HETEROCYCLES, Vol. 84, No. 2, 2012, pp. 1089 - 1112. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 1st August, 2011, Accepted, 6th September, 2011, Published online, 15th September, 2011
DOI: 10.3987/COM-11-S(P)92

APPLICATIONS OF MULTICOMPONENT ASSEMBLY PROCESSES TO THE FACILE SYNTHESES OF DIVERSELY FUNCTIONALIZED NITROGEN HETEROCYCLES‡

James R. Donald, Brett A. Granger, Simon Hardy, James J. Sahn, and Stephen F. Martin*

Department of Chemistry and Biochemistry and Texas Institute for Drug and Diagnostics Development, The University of Texas at Austin, Austin, Texas 78712, United States; E-mail: sfmartin@mail.utexas.edu

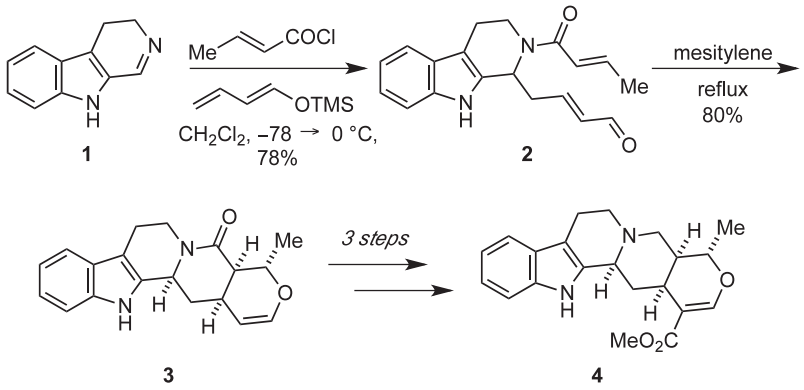
Abstract – Several multicomponent assembly processes have been developed for the synthesis of intermediates that may be elaborated by a variety of cyclizations to generate a diverse array of highly functionalized heterocycles from readily-available starting materials. The overall approach enables the efficient preparation of libraries of small molecules derived from fused, privileged scaffolds.

INTRODUCTION

One of the first challenges in drug discovery programs is identifying small molecules that exhibit activity in biological screening assays that are relevant to treating human health disorders. Once such compounds are identified, they are structurally modified toward optimizing important parameters such as potency, specificity, toxicity, and bioavailability. This approach has also proven to be effective for the development of small molecule probes that can be used for functional and mechanistic studies of biological systems. In this context, the preparation of collections of compounds containing privileged structures, which are molecular scaffolds possessing a recognized ability to elicit biological activity across a range of targets,[1,2] has proven to be a successful paradigm for identifying small molecules with useful pharmacological profiles. When contemplating new strategies for preparing novel compound libraries, it is thus important to develop efficient approaches that enable access to functionalized heterocyclic frameworks that incorporate privileged scaffolds and may be readily diversified.

‡This paper is dedicated to my longtime friend Al Padwa, a true innovator in developing novel entries to diverse classes of heterocyclic compounds, on the occasion of his 75th birthday.

During work directed toward the total synthesis of the complex indole alkaloid (±)-tetrahydroalstonine (**4**), we invented a powerful Mannich-type multicomponent assembly process (MCAP) to generate **2**, which underwent a hetero-Diels-Alder cycloaddition to deliver the pentacyclic core **3** that was then elaborated into the natural product *via* a remarkably short sequence of reactions (Scheme 1).[3] The discovery of this facile method for constructing **2** laid the foundation for the development of the vinylogous Mannich reaction, which has proven an effective construct for alkaloid synthesis.[4] We also realized that related MCAPs could be used as key steps to prepare other alkaloid natural products and applied this strategy to the concise syntheses of (±)-pseudotabersonine (**5**)[5] and (±)-roelactamine (**6**) (Figure 1).[6a]



Scheme 1

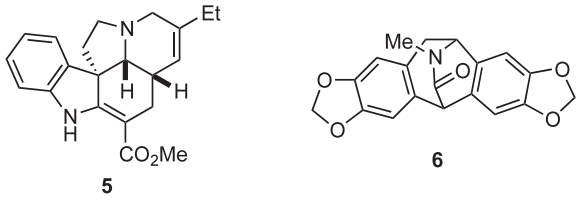
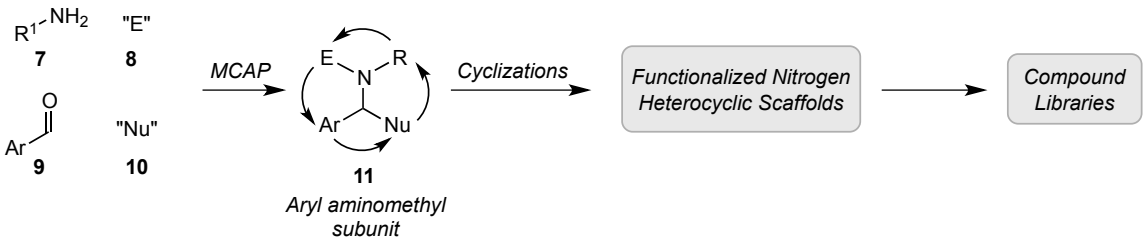


Figure 1

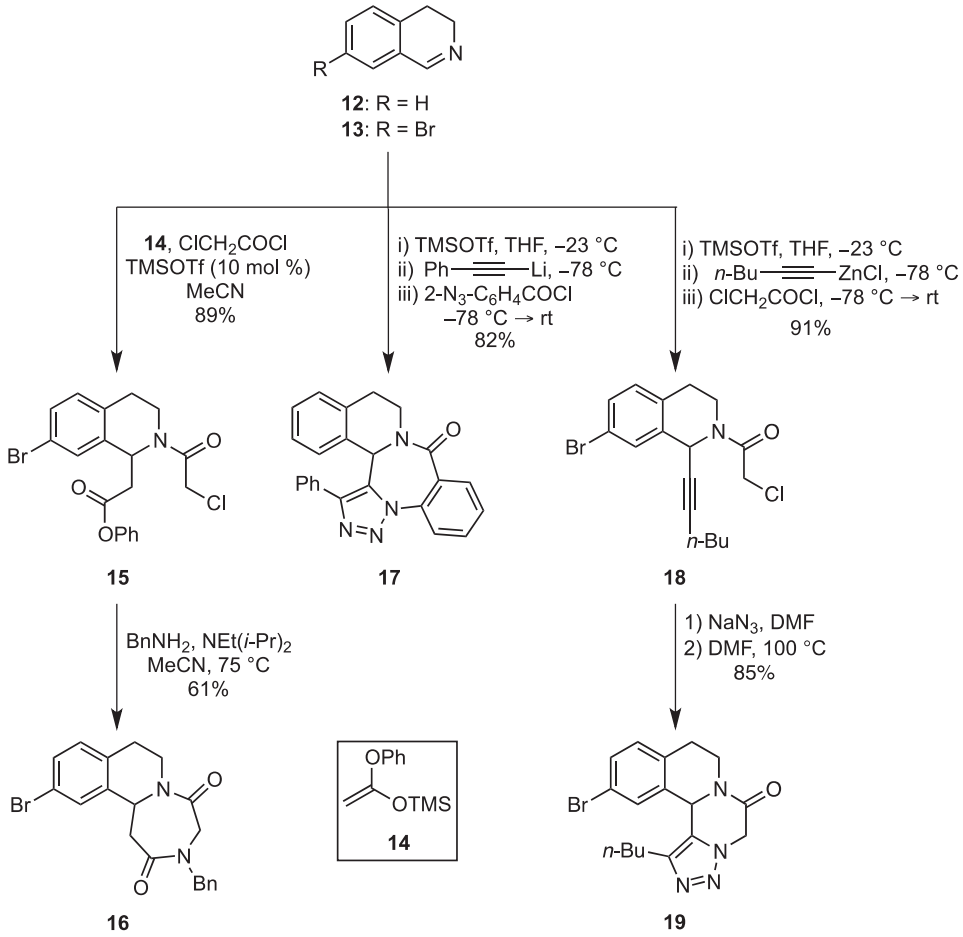
Beyond the obvious application to the synthesis of alkaloids, it was apparent that we could implement such MCAPs as key steps in the assembly of intermediates that could be quickly elaborated into scaffolds of medicinal relevance *via* cyclizations preprogrammed by the functionality resident in the inputs **7**–**10** (Scheme 2).[6] In general terms, our methodology allows rapid access to a diverse array of compounds comprising an aryl aminomethyl subunit **11**, a structural motif common to a range of biologically active compounds, including those containing heterocyclic privileged structures. We herein report the details of some recent applications of this approach to the diversity oriented synthesis (DOS) of skeletally distinct, unnatural products containing fused tetrahydroisoquinolines, benzodiazepines, 2-aryl piperidines, norbenzomorphans, and isoindolinones.[7]



Scheme 2

RESULTS AND DISCUSSION

The tetrahydroisoquinoline ring system, which possesses a constrained aryl aminomethyl subunit, is present in a variety of complex natural products and pharmaceuticals that exhibit a wide range of biological properties, including antihypertensive,[8] anticancer,[9] and antimalarial[10] activities. Starting with dihydroisoquinoline (**12**) or the readily-available 7-bromodihyroisoquinoline (**13**)[11] as a preformed imine input in our MCAPs, we developed several novel MCAP/cyclization sequences to access a diverse array of unique heterocyclic ring systems incorporating the tetrahydroisoquinoline core (Scheme 3). Accordingly, treatment of imine **13** with silyl ketene acetal **14**[12] and chloroacetyl chloride in the presence of a catalytic amount of TMSOTf provided the phenyl ester **15** in 89% yield *via* a Mannich-type process.

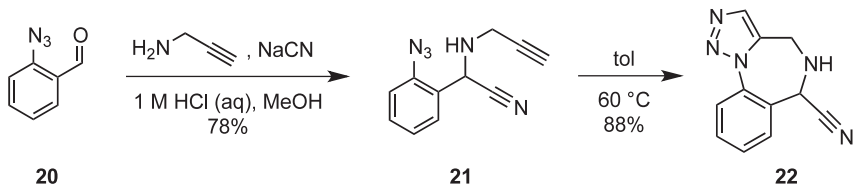


Scheme 3

Subsequent heating of **15** with benzylamine and Hünig's base furnished the fused tricycle **16** in 61% yield. The phenyl ester moiety resident in **15** was necessary to facilitate a one-pot displacement/cyclization process, as the corresponding methyl ester required more forcing conditions for lactam formation, which led to lower yields. In an interesting variant of this Mannich-type process, activation of **12** with TMSOTf,[13] followed by addition of lithium phenylacetylide and *N*-acylation with *o*-azidobenzoyl chloride[14] gave an intermediate amide that underwent a facile Huisgen cycloaddition to form the 1,2,3-triazole-fused 1,5-benzodiazepine-2-one **17** in one-pot and in 82% yield.

