with 1 equiv of Et_2O after trituration. mp 209−211 °C; IR υ 3104, 1759, 1605, 1528 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.85 (m, 1H), 7.80 (d, J = 9.0 Hz, 2H), 7.66−7.61 (m, 1H), 7.56−7.43 (m, 2H), 7.33−7.16 (m, 6H), 6.85 (dd, J = 5.8, 1.6 Hz, 1H), 5.94 (dd, J = 5.8, 2.0 Hz, 1H), 5.66 (d, J = 6.1 Hz, 1H), 5.13 (ddd, J = 6.0, 1.8, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 (C), 151.6 (CH), 149.8 (C), 142.0 (C), 132.4 (C), 130.4 (C), 129.56 (C), 129.54 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (C), 128.2 (2 CH), 127.9 (CH), 124.1 (CH), 123.3 (CH), 123.2 (CH), 123.0 (2 CH), 83.1 (CH), 60.2 (CH); HRESMS m/z calcd for $[C_{23}H_{16}N_2O_6SNa]^+$ 471.0627, found 471.0619.

(*R,*R**)-5-(1-Acetyl-4-methyl-1,2-dihydroquinolin-2-yl)-furan-2(5*H*)-one (22).** Following the general procedure using AcCl (60 μL, 0.84 mmol) as the electrophile, lepidine **21** (93 μL, 0.70 mmol) as the azaheterocycle and **4** (176 μL, 1.05 mmol) as the nucleophile in MeCN (7 mL) afforded compound **22** as a white solid (120 mg, 0.45 mmol, 64%). The ^{1}H NMR spectrum showed the presence of two diastereomers (A/B 60:40) that were not separated. IR υ 3075, 2978, 2922, 1786, 1751, 1659 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−6.96 (m, 5H), 5.92 (d, J = 5.7, 1.6 Hz, 1H), 5.78 (dd, J = 6.1, 1.3 Hz, 0.4H, dia B), 5.75 (dd, J = 6.1, 1.4 Hz, 0.6H, dia A), 5.61−5.30 (m, 1H), 4.88 (ddd, J = 5.2, 1.8, 1.4 Hz, 0.6H, dia A), 4.85−4.81 (m, 0.4H, dia B), 2.18 (s, 1.2H, dia B), 2.16 (s, 1.8H, dia A), 2.07−2.00 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.35 (C, dia B), 172.32 (C, dia A), 170.5 (C, dia B), 170.3 (C, dia A), 152.7 (CH), 135.1 (C), 134.1 (C), 129.1 (C), 127.9 (CH), 125.8 (CH), 124.0 (CH), 122.2 (CH), 122.0 (CH), 83.8 (CH, dia B), 83.2 (CH, dia A), 51.7 (CH), 22.67 (CH_3, dia B), 22.65 (CH_3, dia A), 18.3 (CH_3); HRESMS m/z calcd for $[C_{16}H_{16}NO_3]^+$ 270.1130, found 270.1120.

(*R,*R**)-5-(3-Acetyl-3,4-dihydroquinazolin-4-yl)furan-2(5*H*)-one (24).** Following the general procedure using AcCl (66 μL, 0.93 mmol) as the electrophile, quinazoline **23** (93 μL, 0.77 mmol) as the azaheterocycle and **4** (195 μL, 1.16 mmol) as the nucleophile in MeCN (8 mL) afforded compound **24** as a white solid (120 mg, 0.47 mmol, 60%) slightly contaminated by acetic acid. The ^{1}H NMR spectrum showed the presence of only one diastereomer. mp 144−146 °C; IR υ 3087, 1754, 1734, 1648 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 8.97 (s, 1H), 7.62−7.39 (m, 5H), 6.18 (dd, J = 5.8, 2.0 Hz, 1H), 6.12 (d, J = 2.9 Hz, 1H), 5.38−5.34 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 171.7 (C), 170.4 (C), 153.3 (CH), 149.1 (CH), 133.1 (C), 129.8 (CH), 128.6 (CH), 127.8 (CH), 127.4 (C), 121.9 (CH), 120.4 (CH), 85.0 (CH), 51.4 (CH), 21.8 (CH_3); HRESMS m/z calcd for $[C_{14}H_{13}N_2O_3]^+$ 257.0926, found 257.0916.