Compounds containing a piperazinone ring fused to a tetrahydroisoquinoline, as in **19**, exhibit potent anthelmintic activity.[15] We envisioned an MCAP that would allow the facile synthesis of triazolo piperazinone derivatives of these compounds (Scheme 3). Activation of **13** with TMSOTf, followed by addition of 1-hexynylzinc chloride gave an intermediate *N*-silyl amine that underwent reaction with chloroacetyl chloride to provide amide **18** in 91% yield. Subsequent displacement of the chloride ion with azide ion, followed by dipolar cycloaddition provided the novel triazolo piperazinone **19** in a two-step process.[16]

Aryl aminomethyl subunits bearing an α-aminonitrile moiety are synthetically versatile intermediates that we envisioned might be exploited for the construction of a number of fused heterocyclic ring systems.[17] α-Aminonitriles can be readily accessed *via* the venerable Strecker reaction,[18] wherein an intermediate imine or iminium ion that is formed upon condensation of a carbonyl input and an amine is trapped with cyanide ion. Following our sequential MCAP/cyclization strategy,[5,6] the Strecker reaction was employed to assemble α-aminonitrile **21** from known benzaldehyde **20**.[19] Heating **21** resulted in a facile intramolecular Huisgen cycloaddition to afford the triazolo benzodiazepine scaffold **22** (Scheme 4). It was essential to perform this cycloaddition at low concentration and to maintain the temperature below 60 °C in order to avoid the deleterious elimination of HCN from compound **22**. It is noteworthy that benzodiazepines are the archetypal privileged structures,[1,2] and compounds containing 1,2,3-triazolo-1,4-benzodiazepines are known to bind to the benzodiazepine receptor.[20]

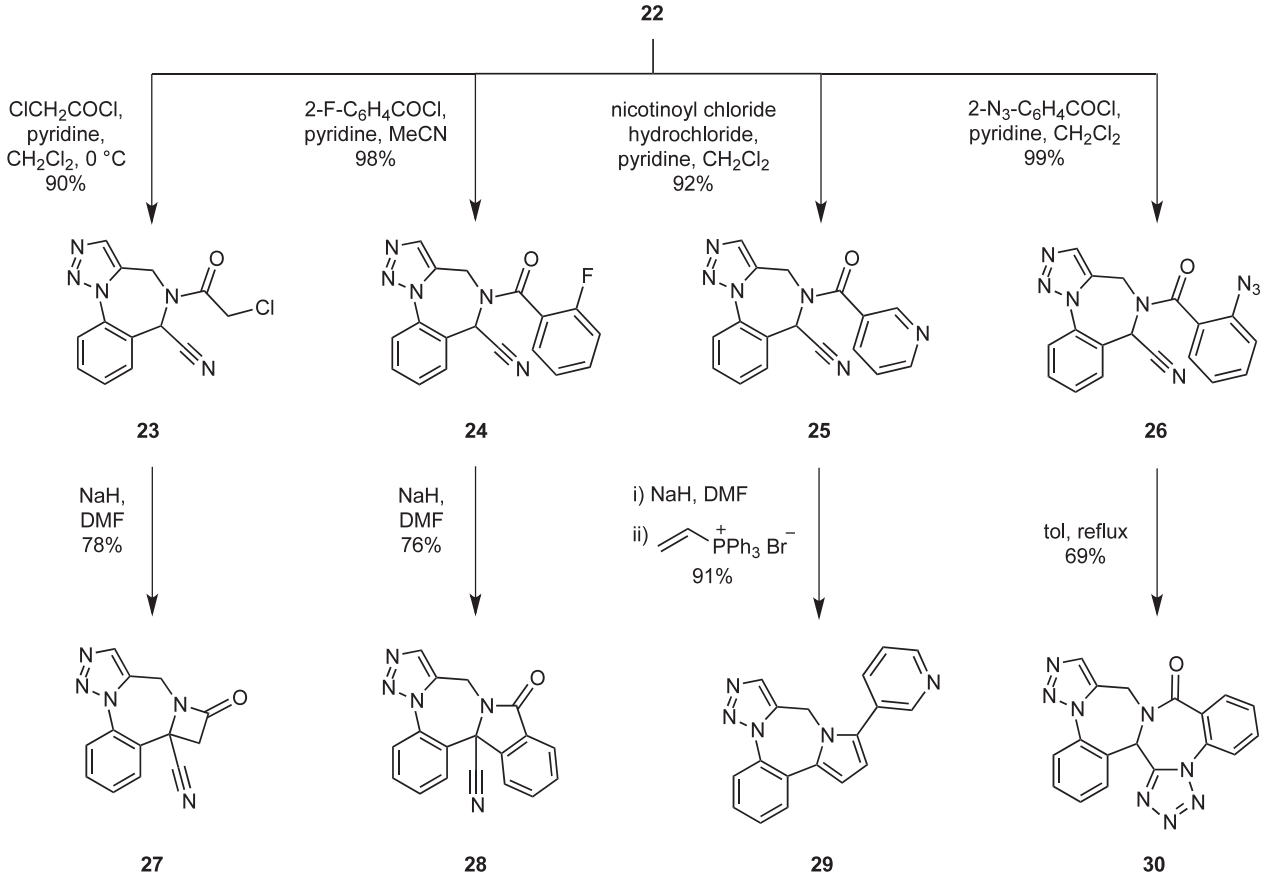


20 21 22

Scheme 4

The α-aryl, α-aminonitrile subunit embedded within **22** was then exploited as a functional handle to access a variety of novel heterocyclic systems incorporating a benzodiazepine ring. To this end, the secondary amine **22** was first acylated with several different acid chlorides to furnish the amides **23**-**26** in

high yields (Scheme 5). Deprotonation of chloroacetamide **23** at the acidic nitrile α-position, followed by the intramolecular displacement of chloride ion afforded the β-lactam **27** in 78% yield. The β-lactam substructure is prevalent within pharmaceutical agents and other biologically important molecules that elicit a diverse range of activities.[21] Treatment of *o*-fluorobenzamide **24** with NaH effected an unprecedented cyclization involving a nucleophilic aromatic substitution by the nitrile anion to form the fused isoindolinone **28** in 76% yield. This sequence represents a novel approach to isoindolinones, which are themselves privileged structures.[22] Indeed, 1,4-benzodiazepine fused isoindolinones are of medicinal interest as potassium channel antagonists.[23]



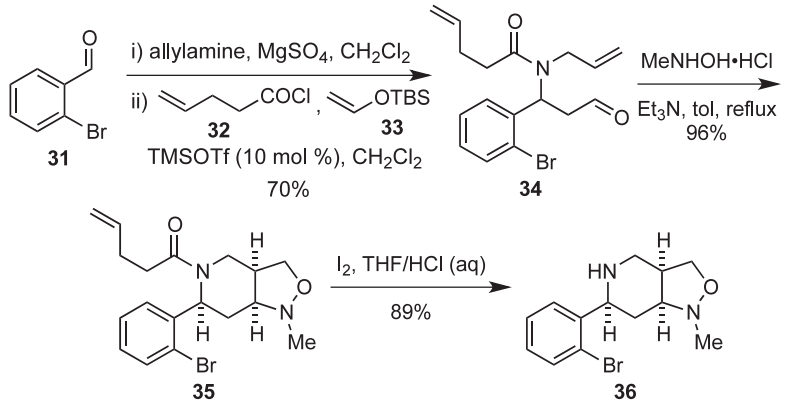
Scheme 5

Inspired by the work of McEwen and Cooney,[24] the anion derived from amide **25** was allowed to react with vinyltriphenylphosphonium bromide (Schweizer's reagent) to produce the pyrrolo benzodiazepine **29** in 91% yield. This transformation capitalizes on both the acidity of the proton adjacent to the nitrile group and the stability of cyanide ion as a leaving group. Notably, this reaction represents the first example of pyrrole formation from a heteroaromatic-substituted amide, further extending the scope of the original report. The Wittig reaction and aromatization steps were complete within ninety minutes at ambient temperature, a stark contrast to the extended reaction times and high temperatures originally

reported for acyclic systems.[24] Some pyrrolo-1,4-benzodiazepines have been identified as HIV-1 reverse transcriptase inhibitors.[25]

The nitrile functionality offers additional possibilities for diversification as a dipolarophile. For example, *o*-azidobenzamide **26** underwent an intramolecular dipolar cycloaddition upon heating to afford hexacycle **30**, the structure of which incorporates two azole fused benzodiazepine units. Garanti and co-workers reported a similar approach to tetrazole fused 1,4-benzodiazepines,[26] structures which are known benzodiazepine receptor binders.[27]

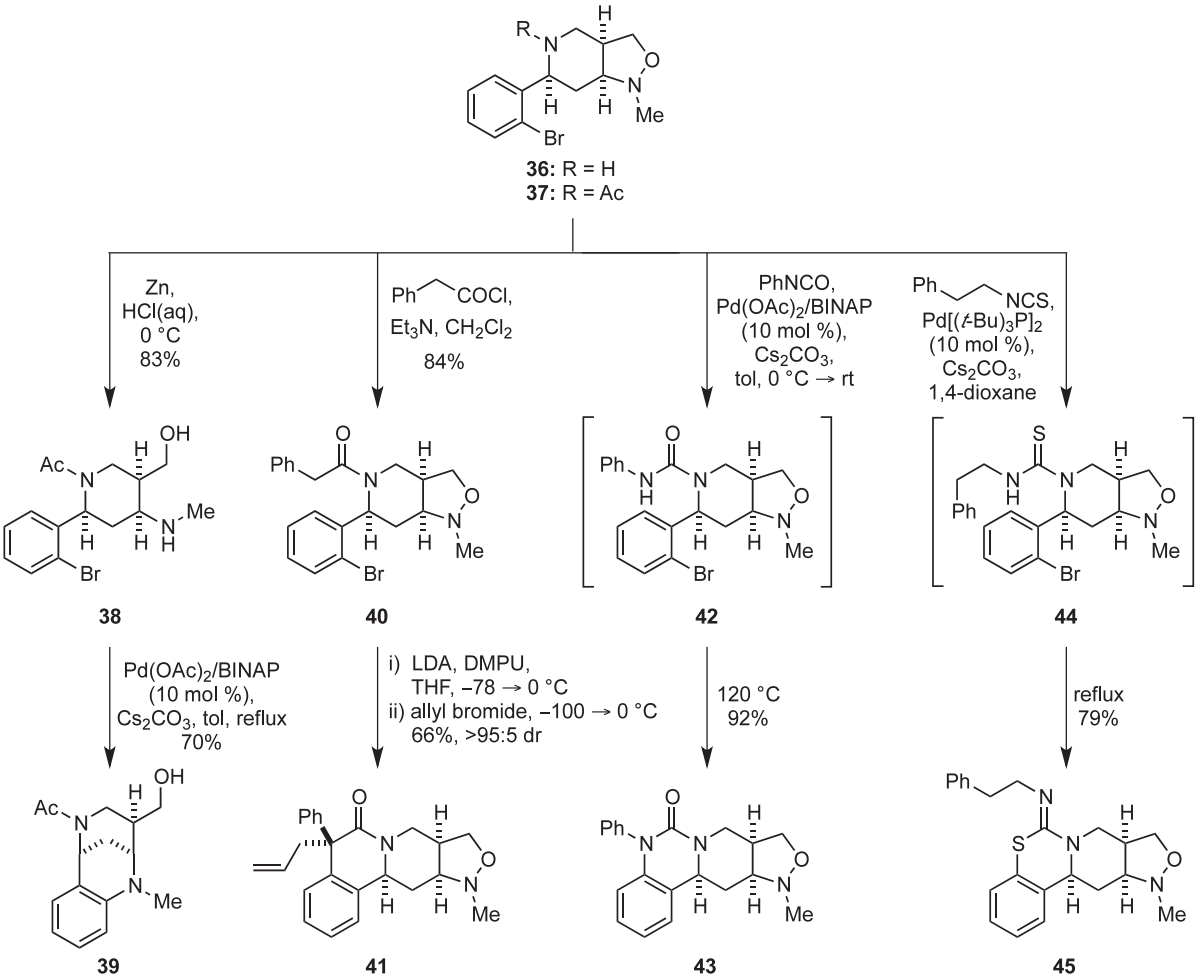
2-Aryl-substituted piperidines are found in a number of biologically active molecules.[2a,28] Compounds containing this heterocyclic scaffold can be rapidly obtained through an MCAP/cyclization sequence to provide 2-arylpiperidines that are well suited to subsequent diversification reactions. When the imine formed upon condensation of allylamine and 2-bromobenzaldehyde (**31**) was treated with 4-pentenoyl chloride (**32**) and vinyl ether **33** in the presence of catalytic amounts of TMSOTf, the β-amido aldehyde **34** was obtained in 70% yield (Scheme 6). Aldehyde **34** then underwent a facile condensation and intramolecular nitrone cycloaddition upon heating with *N*-methylhydroxylamine to furnish the *cis*-fused octahydroisoxazolo[4,3-*c*]pyridine **35** in excellent yield as a single diastereomer. The 4-pentenoyl unit, which both activated the imine toward nucleophilic addition and masked the amino group, was readily cleaved with iodine in a mixture of THF and aqueous HCl to give the secondary amine **36**.[29]



Scheme 6

We then explored several methods by which the 2-bromophenyl substituent could be used in subsequent transformations to give novel heterocyclic scaffolds (Scheme 7). When **37**, which was formed in an analogous fashion to **35**,[6a] was treated with zinc in aqueous HCl at 0 °C, the *N–O* bond was cleaved to afford the amino alcohol **38**. Palladium-catalyzed, intramolecular *N*-arylation furnished the tetrahydroquinoline **39** in 70% yield; this represents a novel entry to this tricyclic scaffold. The combined presence of the piperidine nitrogen atom and the pendant 2-bromophenyl substituent in **36** presented a number of interesting opportunities for ring forming reactions that provided access to some unique, tetracyclic scaffolds. For example, the phenylacetamide **40**, which was obtained by acylation of **36**,

underwent tandem enolate arylation/allylation to give the 4,4-disubstituted dihydroisoquinolin-3-one **41** with high diastereoselectivity (>95:5) upon reaction with excess LDA in the presence of DMPU followed by the addition of allyl bromide.[30] We previously reported an analogous reaction using methyl iodide as the alkylating agent, which proceeded with similar selectivity to give predominantly one diastereomer, for which the relative stereochemistry was determined by X-ray crystallography.[7c] Presumably, in both cases the high degree of diastereoselectivity arises as a result of the preferential approach of the alkylating agent to the more sterically accessible convex face of the intermediate enolate. Protonation of the intermediate enolate was also highly diastereoselective, but the product underwent facile epimerization to afford a 2:1 mixture of diastereomers.