(*R,*R**)-5-(2-Acetyl-1,2-dihydrophthalazin-1-yl)furan-2(5*H*)-one (26).** Following the general procedure using AcCl (66 μL, 0.93 mmol) as the electrophile, phthalazine **25** (100 mg, 0.77 mmol) as the azaheterocycle and **4** (195 μL, 1.16 mmol) as the nucleophile in MeCN (8 mL) afforded compound **26** as an off-white solid (160 mg, 0.63 mmol, 81%) slightly contaminated by 2(5*H*)-furanone. The ^{1}H NMR spectrum showed the presence of two diastereomers (A/B 95:5) that were not separated. mp 170−171 °C; IR υ 3123, 3107, 1744, 1662 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+10%MeOD) (major diastereomer only) δ 7.57 (s, 1H), 7.52−7.36 (m, 3H), 7.31−7.25 (m, 2H), 6.22 (d, J = 3.8 Hz, 1H), 5.91 (dd, J = 5.8, 1.9 Hz, 1H), 5.19 (ddd, J = 3.7, 1.9, 1.7 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + 10% MeOD) (major diastereomer only) δ 172.9 (C), 172.2 (C), 152.0 (CH), 142.3 (CH), 132.0 (CH), 129.4 (CH), 127.44 (CH), 127.40 (C), 126.1 (CH), 124.4 (C), 122.4 (CH), 84.4 (CH), 51.6 (CH), 21.2 (CH_3); HRESMS m/z calcd for $[C_{14}H_{13}N_2O_3]^+$ 257.0926, found 257.0925.

(*R,*R**)-5-(2-Acetyl-9-methyl-2,9-dihydro-1*H*-pyrido[3,4-*b*]-indol-1-yl)furan-2(5*H*)-one (28).** Following the general procedure using AcCl (21 μL, 0.30 mmol) as the electrophile, **27** (50 mg, 0.25 mmol) as the azaheterocycle and **4** (63 μL, 1.16 mmol) as the nucleophile in MeCN (3 mL) afforded compound **28** as an off-white solid (55 mg, 0.18 mmol, 71%). The ^{1}H NMR spectrum showed the presence of only one diastereomer. mp 157−159 °C; IR υ 2937, 1738, 1666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 5.8, 1.6 Hz, 1H), 7.37−7.32 (m, 1H), 7.31−7.24 (m, 1H), 7.21−7.15 (m, 1H), 6.67 (d, J = 4.7 Hz, 1H), 6.52 (d, J = 7.5 Hz, 1H), 6.31 (d, J = 7.6 Hz, 1H), 5.86 (dd, J = 5.8, 1.8 Hz, 1H), 5.19 (ddd, J = 4.9, 1.8, 1.6 Hz, 1H), 3.8 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 169.5 (C), 151.5 (CH), 138.1 (C), 126.8 (C), 122.8 (C), 122.7 (CH), 122.5 (CH), 120.5 (CH), 118.3 (2 CH), 110.0 (CH), 108.5 (C), 106.5 (CH), 82.4 (CH), 50.2 (CH), 30.3 (CH_3), 21.8 (CH_3); HRESMS m/z calcd for $[C_{18}H_{17}N_2O_3]^+$ 309.1239, found 309.1247.

***tert*-Butyl (*R**,*R**)-2-(2-Acetyl-1,2-dihydroisoquinolin-1-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (30).** Following the general procedure using AcCl (66 μL, 0.93 mmol) as the electrophile, isoquinoline **1** (92 μL, 0.77 mmol) as the azaheterocycle and **29** (346 mg, 1.16 mmol) as the nucleophile in MeCN (8 mL) afforded compound **30** as a white solid (260 mg, 0.73 mmol, 95%). The ^{1}H NMR spectrum showed the presence of two diastereomers (A/B 83:17) that were not separated. mp 172−174 °C; IR υ 2980, 2933, 1771, 1739, 1679, 1630, 1396, 1321 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.13 (m, 3H), 7.03 (dd, J = 6.6, 1.9 Hz, 1H), 6.90 (d, J = 7.1 Hz, 0.8H, dia A), 6.82 (d, J = 7.3 Hz, 0.2H, dia B), 6.78 (d, J = 7.9 Hz, 0.8H, dia A), 6.57 (d, J = 5.1 Hz, 0.8H, dia A), 6.52 (dd, J = 8.0, 1.4 Hz, 0.2, dia B), 6.05 (d, J = 5.1 Hz, 0.2H, dia B), 5.99 (d, J = 8.2 Hz, 0.2H, dia B), 5.91 (d, J = 7.9 Hz, 0.8H, dia A), 5.75 (dd, J = 6.2, 1.5 Hz, 0.8H, dia A), 5.70 (d, J = 6.2 Hz, 0.2H, dia B), 4.84 (ddd, J = 5.2, 1.8, 1.8 Hz, 0.8H, dia A), 4.70−4.64 (m, 0.2H, dia B), 2.59 (s, 0.6H, dia B), 2.34 (s, 2.4H, dia A), 1.73 (s, 7.2H, dia A), 1.69 (s, 1.8H, dia B); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer only) δ 169.2 (C), 168.8 (C), 149.1 (C), 144.7 (CH + C), 130.3 (C), 128.8 (CH), 127.8 (CH), 127.6 (2 CH), 125.20 (CH), 125.16 (CH), 124.7 (CH), 110.7 (CH), 83.8 (C), 64.3 (CH), 54.1 (CH), 28.3 (3 CH_3), 21.8 (CH_3; HRESMS m/z calcd for $[C_{20}H_{22}N_2O_4Na]^+$ 377.1477, found 377.1477.

***tert*-Butyl (*R**,*R**)-2-(2-Acetyl-6,7-dimethoxy-1,2-dihydroiso-quinolin-1-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (31).** Following the general procedure using AcCl (45 μL, 0.63 mmol) as the electrophile, **2** (100 mg, 0.53 mmol) as the azaheterocycle and **29** (236 mg, 0.78 mmol) as the nucleophile in MeCN (5 mL) afforded compound **31** as a white solid (210 mg, 0.50 mmol, 96%). The ^{1}H NMR spectrum showed the presence of

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two diastereomers (A/B 83:17) that were not separated. mp 181−183 °C; IR υ 2979, 2938, 1770, 1738, 1671, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, J = 6.5, 2.2 Hz, 0.2H, dia B), 7.10 (dd, J = 6.2, 2.1 Hz, 0.8H, dia A), 6.6 (d, J = 7.8 Hz, 1H), 6.45 (s, 0.2H, dia B), 6.44 (s, 0.8H, dia A), 6.39 (d, J = 5.1 Hz, 1H), 6.29 (s, 0.8H, dia A), 6.23 (s, 0.2H, dia B), 5.85−5.77 (m, 0.2H, dia B), 5.73 (d, J = 7.7 Hz, 0.8H, dia A), 5.65 (dd, J = 6.2, 1.3 Hz, 0.8H, dia A), 5.60 (d, J = 6.3, 0.2H, dia B), 4.72 (ddd, J = 5.1, 1.7, 1.7 Hz, 0.8H, dia A), 4.57−4.52 (m, 0.2H, dia B), 3.75 (s, 3H), 2.46 (s, 0.6H, dia B), 2.22 (s, 2.4H, dia A), 1.63 (s, 7.2H, dia A), 1.57 (s, 1.8 H, dia B); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer only) δ 169.2 (C), 168.9 (C), 149.00 (C), 148.95 (C), 148.1 (C), 144.6 (CH), 127.5 (CH), 123.46 (CH), 123.41 (C), 117.5 (C), 111.2 (CH), 110.5 (CH), 107.8 (CH), 83.6 (C), 64.2 (CH), 56.3 (CH_3), 56.9 (CH_3), 53.7 (CH), 28.2 (3 CH_3), 21.7 (CH_3); HRESMS m/z calcd for $[C_{22}H_{26}N_2O_6Na]^+$ 437.1689, found 437.1690.