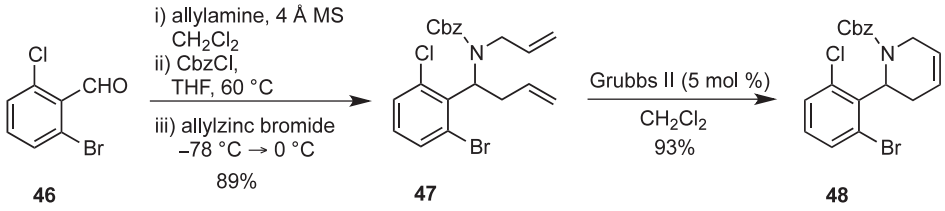


Scheme 7

The free secondary amino group in **36** was also utilized to enable one-pot syntheses of several fused heterocyclic ring systems. For example, treatment of **36** with phenylisocyanate provided an intermediate urea, which underwent a palladium-catalyzed *N*-arylation in the presence of palladium acetate and BINAP to deliver the dihydroquinazolin-2-one **43**. Ferraccioli and co-workers described a similar transformation that was reported to be general for (2-bromophenyl)methylamines.[31] However,

considerable optimization of the catalyst system was required in our hands, and we found that it was essential to ensure complete formation of the intermediate urea **42** *before* heating. Failure to do so resulted in incomplete cyclization, a phenomenon we attributed to catalyst poisoning by unreacted **36** at elevated temperatures. We also developed a related palladium-catalyzed cyclization of thioureas as illustrated by the initial conversion of **36** into **44** by reaction with phenethyl isothiocyanate, followed by an intramolecular *S*-arylation to furnish the 2-imino-1,3-benzothiazinane **45**.[32] This one-pot process for generating and cyclizing thioureas tethered to aryl bromides is an unprecedented tandem process that required the use of $Pd[(t\text{-}Bu)_3P]_2$ to achieve high conversion.

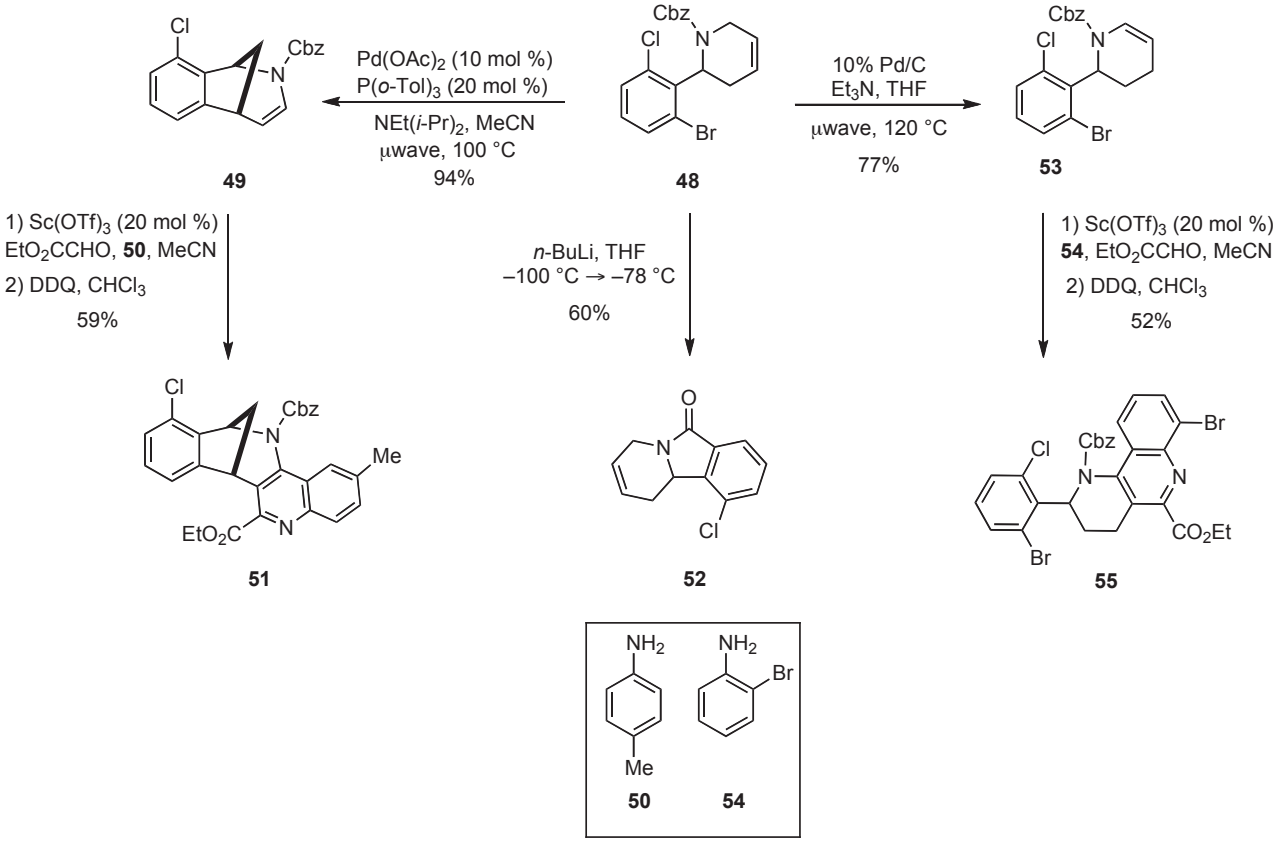
Varying the nucleophilic input in the MCAP by using an allyl zinc reagent provided a convenient means of accessing novel 2-aryl tetrahydropyridines that could be elaborated in a number of useful transformations. For example, sequential treatment of 2-bromo-6-chlorobenzaldehyde (**46**) with allylamine, CbzCl, and allylzinc bromide gave an 89% yield of diene **47**. When **47** was treated with Grubbs II catalyst, it underwent a facile RCM reaction to afford **48** in 93% yield (Scheme 8).



Scheme 8

The tetrahydropyridine **48** proved to be a versatile intermediate that could be readily elaborated into several, skeletally-diverse heterocycles of biological interest. Among these, norbenzomorphans are known to exhibit a variety of important neurological activities, including acetylcholinesterase (AChE) inhibition[33] and codeine-like analgesic activity.[34] We discovered that **48** could be readily converted to the norbenzomorphan core **49** in a single step by an intramolecular Heck cyclization (Scheme 9). Further derivatization of **49** was conveniently achieved by exploiting the electron-rich enecarbamate as a dienophile in the Povarov cyclization.[35] In initial experiments, we found that treating **49** with *p*-toluidine (**50**), ethyl glyoxylate, and a catalytic amount of squaric acid gave a mixture (1.2:1) of diastereomeric cycloadducts.[36] When $Sc(OTf)_3$ was used as the acid catalyst, the reaction was both cleaner and higher yielding. Although this mixture of cycloadducts (1.2:1) could be easily separated by chromatography, both isomers converged to a single quinoline-fused norbenzomorphan **51** upon DDQ oxidation.

The isoindolinone ring system is a structural subunit common to both natural products and pharmacologically important compounds.[22,37-39] It therefore occurred to us that the Parham cyclization[40] might be applied to compounds such as **48** to create novel isoindolinones. In the event, addition of *n*-BuLi to **48** at –100 °C, followed by warming to –78 °C and cyclization of the intermediate aryllithium reagent onto the carbamate carbonyl provided the isoindolinone **52** in 60% yield.



Scheme 9

Compounds containing the 1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine motif elicit a diverse range of biological properties, including selective 5-HT_4 antagonist activity.[41] Accordingly, we envisioned that the tetrahydropyridine **48** could serve as a precursor to this fused tricycle by a sequence of olefin isomerization and a Povarov reaction. Although methods for isomerizing tetrahydropyridines to enecarbamates are known,[42] we found that conventional heating of **48** in the presence of 10% Pd/C required lengthy reaction times (24 h) and gave irreproducible yields. However, when the reaction was promoted with microwave heating, enecarbamate **53** was quickly obtained in 77% yield. Notably, no reduction was observed under these conditions. The enecarbamate **53** underwent a facile Povarov cyclization when exposed to 2-bromoaniline (**54**), ethyl glyoxylate, and 20 mol % $Sc(OTf)_3$ to give a mixture (2:1) of diastereomeric tetrahydroquinolines that were oxidized with DDQ to deliver **55** in 52% overall yield.

In summary, we have extended our sequential MCAP/cyclization approach for DOS to the efficient preparation of several heterocyclic scaffolds containing the tetrahydroisoquinoline, benzodiazepine and 2-aryl piperidine substructures. Implementation of innovative reaction sequences subsequent to the assembly step enabled the facile formation of additional fused heterocyclic ring systems to give novel molecules of potential medicinal interest. The further development and application of these and related tactics to DOS and to the rapid synthesis of diverse compound libraries is an ongoing area of research

within our laboratories, and new findings will be reported in due course.

REPRESENTATIVE EXPERIMENTAL PROCEDURES

Methanol (MeOH), acetonitrile (MeCN), and *N,N*-dimethylformamide (DMF) were dried by filtration through two columns of activated molecular sieves. Tetrahydrofuran (THF) and toluene were passed through two columns of activated neutral alumina prior to use. Triethylamine (Et_3N), *N,N*-diisopropylamine, *N,N*-diisopropylethylamine, benzene, dichloromethane (CH_2Cl_2), pyridine, *N,N'*-dimethylpropylene urea (DMPU), phenyl isocyanate, and 1,4-dioxane were freshly distilled over CaH_2. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was distilled over P_2O_5. Thionyl chloride ($SOCl_2$) was distilled from triphenylphosphite. Zinc granules were activated by stirring with aqueous HCl (1.0 M) for 10 min, then filtered, rinsed with H_2O, MeOH, then Et_2O, and dried under high vacuum (*ca*. 0.5 mmHg) before use. Zinc chloride was fused under high vacuum (*ca*. 0.5 mmHg) prior to use. All other reagents and solvents were reagent grade and were purchased and used as received unless otherwise noted. Reactions were performed under nitrogen or argon atmosphere in round bottom flasks sealed under rubber septa with magnetic stirring, unless otherwise noted. Water sensitive reactions were performed with flame- or oven-dried glassware, stir bars and steel needles. Reaction temperatures are reported as the temperatures of the bath surrounding the vessel. Sensitive reagents and solvents were transferred using plastic or oven-dried glass syringes and steel needles using standard techniques.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were acquired in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (TMS, δ = 0.00 ppm) and are referenced to residual solvent. Coupling constants (*J*) are reported in hertz (Hz) and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; td, triplet of doublets; dq, doublet of quartets; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons. The abbreviations br and app stand for broad and apparent, respectively. Infrared (IR) spectra were obtained with a Thermo Scientific Nicolet IR-100 FT-IR series spectrometer as thin films on sodium chloride plates. Melting points were determined using a Thomas-Hoover Uni-melt capillary melting point apparatus. Thin-layer chromatography (TLC) was performed on EMD 60 F_{254} glass-backed pre-coated silica gel plates and was visualized using one or more of the following methods: UV light (254 nm) and staining with iodine (I_2), basic potassium permanganate ($KMnO_4$) or acidic *p*-anisaldehyde (PAA). Flash chromatography was performed using glass columns and with Silicycle SiliaFlash F60 (40-63 μm) silica gel eluting with the solvents indicated according to the procedure of Still.[43]