***tert*-Butyl (*R**,*R**)-2-(5-Acetyl-5,6-dihydrophenanthridin-6-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (32).** Following the general procedure using AcCl (48 μL, 0.67 mmol) as the electrophile, phenanthridine **3** (100 mg, 0.56 mmol) as the azaheterocycle and **29** (249 mg, 0.84 mmol) as the nucleophile in MeCN (6 mL) afforded compound **32** as a white solid (220 mg, 0.54 mmol, 97%). The ^1H NMR spectrum showed the presence of only one diastereomer. mp 156−158 °C; IR υ 2982, 1772, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82−7.72 (m, 2H), 7.46−7.24 (m, 5H), 7.08 (d, J = 7.3 Hz, 1H), 6.67 (bs, 1H), 6.13 (dd, J = 6.2, 2.3 Hz, 1H), 5.56 (d, J = 6.2 Hz, 1H), 4.91−4.79 (m, 1H), 2.32 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C), 168.6 (C), 149.1 (C), 145.0 (CH), 136.0 (C), 131.0 (CH), 129.0 (CH), 128.7 (C), 128.5 (CH), 128.3 (CH), 128.1 (C), 127.2 (CH), 126.7 (CH), 125.1 (C), 124.6 (CH), 123.1 (2 CH), 83.9 (C), 65.3 (CH), 54.6 (CH), 28.2 (3 CH_3), 22.9 (CH_3); HRESMS m/z calcd for $[C_{24}H_{24}N_2O_4Na]^+$ 427.1634, found 427.1627.

***tert*-Butyl 2-(1-Acetyl-4-methyl-1,2-dihydroisoquinolin-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (33).** Following the general procedure using AcCl (66 μL, 0.93 mmol) as the electrophile, lepidine **21** (102 μL, 0.77 mmol) as the azaheterocycle and **29** (343 mg, 1.16 mmol) as the nucleophile in MeCN (8 mL) afforded compound **33** as two separable diastereomers. The major diastereomer (200 mg, 0.54 mmol, 71%) was isolated as a white amorphous solid slightly contaminated by *N*-Boc-pyrrolidinone (<10% by ^1H NMR). IR υ 3071, 2979, 2931, 1777, 1664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.09 (m, 4H), 6.34 (dd, J = 6.2, 2.2 Hz, 1H), 6.03 (bs, 1H), 5.71 (dd, J = 6.2, 1.5 Hz, 1H), 5.53 (dd, J = 6.1, 1.1 Hz, 1H), 4.66 (ddd, J = 5.8, 1.9, 1.8 Hz, 1H), 2.23 (s, 3H), 1.96 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 169.2 (C), 149.1 (C), 145.2 (CH), 135.6 (C), 133.6 (C), 129.0 (C), 128.0 (CH), 127.3 (CH), 125.8 (CH), 124.1 (CH), 123.6 (CH), 120.2 (CH), 83.6 (C), 64.7 (CH), 51.7 (CH), 28.2 (3 CH_3), 22.9 (CH_3), 18.2 (CH_3); HRESMS m/z calcd for $[C_{21}H_{25}N_2O_4]^+$ 369.1814, found 369.1804. The minor diastereomer was isolated as an off-white amorphous solid (50 mg, 0.14 mmol, 18%). IR υ 2979, 2929, 1774, 1733, 1665 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 7.38−7.31 (m, 1H), 7.26−7.17 (m, 2H), 6.97−6.83 (m, 1H), 6.34 (dd, J = 6.1, 2.2 Hz, 1H), 6.30−6.16 (m, 1H), 5.97 (dd, J = 6.1, 1.6 Hz, 1H), 5.65 (dd, J = 6.1, 1.9 Hz, 1H), 4.64 (ddd, J = 2.9, 2.1, 1.9 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, CD_3CN) δ 170.5 (C), 168.1 (C), 148.6 (C), 146.4 (CH), 135.9 (C), 132.9 (C), 128.7 (C), 127.4 (CH), 125.9 (CH), 125.2 (CH), 125.0 (CH), 123.3 (CH), 122.4 (CH), 81.8 (C), 64.9 (CH), 50.2 (CH), 27.0 (3 CH_3), 21.6 (CH_3), 17.0 (CH_3); HRESMS m/z calcd for $[C_{21}H_{24}N_2O_4Na]^+$ 391.1634, found 391.1648.

***tert*-Butyl (*R**,*R**)-2-(3-Acetyl-3,4-dihydroquinazolin-4-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (34).** Following the general procedure using AcCl (66 μL, 0.92 mmol) as the electrophile, quinazoline **23** (100 mg, 0.77 mmol) as the azaheterocycle and **29** (343 mg, 1.15 mmol) as the nucleophile in MeCN (8 mL) afforded compound **34** as a white solid (130 mg, 0.37 mmol, 48%). The ^1H NMR spectrum showed the presence of two diastereomers (A/B 95:5) that were not separated. mp 180−182 °C; IR υ 3089, 2987, 2935, 1765, 1694, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer only) δ 8.06 (bs, 1H), 7.36−7.15 (m, 3H), 7.01 (dd, J = 6.2, 2.0 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.28 (bs, 1H), 5.82 (dd, J = 6.2, 1.5 Hz, 1H), 4.85−4.78 (m, 1H), 2.50 (s, 3H), 1.70 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer only) δ 169.1 (C), 168.5 (C), 149.2 (C), 143.9 (CH), 141.7 (CH), 139.5 (C), 129.8 (CH), 129.4 (CH), 127.7 (CH), 127.1 (CH), 125.9 (CH), 119.3 (C), 84.1 (C), 64.0 (CH), 52.0 (CH), 28.3 (3 CH_3), 22.0 (CH_3); HRESMS m/z calcd for $[C_{19}H_{22}N_3O_4]^+$ 356.1610, found 356.1616.

***tert*-Butyl (*R**,*R**)-2-(2-Acetyl-1,2-dihydrophthalazin-1-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (35).** Following the general procedure using AcCl (66 μL, 0.92 mmol) as the electrophile, phthalazine **25** (100 mg, 0.77 mmol) as the azaheterocycle and **29** (343 mg, 1.15 mmol) as the nucleophile in MeCN (8 mL) afforded compound **35** as a white solid (260 mg, 0.73 mmol, 95%). The ^1H NMR spectrum showed the presence of two diastereomers (A/B 95:5) that were not separated. mp 156−158 °C; IR υ 2981, 2925, 1743, 1708, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer only) δ 7.55 (s, 1H), 7.48−7.33 (m, 2H), 7.26−7.20 (m, 1H), 7.00−6.90 (m, 2H), 6.69 (d, J = 5.3 Hz, 1H), 5.77 (dd, J = 6.3, 165 Hz, 1H), 4.96 (ddd, J = 5.3, 1.9, 1.6 Hz, 1H), 2.45 (s, 3H), 1.74 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer only) δ 172.4 (C), 168.9 (C), 148.9 (C), 145.0 (CH), 141.9 (CH), 131.8 (CH), 129.4 (CH), 128.4 (CH), 127.6 (CH), 125.9 (C), 125.7 (CH), 124.2 (C), 84.0 (C), 63.5 (CH), 51.4 (CH), 28.3 (3 CH_3), 21.4 (CH_3); HRESMS m/z calcd for $[C_{19}H_{21}N_3O_4Na]^+$ 378.1430, found 378.1446.