Phenyl 2-(7-bromo-2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (15). Trimethylsilyl

trifluoromethanesulfonate (27.1 mg, 22 μL, 0.12 mmol) was added to a solution of imine **13** in THF (4.8 mL) at −78 °C. To this mixture was added silyl ketene acetal **14**[12] (743 mg, 3.57 mmol) followed by chloroacetyl chloride (162 mg, 114 μL, 1.43 mmol) and the reaction was stirred at −78 °C for 22 h. The reaction was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant yellow oil was purified by flash column chromatography eluting with hexanes/EtOAc (7 : 3) to give 446 mg (89%) of **15** as a white powder: mp 139-141 °C; ^{1}H NMR (600 MHz) (rotamers) δ 7.47 (d, *J* = 1.8 Hz, 0.63 H), 7.42-7.36 (comp, 3.45 H), 7.27-7.28 (m, 0.30 H), 7.23-7.21 (m, 0.67 H), 7.11-7.09 (comp, 1.27 H), 7.06-7.05 (comp, 1.71 H), 6.07 (t, *J* = 6.6 Hz, 0.64 H), 5.48 (dd, *J* = 9.6, 4.8 Hz, 0.36 H), 4.73 (dd, *J* = 13.2, 6.0 Hz, 0.38 H), 4.54 (d, *J* = 12.6 Hz, 0.37 H), 4.19-4.09 (comp, 1.69 H), 3.93 (ddd, *J* = 9.0, 4.8, 3.6 Hz, 0.66 H), 3.73 (ddd, *J* = 13.2, 10.2, 4.2 Hz, 0.65 H), 3.24 (dd, *J* = 16.2, 9.6 Hz, 0.38 H), 3.19 (ddd, *J* = 13.2, 12.0, 4.2 Hz, 0.38 H), 3.10-2.94 (comp, 2.73 H), 2.88 (app dt, *J* = 7.8, 4.2 Hz, 0.66 H), 2.77-2.74 (m, 0.37 H); ^{13}C NMR (150 MHz) (rotamers) δ 169.3, 168.6, 166.2, 165.8, 150.5, 150.1, 137.3, 137.0, 133.0, 132.4, 131.3, 131.0, 130.7, 130.5, 130.0, 129.7, 129.5, 129.2, 126.4, 126.0, 121.6, 121.3, 120.5, 120.2, 53.4, 50.1, 41.7, 41.2, 41.1, 40.6, 35.9, 28.6, 27.1; IR (neat) 2946, 1751, 1654, 1485, 1430, 1193, 1136, 816, 750, 690 cm^{-1}; mass spectrum (CI) *m/z* 422.0156 [$C_{19}H_{18}{}^{79}Br^{35}ClNO_3$ (M+1) requires 422.0080].

11-Bromo-3-(3,4-dimethoxyphenethyl)-1,3,4,7,8,12*b*-hexahydro-[1,4]diazepino[7,1-*a*]isoquinoline-2, 5-dione (**16**)**.** A solution of amide **15** (37 mg, 0.092 mmol), benzylamine (11 mg, 12 μL, 0.11 mmol), and *N,N*-diisopropylethylamine (15 mg, 20 μL, 0.11 mmol) in MeCN (2.2 mL) was heated at 75 °C for 24 h. The reaction was cooled to room temperature and partitioned between CH_2Cl_2 (15 mL) and saturated aqueous $NaHCO_3$ (15 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant yellow oil was purified by flash column chromatography eluting with toluene/EtOAc (1 : 1) to provide 21 mg (61%) of **16** as a white solid: mp 60-62 °C; ^{1}H NMR (500 MHz) δ 7.42 (d, *J* = 1.5 Hz, 1 H), 7.38 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.34-7.27 (comp, 3 H), 7.24-7.23 (comp, 2 H), 7.06 (d, *J* = 8.5 Hz, 1 H), 5.09 (dd, *J* = 11.5, 3.5 Hz, 1 H), 4.72 (d, *J* = 14.5 Hz, 1 H), 4.67 (d, *J* = 14.5 Hz, 1 H), 4.31 (ddd, *J* = 9.0, 5.0, 4.5 Hz, 1 H), 4.22 (d, *J* = 16.5 Hz, 1 H), 4.04 (d, *J* = 16.5 Hz, 1 H), 3.26 (dd, *J* = 16.5, 4.0 Hz, 1 H), 3.20 (ddd, *J* = 13.0, 10.5, 4.0 Hz, 1 H), 3.12 (dd, *J* = 16.0, 11.5 Hz, 1 H), 2.93 (ddd, *J* = 16.5, 10.5, 5.5 Hz, 1 H), 2.74 (app dt, *J* = 16.5, 4.0 Hz, 1 H); ^{13}C NMR (125 MHz) δ 169.0, 167.2, 137.2, 136.3, 134.3, 130.8, 130.7, 128.8, 128.6, 128.2, 127.9, 120.5, 54.5, 52.9, 51.8, 41.6, 41.4, 27.9; IR (neat) 2925, 1664, 1636, 1485, 1436, 912, 731, 699 cm^{-1}; mass spectrum (CI) *m/z* 399.0710 [$C_{20}H_{20}{}^{79}BrN_2O_2$ (M+1) requires 399.0630].

20-Bromo-4,5,6,14-tetraazapentacyclo[12.8.0.0^{2,6}.0^{7,12}.0^{17,22}]docosa-2,4,7(12),8,10,17,19,21-octaen-

13-one (**17**)**.** A solution of *o*-azidobenzoic acid (112 mg, 0.69 mmol) in thionyl chloride (1.63 g, 1.0 mL, 13.7 mmol) was heated under reflux for 3 h. The cooled solution was concentrated under reduced pressure, and the residue was azeotroped with anhydrous benzene (3 × 4 mL) to provide crude *o*-azidobenzoyl chloride as a yellow oil.[14] In a separate flask, trimethylsilyl trifluoromethanesulfonate (112 mg, 91 μL, 0.50 mmol) was added dropwise to a solution of dihydroisoquinoline (**12**) (60 mg, 0.46 mmol) in THF (3.6 mL) at −23 °C. In a separate flask, *n*-BuLi (0.22 mL, 0.59 mmol, 2.75 M in hexanes) was added dropwise to a solution of phenylacetylene (65 mg, 70 μL, 0.64 mmol) in THF (1.8 mL) and the brown solution was stirred at room temperature for 10 min.[44] The phenyl acetylide was then added dropwise to the solution of activated imine at −78 °C, and the reaction was stirred at −78 °C for 5 h, whereupon *o*-azidobenzoyl chloride (0.69 mmol) in THF (2.0 mL) was added dropwise at −78 °C. The reaction was warmed to room temperature and stirred for 20 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant yellow oil was purified by flash chromatography eluting with pentane/EtOAc (3 : 2) to give 142 mg (82%) of **16** as a yellow solid: mp 154 °C (dec.); ^{1}H NMR (600 MHz) δ 8.14-8.12 (comp, 2 H) 7.77 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1 H), 7.63 (ddd, *J* = 7.8, 7.4, 1.3 Hz, 1 H), 7.12-7.06 (comp, 2 H), 7.02-6.99 (comp, 3 H), 6.94-6.92 (comp, 2 H), 6.88-6.84 (comp, 2 H), 5.95 (s, 1 H), 4.28 (ddd, *J* = 12.8, 6.5, 4.9 Hz, 1 H), 3.72 (ddd, *J* = 12.8, 8.3, 4.3 Hz, 1 H), 2.93-2.81 (comp, 2 H); ^{13}C NMR (150 MHz) δ 165.9, 143.8, 135.8, 134.1, 133.0, 132.9, 131.8, 129.5, 129.3, 128.7, 128.6, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 126.7, 123.2, 50.6, 39.4, 28.5; IR (neat) 3442, 3060, 2963, 2910, 2862, 1643, 1604, 1484, 1408, 1260, 1084, 1020, 795, 750, 698 cm^{-1}; mass spectrum (CI) *m/z* 379.1558[$C_{24}H_{19}N_4O$ (M+1) requires 379.1481].

1-(7-Bromo-1-(hex-1-ynyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-chloroethanone (18). Trimethylsilyl trifluoromethanesulfonate (344 mg, 0.28 mL, 1.57 mmol) was added slowly to a solution of dihydroisoquinoline **13** (300 mg, 1.43 mmol) in THF (11 mL) at −23 °C, and the reaction was then cooled to −78 °C. In a separate flask, *n*-BuLi (0.9 mL, 1.86 mmol, 2.2 M in hexanes) was added dropwise to a solution of 1-hexyne (164 mg, 0.23 mL, 2.00 mmol) in THF (6 mL) at 0 °C, and the clear colorless solution was stirred for 5 min at 0 °C. $ZnCl_2$ (2.3 mL, 2.3 mmol, 1 M in THF) was added dropwise at 0 °C, and the solution was warmed to room temperature and stirred for 15 min.[45] The solution of freshly prepared organozinc reagent was added dropwise to the solution of activated imine at −78 °C, and the reaction was stirred for 5 h at −78 °C, whereupon chloroacetyl chloride (284 mg, 0.20 mL, 2.57 mmol) was added slowly at −78 °C. The bath was removed, and the reaction was warmed to room temperature and stirred for 10 min. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20

mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant yellow gum was purified by flash chromatography eluting with pentane/EtOAc (8 : 2) to give 479 mg (91%) of **18** as a pale yellow oil: ^{1}H NMR (600 MHz) (rotamers) δ 7.44 (d, *J* = 1.2 Hz, 1 H), 7.33-7.32 (m, 1 H), 7.03-7.00 (m, 1 H), 6.24 (s, 0.58 H), 5.64 (s, 0.33 H), 4.56-4.50 (m, 0.40 H), 4.32-4.30 (m, 0.37 H), 4.16 (d, *J* = 12.0 Hz, 1 H), 4.13-4.10 (m, 0.72 H), 3.94-3.91 (m, 0.62 H), 3.77-3.73 (m, 0.63 H), 3.27 (m, 0.37 H), 3.05-2.98 (m, 0.67 H), 2.85-2.78 (comp, 1.44 H), 2.17-2.16 (comp, 2 H), 1.46-1.43 (comp, 2 H), 1.38-1.32 (comp, 2 H), 0.92-0.87 (comp, 3 H); ^{13}C NMR (150 MHz) (rotamers) δ 165.4, 164.9, 136.6, 135.7, 132.8, 131.5, 130.8, 130.5, 130.4, 130.1, 120.2, 120.1, 86.4, 84.8, 77.8, 48.1, 44.8, 41.3, 41.1, 40.8, 37.2, 30.5, 30.4, 28.5, 27.6, 21.9, 18.4, 13.6; IR (neat) 2957, 2933, 2871, 1657, 1431, 1188, 929, 814, 796, 647 cm^{-1}; mass spectrum (CI) *m/z* 368.0415 [$C_{17}H_{20}{}^{79}Br^{35}ClNO$ (M+1) requires 368.0339].

4-Bromo-16-butyl-10,13,14,15-tetraazatetracyclo[8.7.0.0^{2,7}.0^{3,17}]heptadeca-2,4,6,14,16-pentaen-11-one (19). A mixture of amide **18** (50 mg, 0.14 mmol) and sodium azide (10 mg, 0.15 mmol) in anhydrous DMF (0.6 mL) was stirred at room temperature for 2 h. The reaction was partitioned between H_2O (5 mL) and toluene (5 mL). The layers were separated, and the aqueous layer was extracted with toluene (1 × 5 mL). The combined organic layers were washed with H_2O (5 × 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude yellow azide thus obtained was dissolved in anhydrous DMF (2.7 mL), and the solution was heated at 100 °C for 48 h. The reaction was partitioned between H_2O (10 mL) and toluene (10 mL). The layers were separated, and the aqueous layer was extracted with toluene (1 × 10 mL). The organic layer was washed with H_2O (5 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resultant brown oil was purified by flash column chromatography eluting with pentane/EtOAc (3 : 7) to give 43 mg (85%) of **19** as a white solid: mp 135-136 °C; ^{1}H NMR (600 MHz) δ 7.43 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 6.95 (d, *J* = 2.4 Hz, 1 H), 5.80 (s, 1 H), 5.20 (d, *J* = 18.0 Hz, 1 H), 4.83 (d, *J* = 18.0 Hz, 1 H), 4.53 (ddd, *J* = 13.2, 7.2, 6.0 Hz, 1 H), 3.52-3.47 (m, 1 H), 3.22 (ddd, *J* = 16.2, 7.2, 6.6 Hz, 1 H), 2.96 (ddd, *J* = 13.2, 7.2, 6.6 Hz, 1 H), 2.84 (app dt, *J* = 15.0, 7.2 Hz, 1 H), 2.68 (app dt, *J* = 15.0, 7.2 Hz, 1 H), 1.85-1.80 (comp, 2 H), 1.47-1.41 (comp, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (150 MHz) δ 162.2, 144.6, 136.1, 133.7, 132.0, 130.9, 127.3, 124.5, 120.6, 52.1, 48.9, 42.1, 30.9, 26.6, 25.2, 22.6, 13.8; IR (neat) 2956, 2870, 1667, 1481, 1429, 1258, 828, 734 cm^{-1}; mass spectrum (CI) *m/z* 375.0821 [$C_{17}H_{20}{}^{79}BrN_4O$ (M+1) requires 375.0742].