***tert*-Butyl (5′*R**,1*S**)-2-(2-Acetyl-9-methyl-2,9-dihydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (36).** Following the general procedure using AcCl (23 μL, 0.33 mmol) as the electrophile, **27** (50 mg, 0.27 mmol) as the azaheterocycle and **29** (122 mg, 0.41 mmol) as the nucleophile in MeCN (3 mL) afforded compound **36** as a white solid (60 mg, 0.15 mmol, 54%) contaminated by *N*-Boc-pyrrolidinone (<10% by ^1H NMR) (attempted further purification only led to degradation). The ^1H NMR spectrum showed the presence of only one diastereomer. IR υ 2980, 2933, 1771, 1732, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.33 (dd, J = 6.9, 1.1 Hz, 1H), 7.27−7.22 (m, 1H), 7.14 (d, J = 2.6 Hz, 1H), 6.93 (dd, J = 6.1, 1.7 Hz, 1H), 6.27 (s, 2H), 6.05 (dd, J = 6.2, 1.7 Hz, 1H), 4.71−4.65 (m, 1H), 3.98 (s, 3H), 2.19 (s, 3H), 1.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 167.9 (C), 149.9 (C), 146.0 (CH), 137.9 (C), 129.3 (C), 128.0 (C), 127.8 (CH), 123.1 (C), 122.5 (CH), 120.9 (CH), 120.6 (CH), 118.5 (CH), 109.8 (CH), 105.7 (CH), 83.6 (C), 66.1 (CH), 48.3 (CH), 30.1 (CH_3), 28.3 (3 CH_3), 21.9 (CH_3); HRESMS m/z calcd for $[C_{23}H_{25}N_3O_4Na]^+$ 430.1743, found 430.1755.

(3a*R,4*S**,12b*R**,12c*R**)-4-Ethyl-3a,4,12b,12c-tetrahydro-2*H*-furo[2′,3′:3,4]pyrido[2,1-*a*]isoquinoline-2,5(3*H*)dione (37).** Under argon, *n*-BuLi (1.6 M, 950 μL, 1.52 mmol) was added dropwise to a solution of **7** (500 mg, 1.38 mmol) in THF (69 mL) at −78 °C (dry ice/acetone). The reaction was quenched by the addition of a small amount of saturated aqueous NH_4Cl, and the solvents were evaporated under reduced pressure. Chromatography of the residue on a silica gel cartridge (heptane/AcOEt 90/10−40/60) afforded compound **37** as a white solid (275 mg, 0.97 mmol, 70%). This compound was identical to that prepared by the zinc route.[14]

Methyl (3a*R,12b*R**,12c*R**)-2,5-Dioxo-3,3a,4,5,12b,12c-hexahydro-2*H*-furo[2′,3′:3,4]pyrido[1,2-*c*]isoquinoline-4-carboxylate (38).** MeONa (517 mg, 9.57 mmol) was added to a solution of **6** (1.00 g, 3.19 mmol) in DCM (160 mL). The solution was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM. The pooled organic layers were dried over $MgSO_4$ and evaporated. Chromatography on a silica cartridge (heptane/AcOEt) afforded compound **38** as an off-white amorphous solid after trituration in $CDCl_3$ (870 mg, 2.78 mmol, 87%) and as a mixture of 2 diastereomers (A/B 80:20)

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that were not separated. IR υ 2952, 2917, 1776, 1736, 1652 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.43−7.04 (m, 5H), 5.82−5.73 (m, 1H), 5.64 (d, J = 1.7 Hz, 0.8H, dia A), 5.49 (dd, J = 8.6, 1.7 Hz, 0.2H, dia B), 5.41 (dd, J = 9.2. 2.1 Hz, 0.8H, dia A), 5.25 (d, J = 1.7 Hz, 0.2H, dia B), 4.02 (d, J = 4.8 Hz, 0.8H, dia A), 3.99−3.96 (m, 0.2H, dia B), 3.75 (s, 0.6H, dia B), 3.74 (s, 2.4H, dia A), 3.68−3.60 (m, 0.2H, dia B), 3.50 (dddd, J = 11.2, 9.2, 6.4, 4.8 Hz, 0.8H, dia A), 3.12 (dd, J = 18.8, 11.5 Hz, 0.2H, dia B), 2.94 (dd, J = 19.4, 11.2 Hz, 0.8H, dia A), 2.30 (dd, J = 19.3, 6.4 Hz, 0.8H, dia A), 2.24 (dd, J = 18.8, 5.0 Hz, 0.2H, dia B); ^{13}C NMR (75 MHz, DMSO) δ 175.2 (C), 168.4 (C), 165.3 (C), 129.7 (C), 128.9 (C, dia A), 128.7 (C, dia B), 128.1 (CH, dia B), 128.0 (CH, dia A), 127.37 (CH, dia A), 127.33 (CH, dia B), 126.0 (CH, dia B), 125.8 (CH, dia A), 125.7 (CH), 121.6 (CH, dia B), 121.1 (CH, dia A), 106.6 (CH, dia B), 106.4 (CH, dia A), 82.6 (CH, dia A), 81.7 (CH, dia B), 56.8 (CH, dia A), 56.1 (CH, dia B), 53.2 (CH_3, dia B), 53.0 (CH, dia B), 52.1 (CH_3, dia A), 49.2 (CH, dia A), 31.0 (CH, dia B), 30.7 (CH, dia A), 30.4 (CH, dia A), 30.3 (CH, dia B); HRESMS m/z calcd for $[C_{17}H_{16}NO_5]^+$ 314.1028, found 314.1021.

Methyl (3a*R,12b*R**,12c*R**)-10,11-Dimethoxy-2,5-dioxo-3,3a,4,5,12b,12c-hexahydro-2*H*-furo[2′,3′:3,4]pyrido[2,1-*a*]-isoquinoline-4-carboxylate (39).** MeONa (143 mg, 2.6 mmol) was added to a solution of **9** (194 mg, 0.52 mmol) in DCM (28 mL). The solution was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM. The pooled organic layers were dried over $MgSO_4$ and evaporated. Chromatography of the residue on a silica gel cartridge (heptane/AcOEt) afforded compound **39** as an off-white amorphous solid (154 mg, 0.41 mmol, 78%) and as a mixture of two diastereomers (A/B 75:25) that were not separated. IR υ 2928, 1774, 1672, 1522 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + 10% MeOD) δ 7.09 (d, J = 8.2 Hz, 0.25H, dia B), 7.05 (d, J = 8.2 Hz, 0.75H, dia A), 6.59 (s, 0.75H, dia A), 6.57 (s, 0.25H, dia B), 6.50 (s, 0.75H, dia A), 6.47 (s, 0.25H, dia B), 5.60 (d, J = 8.2 Hz, 0.75H, dia A), 5.59 (d, J = 8.2 Hz, 0.25H, dia B), 5.30 (dd, J = 9.0, 2.2 Hz, 0.25H, dia B), 5.23 (dd, J = 9.1, 2.4 Hz, 0.75H, dia A), 5.19−5.16 (m, 0.75H, dia A), 5.06−5.01 (m, 0.25H, dia B), 3.82−3.75 (m, 9H), 3.74−3.60 (m, 1H), 3.43−3.28 (m, 1H), 2.98−2.84 (m, 1H), 2.64−2.52 (m, 0.75H, dia A), 2.33−2.23 (m, 0.25H, dia B); ^{13}C NMR (75 MHz, $CDCl_3$ + 10% MeOD) δ 174.9 (C), 174.3 (C), 167.9 (C), 149.1 (C), 148.6 (C), 123.3 (C), 122.9 (C), 119.3 (CH, dia B), 119.2 (CH, dia A), 109.7 (CH, dia A), 109.5 (CH, dia B), 108.8 (CH, dia B), 108.7 (CH, dia A), 107.9 (CH, dia B), 107.7 (CH, dia A), 81.4 (CH, dia A), 81.3 (CH, dia B), 57.9 (CH, dia A), 56.8 (CH, dia B), 56.2 (CH_3), 55.9 (CH_3); 53.6 (CH), 52.8 (CH_3), 30.9 (CH_2), 30.7 (CH_3); HRESMS m/z calcd for $[C_{19}H_{20}NO_7]^+$ 374.1240, found 374.1227.