2-(2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)phenyl)-2-(prop-2-ynylamino)acetonitrile (21). Aqueous HCl (4.28 mL, 1.0 M, 4.28 mmol) was added dropwise to a solution of *o*-azidobenzaldehyde **20** (600 mg, 4.08 mmol),[19] propargylamine (236 mg, 274 μL, 4.28 mmol) and sodium cyanide (210 mg, 4.28 mmol) in MeOH (8.6 mL) and the reaction stirred at room temperature for 2.5 h. The reaction was diluted with H_2O (50 mL) and the pH raised to 10 with aqueous NaOH (*ca*. 300 μL, 1.0 M). The resulting mixture was

extracted with EtOAc (3 × 70 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/Et_2O (4 : 1 → 3 : 2) to give 673 mg of amine **21** (78%) as an orange oil: ^{1}H NMR (500 MHz) δ 7.53 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.45 (ddd, *J* = 8.1, 7.6, 1.5 Hz, 1 H), 7.22 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.20 (app td *J* = 7.6, 1.5 Hz, 1 H), 5.11 (d, *J* = 7.5 Hz, 1 H), 3.62 (m, 2 H), 2.34 (t, *J* = 2.5 Hz, 1 H) 2.00 (m, 1 H); ^{13}C NMR (100 MHz) δ 138.1, 130.8, 129.4, 125.4, 125.2, 118.7, 117.9, 79.6, 73.2, 48.6, 36.5; IR (neat) 3295, 2132, 1586, 1491, 1452, 1297, 1106 cm^{-1}; mass spectrum (CI) *m/z* 212.0940 [$C_{11}H_{10}N_5$ (M+1) requires 212.0936].

5,6-Dihydro-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine-6-carbonitrile (22). A solution of amine **21** (667 mg, 3.02 mmol) in toluene (158 mL) was stirred at 60 °C for 34 h. The cooled reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with toluene/EtOAc (1 : 1 → 0 : 1) to give 589 mg of amine **22** (88%) as a colorless solid: mp 133 °C (dec.) (colorless needles from hexanes/CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, *J* = 7.9 Hz, 1 H), 7.90 (s, 1 H), 7.75-7.66 (comp, 2 H), 7.61 (app t, *J* = 7.2 Hz, 1 H), 5.49 (d, *J* = 5.1 Hz, 1 H), 4.20 (ddd, *J* = 6.3, 5.1, 4.9 Hz, 1 H), 4.10 (dd, *J* = 14.6, 4.9 Hz, 1 H), 3.73 (dd, *J* = 14.6, 6.3 Hz, 1 H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 135.4, 135.2, 132.2, 131.0, 130.1, 129.7, 127.0, 123.4, 119.2, 48.9, 36.7; IR (neat) 3312, 2920, 2851, 1495, 1469, 1230, 1136, 1095 cm^{-1}; mass spectrum (CI) *m/z* 212.0940 [$C_{11}H_{10}N_5$ (M+1) requires 212.0936].

5-(2-Fluorobenzoyl)-5,6-dihydro-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine-6-carbonitrile (24). 2-Fluorobenzoyl chloride (90 mg, 68 μL, 0.57 mmol) was added to a solution of amine **22** (60 mg, 0.28 mmol) and pyridine (67 mg, 69 μL, 0.85 mmol) in anhydrous MeCN (1.5 mL) at 0 °C, and the reaction was stirred at room temperature for 1 h. The reaction was diluted with CH_2Cl_2 (20 mL) and the mixture was washed with aqueous HCl (10 mL, 1.0 M) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes/EtOAc (4 : 6) to give 93 mg (98%) of amide **24** as a colorless solid: mp 217-219 °C (colorless prisms from hexanes/EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.01 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.96 (s, 1 H), 7.93-7.80 (m, 1 H), 7.83 (app td, *J* = 7.8, 1.4 Hz, 1 H), 7.67 (app td, *J* = 7.8, 1.2 Hz, 1 H), 7.66-7.60 (m, 1 H), 7.54 (app td, *J* = 7.4, 1.8 Hz, 1 H), 7.41-7.32 (comp, 2 H), 6.90-6.52 (m, 1 H), 5.28-4.89 (m, 1 H), 4.33 (d, *J* = 15.3 Hz, 1 H); ^{13}C NMR (125 MHz, d_6-DMSO, 100 °C) δ 164.5, 157.6 ($J_{C\text{-}F}$ = 347.6 Hz), 134.7, 132.8, 132.3 ($J_{C\text{-}F}$ = 8.3 Hz), 131.8, 131.3, 131.0, 129.5, 128.6, 124.7 ($J_{C\text{-}F}$ = 3.5 Hz), 123.3, 123.3, 121.5 ($J_{C\text{-}F}$ = 16.7 Hz), 115.8 ($J_{C\text{-}F}$ = 21.0 Hz), 115.3, 47.1, 38.2; IR (neat) 3063, 2923, 1652, 1614, 1450, 1455, 1394, 1325, 1236, 1093 cm^{-1}; mass spectrum (ESI) *m/z* 356.0918 [$C_{18}H_{12}N_5OFNa$ (M+Na) requires 356.0918].

5-Nicotinoyl-5,6-dihydro-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine-6-carbonitrile (25). A

mixture of amine **22** (110 mg, 0.52 mmol), nicotinoyl chloride hydrochloride (185 mg, 1.0 mmol) and pyridine (164 mg, 168 μL, 2.1 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was stirred at rt for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) was added and the reaction was stirred at rt for 20 min. The reaction was then diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (24 : 1 → 19 : 1) to give 153 mg (92%) of amide **25** as a colorless solid: mp 187-189 °C (colorless microcrystals from *i*-PrOH); ^{1}H NMR (400 MHz) δ 8.88-8.76, (comp, 2 H), 8.09 (d, *J* = 8.2 Hz, 1 H), 7.95 (app dt, *J* = 7.9, 2.0 Hz, 1 H), 7.90-7.74 (comp, 2 H), 7.70-7.46 (comp, 2 H), 7.51 (dd, *J* = 7.9, 5.0 Hz, 1 H), 6.49 (br s, 1 H), 5.10 (br s, 1 H), 4.34 (br s, 1 H); ^{13}C NMR (100 MHz) δ 168.0, 152.7, 148.4, 135.9, 135.5, 133.8, 132.9, 131.5, 130.6, 130.2, 129.2, 124.7, 124.1, 123.3, 115.1, 47.7, 40.9; IR (neat) 2941, 2361, 1651, 1589, 1501, 1391, 1326, 1238, 1102 cm^{-1}; mass spectrum (CI) *m/z* 317.1154 [$C_{17}H_{13}N_6O$ (M+1) requires 317.1151].

11-Oxo-11,13*a*-dihydro-9*H*-benzo[*f*]isoindolino[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepine-13*a*-carbonitrile (28). A solution of amide **24** (28 mg, 0.084 mmol) in anhydrous DMF (0.7 mL) was added to a suspension of sodium hydride (3.7 mg, 0.092 mmol, 60% dispersion in mineral oil) in DMF (0.7 mL) and the reaction was stirred at room temperature for 2 h. The solution was diluted with toluene (30 mL) and the mixture was washed with H_2O (3 × 15 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes/EtOAc (4 : 6) to give 20 mg (76%) of isoindolinone **28** as a colorless solid: mp 245-247 °C; ^{1}H NMR (400 MHz) δ 8.10 (dd, *J* = 8.0, 1.2, Hz, 1 H), 8.02 (d, *J* = 7.6 Hz, 1 H), 7.99 (s, 1 H), 7.87 (app t, *J* = 7.5 Hz, 1 H), 7.82-7.72 (comp, 3 H), 7.50 (app td, *J* = 7.8, 1.2 Hz, 1 H), 7.20 (dd, *J* = 7.8, 1.4 Hz, 1 H), 5.47 (d, *J* = 15.1 Hz, 1 H), 4.25 (d, *J* = 15.1 Hz, 1 H); ^{13}C NMR (100 MHz) δ 165.9, 139.2, 135.8, 134.1, 133.7, 132.5, 131.6, 131.3, 130.7, 130.3, 127.0, 126.1, 126.0, 125.4, 125.3, 115.9, 61.0, 35.1; IR (neat) 3084, 2924, 2855, 1714, 1493, 1468, 1358, 1238, 1153, 1104 cm^{-1}; mass spectrum (ESI) *m/z* 314.1038 [$C_{18}H_{12}N_5O$ (M+1) requires 314.1036].

11-(Pyridin-3-yl)-9*H*-benzo[*f*]pyrrolo[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepine (29). A solution of amide **25** (78 mg, 0.25 mmol) in DMF (2.8 mL) was added dropwise over 2 min to sodium hydride (10.8 mg, 0.27 mmol), and the mixture was stirred at room temperature for 45 min. A solution of triphenylvinylphosphonium bromide (105 mg, 0.28 mmol) in DMF (1.8 mL) was added, and the reaction was stirred at room temperature for 1.5 h. The reaction was diluted with toluene (30 mL) and washed with H_2O (3 × 15 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with toluene/EtOAc/MeOH (50 : 50 : 1) to give 67 mg (91%) of pyrrole **29** as a pale yellow solid: mp 182-184 °C (pale yellow needles from hexanes/EtOAc); ^{1}H NMR (400 MHz) δ 8.72-8.67 (m, 1 H),

8.67-8.62 (m, 1 H), 8.13-8.06 (m, 1 H), 7.79-7.74 (comp, 2 H), 7.72 (app dt, *J* = 7.8, 2.0 Hz, 1 H), 7.56-7.48 (comp, 2 H), 7.45 (dd, *J* = 7.8, 4.9 Hz, 1 H), 6.60 (d, *J* = 3.9 Hz, 1 H), 6.39 (d, *J* = 3.9 Hz, 1 H), 5.12 (br s, 2 H); ^{13}C NMR (100 MHz) δ 149.7, 148.9, 136.2, 134.2, 132.7, 132.0, 131.9, 130.9, 129.7, 129.5, 128.6, 128.1, 124.4, 124.0, 123.8, 111.5, 110.7, 37.5; IR (neat) 3031, 2924, 2854, 1567, 1482, 1454, 1421, 1335, 1253, 1231 cm^{-1}; mass spectrum (ESI) *m/z* 300.1245 [$C_{18}H_{14}N_5$ (M+1) requires 300.1244].

***N*-Allyl-*N*-(1-(2-bromophenyl)-3-oxopropyl)pent-4-enamide (34).** Vinyl TBS ether (**33**) was prepared according to the procedure of Kawakamie and coworkers.[46] 4-Pentenoyl chloride (**32**) was prepared according to the procedure of Rosenblum and coworkers and purified by fractional distillation under nitrogen prior to use.[47] Allylamine (1.9 g, 2.5 mL, 33 mmol), $MgSO_4$ (8.1 g, 67 mmol) and 2-bromobenzaldehyde (4.15 g, 22.4 mmol) were combined in CH_2Cl_2 (44 mL) and the mixture was stirred for 24 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the allylimine, which was used without further purification. Vinyl TBS ether (**33**) (10.6 g, 67 mmol) and CH_2Cl_2 (29 mL) were added and the solution was cooled to 0 ºC, followed by dropwise addition of 4-pentenoyl chloride (**32**) (2.9 g, 2.7 mL, 24 mmol). After 5 min, TMSOTf (0.50 g, 0.41 mL, 2.2 mmol) was added dropwise and the mixture was warmed to room temperature and stirred for 40 h. The mixture was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (70 mL) and saturated aqueous $NaHCO_3$ (70 mL), and the mixture was stirred rapidly for 1 h. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/EtOAc/MeOH (75 : 25 : 1 → 50 : 50 : 1 → 25 : 75 : 1) to give 5.50 g (70%) of the aldehyde **34** as a viscous, golden oil: ^{1}H NMR (600 MHz) (9 : 1 rotamer mixture, data given for the major rotamer) δ 9.76 (dd, *J* = 2.7, 2.1 Hz, 1 H), 7.64-7.58 (m, 1 H), 7.37-7.30 (comp, 2 H), 7.20 (ddd, *J* = 8.1, 6.6, 2.4 Hz ,1 H), 6.26 (dd, *J* = 8.8, 6.3 Hz, 1 H), 5.90-5.79 (m, 1 H), 5.54-5.44 (m, 1 H), 5.08-4.94 (comp, 4 H), 3.72 (ddt, *J* = 17.4, 5.1, 1.7 Hz, 1 H), 3.64 (dd, *J* = 17.4, 5.9 Hz, 1 H), 3.18 (ddd, *J* = 15.6, 8.8, 2.7 Hz, 1 H), 2.99 (ddd, *J* = 15.6, 6.3, 2.1 Hz, 1 H), 2.48-2.34 (comp, 4 H); ^{13}C NMR (150 MHz) (9 : 1 rotamer mixture, data given for the major rotamer): δ 199.6, 172.9, 137.4, 137.2, 133.9, 133.6, 129.8, 129.4, 127.6, 125.5, 117.2, 115.2, 53.2, 47.6, 46.4, 33.0, 29.2; IR (neat) 2979, 1723, 1643, 1470, 1415, 1025 cm^{-1}; mass spectrum (ESI) *m/z* 350.0750 [$C_{17}H_{21}NO_2{}^{79}$Br (M+1) requires 350.0750].

1-((3*aR*,6*S*,7*aS*)-6-(2-Bromophenyl)-1-methyltetrahydroisoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl)-pent-4-en-1-one (35). *N*-Methylhydroxylamine hydrochloride (1.25 g, 15.0 mmol), aldehyde **34** (3.50 g, 9.99 mmol) and Et_3N (3.0 g, 4.2 mL, 30 mmol) were combined in toluene (116 mL) and the mixture was heated under reflux for 90 min. After cooling to room temperature, H_2O (60 mL) was added and the layers were separated. The aqueous layer was saturated with NaCl then extracted with CH_2Cl_2 (2 × 30

mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by column chromatography eluting with hexanes/EtOAc/MeOH (75 : 25 : 1 → 50 : 50 : 1 → 0 : 95 : 5) to afford 3.63 g (96%) of the isoxazolidine **35** as a highly viscous, pale yellow gum that crystallized on standing: mp 70-71 ºC; ^{1}H NMR (600 MHz) (rotamers) δ 7.55 (dd, *J* = 8.1, 1.1 Hz, 0.75 H), 7.51 (d, *J* = 7.7 Hz, 0.25 H), 7.35-7.30 (m, 0.75 H), 7.25 (dd, *J* = 8.5, 1.7 Hz, 0.75 H), δ 7.25-7.20 (m, 0.25 H), 7.18-7.13 (m, 0.75 H), 7.11 (dd, *J* = 7.8, 1.2 Hz, 0.25 H), 7.08-7.04 (m, 0.25 H), 5.86-5.77 (m, 0.25 H), 5.73-5.63 (m, 0.75 H), 5.23 (dd, *J* = 13.7, 4.8 Hz, 0.25 H), 5.07-5.00 (comp, 1 H), 5.00-4.92 (comp, 1 H), 4.91-4.84 (comp, 1.5 H), 4.20-4.10 (comp, 1 H), 3.97 (dd, *J* = 13.7, 5.4 Hz, 0.25 H), 3.60-3.53 (comp, 1.25 H), 3.07-2.88 (comp, 2.75 H), 2.70 (s, 3 H), 2.55-2.47 (m, 0.25 H), 2.47-2.39 (m, 0.25 H), 2.39-2.32 (m, 1.5 H), 2.32-2.20 (comp, 1.5 H), 2.16-2.07 (m, 0.75 H), 1.86-1.77 (m, 0.75 H), 1.77-1.67 (comp, 1 H); ^{13}C NMR (150 MHz) (rotamers) δ 173.2, 171.2, 142.7, 142.5, 137.4, 137.2, 133.2, 129.2, 128.7, 128.3, 127.9, 126.4, 125.3, 121.8, 121.1, 115.3, 115.1, 68.3, 68.0, 64.6, 55.7, 54.6, 43.9, 43.7, 42.8, 39.6, 33.3, 33.1, 32.6, 31.8, 29.0, 28.9; IR (neat) 2956, 2876, 1650, 1418, 1240, 1026, 915, 756 cm^{-1}; mass spectrum (ESI) *m/z* 379.1017 [$C_{18}H_{24}N_2O_2{}^{79}Br$ (M+1) requires 379.1016].

(3*a*R,6S,7*a*S)-6-(2-Bromophenyl)-1-methyloctahydroisoxazolo[4,3-*c*]pyridine (36). Iodine (6.67 g, 26.3 mmol) was added to a stirred solution of the amide **35** (2.00 g, 5.27 mmol) in THF (41 mL) and 1.5 M aqueous HCl (15 mL) at 0 ºC. The stirred mixture was warmed to room temperature and after 60 min, saturated aqueous $Na_2S_2O_3$ was added until the solution became colorless. The mixture was then diluted with H_2O (120 mL) and washed with Et_2O (3 × 120 mL). The pH of the aqueous layer was adjusted to 12 by addition of 1 M aqueous NaOH and the solution was then saturated with NaCl and extracted with CH_2Cl_2 (4 × 100 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with EtOAc/MeOH (100 : 1 → 90 : 10) to give 1.40 g (89%) of the amine **36** as a brown solid: mp 106-108 ºC (pale yellow needles from EtOAc/hexanes); ^{1}H NMR (400 MHz): δ 7.60-7.49 (comp, 2 H), 7.34-7.27 (m, 1 H), 7.11 (td, *J* = 7.7, 1.6 Hz, 1 H), 4.24 (dd, *J* = 9.2, 7.2 Hz, 1 H), 3.96 (dd, *J* = 9.8, 2.2 Hz, 1 H), 4.02-3.94 (m, 1 H), 3.29 (d, *J* = 12.5 Hz, 1 H), 3.26-3.16 (comp, 2 H), 3.07-2.95 (m, 1 H), 2.68 (s, 3 H), 2.12-2.02 (m, 1 H), 1.68-1.50 (comp, 2 H); ^{13}C NMR (100 MHz): 142.7, 132.7, 128.7, 127.9, 127.9, 123.2, 68.0, 64.4, 57.7, 44.6, 44.6, 37.8, 34.8; IR (neat) 3313, 2950, 1469, 1438, 1023 cm^{-1}; mass spectrum (ESI) *m/z* 297.0597 [$C_{13}H_{18}NO_2{}^{79}Br$ (M+1) requires 297.0602].

1-((2*S*,4*S*,5*R*)-2-(2-Bromophenyl)-5-(hydroxymethyl)-4-(methylamino)piperidin-1-yl)ethanone (38). Zinc dust (3.9 g, 60 mmol) was added at 0 °C to a stirred solution of isoxazolidine **37**[6a] (1.00 g, 2.95 mmol) in 10% aqueous HCl (45 mL). After 1 h, the mixture was filtered through Celite rinsing with 10% aqueous HCl (20 mL). The pH of the combined filtrate and rinsings was adjusted to 12 by the addition of 30% aqueous NH_4OH and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic

layers were dried (Na_2SO_4) and concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with CH_2Cl_2/MeOH (100 : 1 → 1 : 1) to give 837 mg (83%) of the amino alcohol **38** as a clear, colorless gum: ^{1}H NMR (500 MHz, DMSO-d_6, 130 °C) δ 7.53-7.57 (m, 1 H), 7.32 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.32-7.27 (m, 1 H), 7.14 (ddd, *J* = 7.9, 6.0, 2.7 Hz, 1 H), 5.21 (app t, *J* = 7.7 Hz, 1 H), 4.16 (dd, *J* = 13.7, 6.1 Hz, 1 H), 3.59 (dd, *J* = 11.0, 5.4 Hz, 1 H), 3.55 (dd, *J* = 11.0, 6.4 Hz, 1 H), 3.03 (br s, 2 H), 2.84 (ddd, *J* = 9.1, 6.1, 3.3 Hz, 1 H), 2.18-2.12 (comp, 2 H), 2.16 (s, 3 H), 1.95-1.90 (m, 1 H), 1.94 (ddd, *J* = 13.9, 8.8, 7.7 Hz, 1 H), 1.92 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 130 °C) δ 168.9, 142.5, 132.0, 127.6, 127.1, 126.0, 120.4, 59.9, 54.6, 54.5, 41.5, 39.2, 33.1, 31.0, 20.6; IR (neat) 3323, 2923, 1633, 1420, 1024 cm^{-1}; mass spectrum (ESI) *m/z* 341.0858 [$C_{15}H_{22}N_2O_2{}^{79}Br$ (M+1) requires 341.0859].

1-[(1*S*,9*S*,10*R*)-10-(Hydroxymethyl)-8-methyl-8,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-12-yl]ethan-1-one (39). $Pd(OAc)_2$ (6.0 mg, 0.027 mmol) and (±)-BINAP (20 mg, 0.032 mmol) were combined in toluene (5 mL) and heated at 40 °C until all solid had dissolved. The solution was cooled to room temperature over 10 min, then combined with amine **38** (92 mg, 0.27 mmol) and Cs_2CO_3 (177 mg, 0.543 mmol). The mixture was heated under reflux for 14 h, then cooled to room temperature and filtered through celite, rinsing with toluene (5 mL). The combined filtrate and rinsings were concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with $CHCl_3$/MeOH (95 : 5) to afford 49 mg (70%) of the tetrahydroquinoline **39** as a pale yellow gum: ^{1}H NMR (600 MHz) (rotamers) δ 7.22-7.15 (comp, 1.6 H), 7.01 (dd, *J* = 7.6, 1.5 Hz, 0.4 H), 6.62-6.55 (comp, 2 H), 5.91 (br s, 0.6 H), 4.93 (br s, 0.4 H), 4.36 (dd, *J* = 13.3, 4.8 Hz, 0.4 H), 3.83 (d, *J* = 1.8 Hz, 0.4 H), 3.72 (d, *J* = 2.1 Hz, 0.6 H), 3.66 (dd, *J* = 10.4, 7.6 Hz, 0.6 H), 3.60-3.49 (comp, 2 H), 3.14 (s, 1.2 H), 3.08 (s, 1.8 H), 2.72 (br s, 1 H), 2.69 (app t, *J* = 12.8 Hz, 0.6 H), 2.34 (s, 1.2 H), 2.11 (app t, *J* = 13.3 Hz, 0.4 H), 2.05-1.81 (comp, 3 H), 2.04 (s, 1.8 H); ^{13}C NMR (150 MHz) (rotamers) δ 168.7, 168.1, 146.5, 146.4, 129.9, 129.7, 129.2, 128.9, 120.5, 119.3, 115.6, 115.3, 109.7, 109.5, 62.7, 62.3, 54.4, 53.6, 46.6, 45.8, 45.7, 42.0, 40.0, 39.8, 36.4, 29.3, 28.4, 22.0, 22.0; IR (neat) 3392, 2931, 1614, 1503, 1436, 1045 cm^{-1}; mass spectrum (CI) *m/z* 260.1522 [$C_{15}H_{20}N_2O_2$ ($M^{+\cdot}$) requires 260.1525].