(3a*S,12b*R**,12c*R**)-3a,4,12b,12c-Tetrahydro-2*H*-furo-[2′,3′:3,4]pyrido[2,1-*a*]isoquinoline-2,5(3*H*)-dione (40).** NaCl (140 mg, 2.39 mmol) was added to a solution of **38** (500 mg, 1.60 mmol) in DMSO (4 mL) and water (90 μL). The solution was heated to 150 °C for 1 h. The solution was poured into water and extracted with AcOEt. The organic layers were dried over $MgSO_4$ and evaporated. Purification of the residue on a silica gel cartridge (AcOEt/MeOH 10/0−9/1) afforded compound **40** as a light brown solid (245 mg, 0.96 mmol, 60%). The ^1H NMR spectrum showed the presence of only one diastereomer. mp 214−216 °C; IR υ 1774, 1674, 1650, 1407 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (m, 1H), 7.26−7.18 (m, 2H), 7.15 (d, J = 8.2 Hz, 1H), 7.11−7.03 (m, 1H), 5.68 (d, J = 8.2 Hz, 1H), 5.51 (s, 1H), 5.37 (dd, J = 8.8, 1.8 Hz, 1H), 3.22 (dddd, J = 11.3, 8.8, 6.7, 4.5 Hz, 1H), 2.96 (dd, J = 18.8, 11.3, Hz, 1H), 2.72 (dd, J = 15.1, 6.7 Hz, 1H), 2.39 (dd, J = 15.1, 1.8 Hz, 1H), 2.04 (dd, J = 18.8, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0 (C), 168.7 (C), 130.5 (C), 129.9 (C), 128.4 (CH), 127.6 (CH), 126.2 (CH), 126.0 (CH), 122.2 (CH), 105.7 (CH), 83.8 (CH), 57.2 (CH), 36.6 (CH_2), 33.8 (CH), 28.4 (CH); HRESMS m/z calcd for $[C_{15}H_{13}NO_3Na]^+$ 278.0793, found 278.0804.

(3a*S,12b*R**,12c*R**)-10,11-Dimethoxy-3a,4,12b,12c-tetrahydro-2*H*-furo[2′,3′:3,4]pyrido[2,1-*a*]isoquinoline-2,5(3*H*)-dione (41).** NaCl (146 mg, 2.50 mmol) was added to a solution of **39** (850 mg, 2.27 mmol) in DMSO (5 mL) and water (130 μL). The solution was heated at 160 °C for 1.5 h. The solution was poured into water and extracted with AcOEt. The organic layers were dried over $MgSO_4$ and evaporated. Purification of the residue on a silica gel cartridge (AcOEt/MeOH 10/0−9/1) afforded compound **41** as a light brown solid (360 mg, 1.42 mmol, 50%). The ^1H NMR spectrum showed the presence of only one diastereomer. mp 206−208 °C; IR υ 2973, 1772, 1675, 1651 cm^{-1}; ^1H NMR (300 MHz, acetone−d_6) δ 7.15 (d, J = 8.1 Hz, 1H), 7.04 (s, 1H), 6.72 (s, 1H), 5.62 (d, J = 8.1 Hz, 1H), 5.53 (dd, J = 8.9, 1.7 Hz, 1H), 5.50−5.46 (m, 1H), 3.83 (s, 6H), 3.47−3.33 (m, 1H), 2.97 (dd, J = 18.8, 11.4 Hz, 1H), 2.76 (dd, J = 15.2, 6.7 Hz, 1H), 2.50 (dd, J = 15.2, 1.8 Hz, 1H), 2.16 (dd, J = 18.8, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 176.0 (C), 168.5 (C), 148.6 (C), 148.32 (C), 123.4 (C), 121.9 (C), 120.4 (CH), 110.3 (CH), 109.8 (CH), 105.8 (CH), 83.4 (CH), 57.1 (CH), 56.2 (CH_3), 56.0 (CH_3), 36.7 (CH_2), 33.9 (CH_2), 28.3 (CH); HRESMS m/z calcd for $[C_{17}H_{17}NO_5Na]^+$ 338.1004, found 338.1014.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR and ^{13}C NMR spectra of all new compounds and precursors. X-ray crystal data and structures of compounds **11**, **19**, **26**, **31**, **32**. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

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