1-((3*aR*,6*S*,7*aS*)-6-(2-Bromophenyl)-1-methyltetrahydroisoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl)-2-phenylethanone (40). Phenylacetyl chloride (64 mg, 55 μL, 0.41 mmol) was added dropwise to a solution of amine **36** (100 mg, 0.336 mmol) and Et_3N (47 mg, 65 μL, 0.46 mmol) in CH_2Cl_2 (2 mL). After 1 h, the mixture was diluted with CH_2Cl_2 (10 mL) and partitioned with saturated aqueous $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/EtOAc (1 : 1 → 1 : 3) to afford 117 mg (84%) of the amide **40** as a white foam: ^{1}H NMR (400 MHz) (rotamers) δ 7.57 (d, *J* = 8.0 Hz, 0.7 H),

7.51 (d, *J* = 7.8 Hz, 0.3 H), 7.35-7.03 (comp, 7.7 H), 7.00 (d, *J* = 6.6 Hz, 0.3 H), 5.24 (dd, *J* = 13.5, 4.7 Hz, 0.3 H), 5.04 (dd, *J* = 12.5, 5.1 Hz, 0.7 H), 5.01-4.93 (m, 0.7 H), 4.20-4.08 (m, 0.7 H), 4.05-3.92 (comp, 0.6 H), 3.75 (s, 0.6 H), 3.60-3.53 (m, 0.7 H), 3.48-3.39 (comp, 0.6 H), 3.36 (d, *J* = 15.1 Hz, 0.7 H), 3.28 (d, *J* = 15.1 Hz, 0.7 H), 3.10-2.82 (comp, 2.4 H), 2.75-2.53 (m, 0.3 H), 2.66 (s, 2 H), 2.64 (s, 1 H), 2.44-2.27 (comp, 1 H), 1.77-1.57 (comp, 1 H); ^{13}C NMR (100 MHz) (rotamers) δ 171.8, 169.9, 142.5, 142.4, 134.6, 134.5, 133.4, 133.2, 129.4, 129.0, 128.8, 128.7, 128.5, 128.4, 127.8, 127.1, 126.8, 126.4, 125.3, 121.9, 121.1, 68.3, 67.9, 64.5, 55.8, 54.7, 44.3, 43.7, 43.5, 42.5, 42.1, 40.6, 39.9, 32.8, 31.8; IR (neat) 2955, 2874, 1646, 1414, 1026 cm^{-1}; mass spectrum (ESI) *m/z* 415.1016 [$C_{22}H_{25}N_2O_2{}^{79}Br$ (M+1) requires 415.1016].

(1*S*,8*R*,12*R*,16*S*)-8-Allyl-15-methyl-8-phenyl-14-oxa-10,15-diazatetracyclo[8.7.0.0^{2,7}.0^{12,16}]heptadeca-2(7),3,5-trien-9-one (41). LDA was prepared by addition of *n*-BuLi (3.90 mL, 9.0 mmol, 2.3 M in hexanes) to a solution of diisopropylamine (1.09 g, 0.78 mL, 10.8 mmol) in THF (9.0 mL) at 0 ºC. After 30 minutes, the solution was warmed to room temperature. A portion of the LDA solution so obtained (0.65 M in THF/hexanes, 2.2 mL, 1.4 mmol) was added dropwise to a solution of amide **40** (100 mg, 0.241 mmol) and DMPU (0.37 g, 0.35 mL, 2.9 mmol) in THF (3 mL) at −78 ºC. The solution was then warmed to 0 ºC and stirred for 1 h. The mixture was recooled to −100 ºC, and a solution of allyl bromide (0.35 g, 0.25 mL, 2.9 mmol) in THF (2 mL) was added dropwise. The mixture was warmed to −78 ºC and held at this temperature for 20 min, before warming to 0 ºC. Toluene (5 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the mixture was concentrated under reduced pressure to remove the THF. The residue was partitioned between H_2O (5 mL) and toluene (5 mL), and the layers were separated. The toluene layer was washed with H_2O (4 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with pentane/ EtOAc/MeOH (25 : 75 : 1 → 0 : 100 : 1) to afford 60 mg (66%) of the dihydroisoquinolin-3-one **41** as a yellow gum: ^{1}H NMR (400 MHz) δ 7.36-7.27 (m, 2 H), 7.26-7.12 (comp, 7 H), 5.50-5.38 (m, 1 H), 5.04 (dd, *J* = 17.1, 1.5 Hz, 1 H), 5.03-4.94 (m, 1 H), 4.90 (dd, *J* = 10.3, 1.5 Hz, 1 H), 4.45 (dd, *J* = 12.6, 2.2 Hz, 1 H), 4.08-4.00 (m, 1 H), 3.77 (dd, *J* = 14.0, 6.8 Hz, 1 H), 3.39-3.28 (m, 1 H), 3.14-2.97 (comp, 3 H), 2.88 (dd, *J* = 14.0, 7.2 Hz, 1 H), 2.58 (s, 3 H), 2.26-2.16 (m, 1 H), 1.47 (app q, *J* = 12.6 Hz, 1 H); ^{13}C NMR (75 MHz) δ 170.4, 145.0, 136.0, 134.4, 134.2, 129.0, 128.5, 127.8, 127.3, 127.2, 127.1, 125.4, 118.3, 67.4, 64.0, 57.4, 53.8, 44.5, 43.4, 40.6, 38.1, 37.9; IR (neat) 2953, 2680, 1643, 1443, 1243 cm^{-1}; mass spectrum (CI) *m/z* 374.1994 [$C_{24}H_{26}N_2O_2$ (M+1) requires 374.1994].

(1*S*,12*R*,16*S*)-15-Methyl-8-phenyl-14-oxa-8,10,15-triazatetracyclo[8.7.0.0^{2,7}.0^{12,16}]heptadeca-2(7),3,5-trien-9-one (43). $Pd(OAc)_2$ (2.4 mg, 0.011 mmol) and (±)-BINAP (7.8 mg, 0.013 mmol) were combined in toluene (0.8 mL) and heated at 40 °C until all solid had dissolved. The mixture was cooled to room temperature, then combined with amine **36** (30 mg, 0.10 mmol) and Cs_2CO_3 (67 mg, 0.21 mmol) in a

screw-cap vial. The mixture was cooled to 0 °C before dropwise addition of a solution of phenyl isocyanate (24 mg, 0.20 mmol) in toluene (0.2 mL). The mixture was warmed to room temperature and stirred for 30 min, before heating at 120 °C for 13 h. The mixture was filtered through Celite and concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with EtOAc/MeOH (100 : 1 → 90 : 10) to give 31 mg (92%) of the dihydroquinazolin-2-one **43** as a yellow glass: ^{1}H NMR (400 MHz) δ 7.50 (t, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.30-7.25 (m, 2 H), 7.10 (dd, *J* = 7.3, 1.6 Hz, 1 H), 7.04 (td, *J* = 8.0, 1.6 Hz, 1 H), 6.98 (td, *J* = 7.3, 1.1 Hz, 1 H), 6.21 (dd, *J* = 8.0, 1.1 Hz, 1 H), 4.62 (dd, *J* = 14.3, 2.0 Hz, 1 H), 4.56 (dd, *J* = 12.5, 2.3 Hz, 1 H), 4.25 (app t, *J* = 8.6 Hz, 1 H), 3.78 (app t, *J* = 8.6 Hz, 1 H), 3.39-3.23 (comp, 2 H), 3.13-3.02 (m, 1 H), 2.69 (s, 3 H), 2 .29-2.18 (m, 1 H), 1.99 (app q, *J* = 12.5 Hz, 1 H); ^{13}C NMR (75 MHz) δ 153.9, 139.1, 138.3, 2 × 129.8, 128.2, 128.1, 125.1, 122.3, 121.4, 115.1, 67.8, 64.1, 55.0, 44.3, 41.5, 38.5, 35.6; IR (neat) 2952, 1659, 1465, 1289, 1266 cm^{-1}; mass spectrum (ESI) *m/z* 336.1706 [$C_{20}H_{22}N_3O_2$ (M+1) requires 336.1707].

Allyl-[1-(2-bromo-6-chloro-phenyl)-but-3-enyl]carbamic acid benzyl ester (47). A mixture of allylamine (971 mg, 1.27 mL, 17.0 mmol), 2-bromo-6-chlorobenzaldehyde (**46**) (1.87 g, 8.51 mmol) and 4 Å molecular sieves (2.0 g) was stirred in CH_2Cl_2 (20 mL) for 12 h at room temperature. The sieves were removed by filtration through Celite, and the filtrate was concentrated under reduced pressure to afford 2.20 g (*ca.* 100%) of crude imine, which was used directly in the next step. Benzyl chloroformate (1.60 g, 1.34 mL, 9.39 mmol) was added to a solution of imine in THF (17 mL) and was heated at 60 °C for 1 h. The reaction was then cooled to –78 °C, and a freshly prepared solution of allylzinc bromide[48] (*ca.* 13.1 mmol) in THF (10 mL) was added and the reaction stirred for 2 h. The cooling bath was removed, and the reaction was allowed to warm to 0 °C and quenched with saturated aqueous NH_4Cl (~10 mL). The mixture was partitioned between water (100 mL) and Et_2O (100 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with hexanes/EtOAc (100 : 0 → 95 : 5 → 90 : 10 → 85 : 15) to give 3.31 g (89%) of **47** as a pale yellow oil: ^{1}H NMR (400 MHz) δ 7.60-7.40 (m, 1 H), 7.40-7.10 (comp, 6 H), 7.00 (t, *J* = 10.8 Hz, 1 H), 5.94-5.82 (m, 1 H), 5.80-5.66 (comp, 2 H), 5.35-4.80 (comp, 6 H), 4.32 (br d, *J* = 22.4 Hz, 1 H), 4.05 (dd, *J* = 23.0, 6.80 Hz, 1 H), 3.05-2.94 (m, 1 H), 2.89-2.81 (m, 1 H); ^{13}C NMR (75 MHz) δ 155.9, 137.3, 136.4, 135.5, 133.4, 132.5, 130.1, 128.7, 128.2, 127.9, 127.7, 117.9, 115.1, 67.1, 59.3, 47.6, 35.0; IR (neat) 3078, 2978, 1715, 1448, 1401, 1254 cm^{-1}; mass spectrum (ESI) *m/z* 434.0518 [$C_{21}H_{22}NO_2{}^{35}Cl^{79}Br$ (M+1) requires 434.0517].

Benzyl 6-(2-bromo-6-chlorophenyl)-5,6-tetrahydropyridine-1(2*H*)-carboxylate (48). Grubbs 2nd generation catalyst (49 mg, 58 μmol) was added to a solution of **47** (500 mg, 1.15 mmol) in CH_2Cl_2 (25

mL). After stirring for 14.5 h at room temperature, the reaction was concentrated under reduced pressure. The residue was dissolved in 15% EtOAc/hexanes and filtered through a plug of silica gel to remove the catalyst. The filter plug was rinsed with 15% EtOAc/hexanes (3 × 20 mL) and the combined washings and filtrate were concentrated under reduced pressure to give the crude product, which was purified *via* flash column chromatography eluting with hexanes/EtOAc (100 : 0 → 95 : 5) to give 434 mg (93%) of **48** as a colorless oil: ^{1}H NMR (400 MHz) δ 7.42 (d, *J* = 7.8 Hz, 1 H), 7.28-7.05 (comp, 6 H), 6.97 (t, *J* = 8.4 Hz, 1 H), 6.16-6.03 (comp, 2 H), 5.43 (t, *J* = 8.0 Hz, 1 H), 5.03 (d, *J* = 11.6 Hz, 1 H), 4.92-4.84 (m, 1 H), 4.47-4.43 (m, 1 H), 4.00 (d, *J* = 16.8 Hz, 1 H), 2.49 (app d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (75 MHz) δ 155.9, 139.9, 136.6, 133.5, 132.7, 130.4, 128.5, 128.4, 128.3, 128.0, 127.4, 126.3, 123.8, 67.5, 55.1, 53.7, 42.7, 27.7; IR (neat) 3044, 2944, 2851, 1695, 1415, 1328, 1228 cm^{-1}; mass spectrum (ESI) *m/z* 428.0023 [$C_{19}H_{17}NO_2Na^{35}Cl^{79}Br$ (M+Na) requires 428.0023].

10-Chloro-1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (52). *n*-BuLi (0.16 mL, 0.33 mmol, 2.04 M in hexanes) was added to a solution of dry THF (2.0 mL) and **48** (135 mg, 0.33 mmol) at −100 °C and stirred for 5 min. The reaction was warmed to −78 °C for 10 min then quenched with a solution of MeOH and saturated aqueous NH_4Cl (1:1; 2 mL). After warming to room temperature, the mixture was concentrated under reduced pressure and the residue purified *via* radial plc eluting with hexanes/EtOAc (100 : 0 → 90 : 10 → 80 : 20 → 70 : 30) to give 41 mg (60%) of **52** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.78 (d, *J* = 7.2 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 5.94-5.85 (m, 2 H), 4.70-4.64 (m, 1 H), 4.54 (dd, *J* = 10.8, 4.8 Hz, 1 H), 3.88-3.86 (m, 1 H), 3.19-3.12 (m, 1 H), 2.02-1.92 (m, 1 H); ^{13}C NMR (75 MHz) δ 166.1, 143.5, 135.1, 131.9, 130.0, 129.4, 128.7, 127.9, 127.2, 123.6, 123.3, 122.4; IR (neat) 3038, 2851, 1688, 1468, 1421, 1274 cm^{-1}; mass spectrum (ESI) *m/z* 220.0524 [$C_{12}H_{11}NO^{35}Cl$ (M+1) requires 220.0524].

2-(2-Bromo-6-chlorophenyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (53). A microwave vial containing tetrahydropyridine **48** (225 mg, 0.55 mmol) in dry THF (2.0 mL) and Et_3N (0.5 mL) was degassed with Ar for 20 min with stirring. The vial was sealed and heated in the microwave (120 °C, 300 W) for 50 min with vigorous stirring. The reaction was cooled to room temperature and concentrated under reduced pressure. EtOAc (30 mL) was added and the mixture was filtered through Celite and rinsed with EtOAc (2 × 10 mL). The combined filtrate and washings were concentrated under reduced pressure, and the residue was purified *via* radial plc eluting with hexanes/EtOAc (100 : 0 → 95 : 5) to give 173 mg (77%) of **53** as a colorless oil: ^{1}H NMR (400 MHz) δ 7.50-7.15 (comp, 6 H), 7.02-6.86 (comp, 3 H), 5.63-5.53 (m, 1 H), 5.25-4.85 (comp, 3 H), 2.20-1.98 (comp, 4 H); ^{13}C NMR (125 MHz) (rotamers) δ 153.4, 152.7, 139.0, 138.5, 136.1, 135.4, 133.6, 132.7, 131.8, 130.8, 129.4, 127.8, 126.5, 126.2, 124.8, 120.5, 107.1, 67.4, 57.2, 54.9, 26.6, 19.8; IR (neat) 3073, 2942, 2846, 1712, 1657, 1403, 1320, 1128, 1073, 922 cm^{-1}; mass spectrum (ESI) *m/z* 406.0206 [$C_{19}H_{18}NO_2{}^{35}Cl^{79}Br$ (M+1) requires

406.0209].

ACKNOWLEDGMENTS

We thank the National Institutes of Health (GM 24539 and GM 86192) and the Robert A. Welch Foundation (F-0652) for their generous support of this work. We are also grateful to Dr. Richard Pederson (Materia, Inc.) for providing metathesis catalysts used in these studies.

REFERENCES AND NOTES

1. For the origin of the term "privileged scaffolds", see: B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235.
2. For reviews on privileged scaffolds, see: (a) D. A. Horton, G. T. Bourne, and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; (b) R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow, and D. A. Pippin, *Comb. Chem. High Throughput Screening*, 2004, **7**, 473; (c) L. Constantino and D. Barlocco, *Curr. Med. Chem.*, 2006, **13**, 65; (d) M. E. Welsch, S. A. Snyder, and B. R. Stockwell, *Curr. Opin. Chem. Biol.,* 2010, **14**, 347.
3. S. F. Martin, B. Benage, and J. E. Hunter, *J. Am. Chem. Soc.*, 1988, **110**, 5925.
4. S. F. Martin, *Acc. Chem. Res.*, 2002, **35**, 895.
5. B. Cheng, J. D. Sunderhaus, and S. F. Martin, *Org. Lett.*, 2010, **12**, 3622.
6. (a) J. D. Sunderhaus, C. Dockendorff, and S. F. Martin, *Org. Lett.*, 2007, **9**, 4223; (b) J. D. Sunderhaus, C. Dockendorff, and S. F. Martin, *Tetrahedron*, 2009, **65**, 6454; (c) J. D. Sunderhaus and S. F. Martin, *Chem. Eur. J.*, 2009, **15**, 1300.
7. For preliminary accounts of some of this work, see: (a) J. R. Donald and S. F. Martin, *Org. Lett.*, 2011, **13**, 852; (b) J. J. Sahn, J. Y. Su, and S. F. Martin, *Org. Lett.*, 2011, **13**, 2590; (c) S. Hardy and S. F. Martin, *Org. Lett.*, 2011, **13**, 3102; (d) B. A. Granger, K. Kaneda, and S. F. Martin, *Org. Lett.*, 2011, **13**, 4542.
8. I. Gavras, D. Vlahakos, J. C. Melby, and H. Gavras, *J. Clin. Pharm.*, 1984, **24**, 343.
9. T. Asaoka, K. Yazawa, Y. Mikami, and K. Takahashi, *J. Antibiot.*, 1982, **35**, 1708.
10. G. Francois, G. Bringmann, J. D. Phillipson, M. R. Boyd, L. A. Assi, C. Schneider, and G. Timperman, PCT Int. Appl. WO 9521616 A1 19951717.
11. (a) D. E. Worrall, *Org. Syn.*, 1929, **9**, 66; (b) R. W. Schumacher and B. S. Davidson, *Tetrahedron*, 1999, **55**, 935; (c) A. M. M. Mjalli, D. R. Gohimmukkulah, and S. Tyagi, PCT Int. Appl. WO 2006093823.
12. N. Slougui and G. Rousseau, *Synth. Commun.*, 1987, **17**, 1.

13. T. Kawate, M. Nakagawa, H. Yamazaki, M. Hirayama, and T. Hino, *Chem. Pharm. Bull.*, 1993, **41**, 287.
14. P. Cledera, C. Avendaño, and J. C. Menéndez, *Tetrahedron*, 1998, **54**, 12349.
15. Y. Dong, J. Chollet, M. Vargas, N. R. Mansour, Q. Bickle, Y. Alnouti, J. Huang, J. Keiser, and J. L. Vennerstrom, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2481.
16. This procedure can be telescoped in a one pot procedure, although in preliminary experiments we found the yields were less reproducible.
17. For recent reviews on the use of α-amino nitriles in the generation of molecular diversity, see: (a) T. Opatz, *Synthesis*, 2009, **12**, 1941; (b) J. A. González-Vera, M. T. García-López, and R. Herranz, *Mini-Rev. Org. Chem.*, 2008, **5**, 209; (c) D. Enders and J. P. Shilvock, *Chem. Soc. Rev.*, 2000, **29**, 359.
18. For a recent review, see: P. Galatsis, In *Name Reactions for Functional Group Transformations*, ed. by J. J. Li and E. J. Corey, Wiley: Hoboken, 2007, 477.
19. E. T. Pelkey and G. W. Gribble, *Tetrahedron Lett.*, 1997, **38**, 5603.
20. L. Bertelli, G. Biagi, I. Giorgi, O. Livi, C. Manera, V. Scartoni, C. Martini, G. Giannaccini, L. Trincavelli, and P. L. Barili, *Farmaco*, 1998, **53**, 305.
21. (a) C. del Pozo, A. Macías, F. López-Oritz, M. A. Maestro, E. Alonso, and J. González, *Eur. J. Org. Chem.*, 2004, 535; (b) P. D. Mehta, N. P. S. Sengar, and A. K. Pathak, *Eur. J. Med. Chem.*, 2010, **45**, 5541.
22. A. Salcedo, L. Neuville, and J. Zhu, *J. Org. Chem.*, 2008, **73**, 3600.
23. (a) J. J. Baldwin, D. A. Claremon, J. M. Elliott, N. Liverton, D. C. Remy, and H. G. Selnick, Merck & Co. Inc., World Patent WO 9514471 (A1), 1995; (b) J. J. Lynch Jr., and J. J. Salata, Merck & Co. Inc., World Patent WO 9800405 (A1), 1998.
24. (a) J. V. Cooney and W. E. McEwen, *J. Org. Chem.*, 1981, **46**, 2570; (b) J. V. Cooney, B. D. Beaver, and W. E. McEwen, *J. Heterocycl. Chem.*, 1985, **22**, 635.
25. G. V. De Lucca and M. J. Otto, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 1639.
26. G. Broggini, L. Garanti, G. Molenti, and G. Zecchi, *Heterocycles*, 1999, **51**, 1295.
27. M. Boulouard, A. C. Gillard, P. O. Guillaumat, M. Daoust, E. Legrand, M. A. Quermonne, and S. Rault, *Pharm. Pharmacol. Commun.*, 1998, **4**, 43.
28. D. Xiao, A. Palani, C. Wang, H.-C. Tsui, N.-Y. Shih, and G. A. Reichard, European Patent EP 1,747,221, 2005.
29. For the original report of this method to cleave 4-pentenamides, see: R. Madsen, C. Roberts, and B. Fraser-Reid, *J. Org. Chem.*, 1995, **60**, 7920.
30. For the only other known example of a tandem enolate arylation/alkylation process, see: R. R.

Goehring, Y. P. Sachdeva, J. S. Pisipati, M. C. Sleevi, and J. F. Wolfe, *J. Am. Chem. Soc.*, 1985, **107**, 435.

31. R. Ferraccioli and D. Carenzi, *Synthesis*, 2003, **9**, 1383.
32. For a similar reaction, using aryl iodides in conjunction with pre-formed thioureas, see: D. Orain, A.-C. Blumstein, E. Tasdelen, and S. Haessig, *Synlett*, 2008, **16**, 2433.
33. S. Jones, J. Johnson, J. Ives, K. Hedberg, A. Dunaiskis, D. Chapin, J. Nielsen, D. Liston, and Y. L. Chen, *J. Med. Chem.*, 1994, **37**, 1996.
34. A. E. Jacobson and M. Mokotoff, *J. Med. Chem.*, 1970, **13**, 7.
35. (a) L. S. Povarov, *Russ. Chem. Rev.*, 1967, **36**, 656; (b) V. V. Kouznetsov, *Tetrahedron*, 2009, **65**, 2721.
36. C. Xia, L. Heng, and D. Ma, *Tetrahedron Lett.*, 2002, **43**, 9405.
37. K. Minagawa, S. Kouzuki, and T. Kamigauchi, *J. Antibiot.*, 2002, **55**, 165.
38. D. K. Luci, E. C. Lawson, E. Ghosh, W. A. Kinny, C. E. Smith, J. Qi, Y. Wang, L. K. Minor, and B. E. Maryanoff, *Tetrahedron Lett.*, 2009, **50**, 4958.
39. M. L. Curtin, R. R. Frey, R. H. Heyman, K. A. Sarris, D. H. Steinman, J. H. Holmes, P. J. Bousquet, G. A. Cunha, M. D. Moskey, A. A. Ahmed, L. J. Pease, K. B. Glaser, K. D. Stewart, S. K. Davidsen, and M. R. Michaelides, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4505.
40. W. E. Parham and C. K. Bradsher, *Acc. Chem. Res.*, 1982, **15**, 300.
41. A. Hinschberger, S. Butt, B. Lelong, M. Boulouard, A. Dumuis, D. Francois, R. Bureau, B. Pfeiffer, P. Renard, and S. Rault, *J. Med. Chem.*, 2003, **46**, 138.
42. For example, see: F. F. Painter and K. T. Wanner, *Tetrahedron*, 1994, **50**, 3113.
43. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
44. C. A. Sperger and K. T. Wanner, *Tetrahedron*, 2009, **65**, 5824.
45. A. O. King, E. Negishi, F. J. Villani, Jr., and A. Silveira, Jr., *J. Org. Chem.*, 1978, **43**, 358.
46. Y. Kawakamie, T. Aoki, and Y. Yamashita, *Polym. Bull.*, 1987, **18**, 473.
47. S. B. Rosenblum, T. Huynh, A. Afonso, and H. R. Davis Jr., *Tetrahedron*, 2000, **56**, 5735.
48. E. Negishi, L. D. Boardman, S. Vahid, A. Bagheri, T. Stoll, J. M. Tour, and C. L. Rand, *J. Am. Chem. Soc.*, 1988, **110**, 5383.