Construction of bicyclic tetrahydroisoquinolinones by combination of an IMDAF-ring cleavage reaction of *N*-allyl-2-furan-2-yl-acetamides

Albert Padwa and Thomas S. Reger

Abstract: The intramolecular Diels–Alder reaction of furanyl amides derived from 2-furylacetic acid has been examined. Substrates containing either an imide or tertiary amide linkage between the furan and the dienophile underwent smooth cycloaddition upon thermolysis. By varying the reaction conditions, either the primary cycloadduct or the ring-opened and acetylated product could be isolated in excellent yield. The stereochemical outcome of the IMDAF cycloaddition has the side arm of the tethered alkenyl group oriented *syn* with respect to the oxygen bridge. Semi-empirical AM1 calculations show that the *exo*-cycloadduct is 11 kcal lower in energy than the corresponding *endo* adduct and, presumably, some of this energy difference is reflected in the transition state for the cycloaddition. The IMDAF reaction of *N*-allyl-[2-(3,4-dimethoxyphenethyl)]-2-furanyl-2-yl-acetamide proceeded in 90% yield upon heating in xylene. The 4+2-cycloadduct undergoes ring-opening on treatment with base and the resulting alcohol was converted into the corresponding benzyl ether. Raney nickel reduction followed by Bischler–Napieralski cyclization furnished the tetracyclic skeleton of the berberine alkaloids.

Key words: intramolecular, cycloaddition, Diels–Alder, furanylamide, heterocycle.

Résumé : On a étudié la réaction de Diels–Alder intramoléculaire de furanylamides (« IMDAF ») dérivés de l'acide furyl-2-acétique. Par thermolyse, les substrats comportant soit une liaison imide ou amide tertiaire entre le furane et le diénophile subissent une cycloaddition facile. En faisant varier les conditions réactionnelles, on peut isoler avec un excellent rendement soit le cycloadduit primaire ou le produit dérivant d'une ouverture de cycle et d'une acétylation. D'un point de vue stéréochimique, la cycloaddition « IMDAF » conduit à un produit dans lequel la chaîne latérale du groupe alcényle prend une orientation *syn* par rapport au pont oxygéné. Des calculs semi-empiriques AM1 montrent que l'énergie du cycloadduit *exo* est inférieure de 11 kcal par rapport à celle de l'adduit *endo* correspondant; il est vraisemblable qu'une partie de cette différence d'énergie se reflète dans l'état de transition de la cycloaddition. La réaction « IMDAF » du *N*-allyl-[2-(3,4-diméthoxyphénéthyl)]-2-furanyl-2-yl-acétamide se produit avec un rendement de 90% par chauffage dans le xylène. Le cycloadduit 4+2 subit une ouverture de cycle par traitement avec une base et l'alcool qui en résulte a été transformé en éther benzylique correspondant. Une réduction à l'aide de nickel de Raney, suivie d'une cyclisation de Bischler–Napieralski, conduit au squelette tétracyclique des alcaloïdes de la berbérine.

Mots clés : intramoléculaire, cycloaddition, Diels–Alder, furanylamide, hétérocycle.

Introduction

Furans are common substructures found in numerous natural products and are also present in many commercial products, including pharmaceuticals, fragrances, and dyes (1–4). Furans also play an important role as intermediates in many synthetic pathways, primarily because they react as a special class of vinyl ethers (5, 6) or as dienes in the Diels–Alder reaction (7). The resultant 7-oxabicyclo-[2.2.1]heptanes are valuable synthetic intermediates which have been further elaborated to substituted arenes, carbohydrate derivatives, and various natural products (8–17). A crucial synthetic transformation employing these oxabicyclic compounds involves cleavage of the oxygen bridge to produce functionalized cyclohexene derivatives (18–23). The intramolecular Diels–Alder reactions of furans, often designated as IMDAF, has proven to be an extremely valuable method for the construction of more complex oxygenated, bicyclic structures (7). The IMDAF generally proceeds at lower temperature than its bimolecular counterpart and, more importantly, often allows for the use of unactivated alkenes as dienophiles (24). Recent work in our laboratory has shown that the intramolecular Diels–Alder of 2-amido substituted furans such as **1** represents an effective route to indolines and tetrahydroquinolines (25). This methodology has also been utilized for the synthesis of the hexahydroindolinone skeleton found in numerous alkaloids (26). Intramolecular cycloaddition of the 2-amidofuran followed by ring opening gives a zwitterionic intermediate **3** that can be channeled to different products depending on the

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This paper is dedicated to Stephen Hanessian on the occasion of his 65th birthday and for his many significant contributions to the art of organic synthesis.

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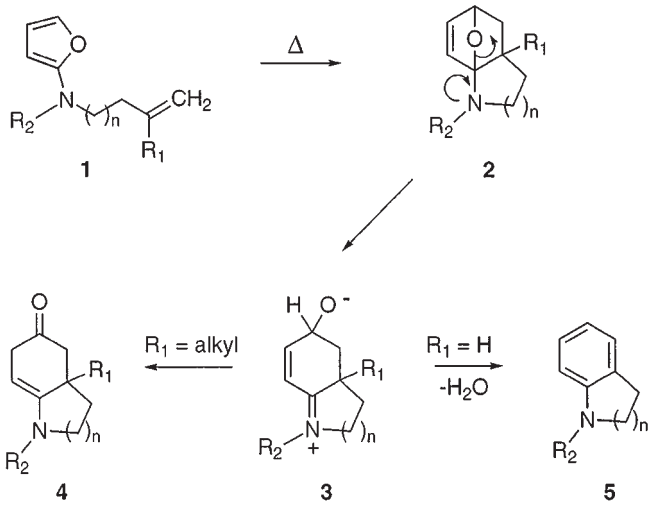
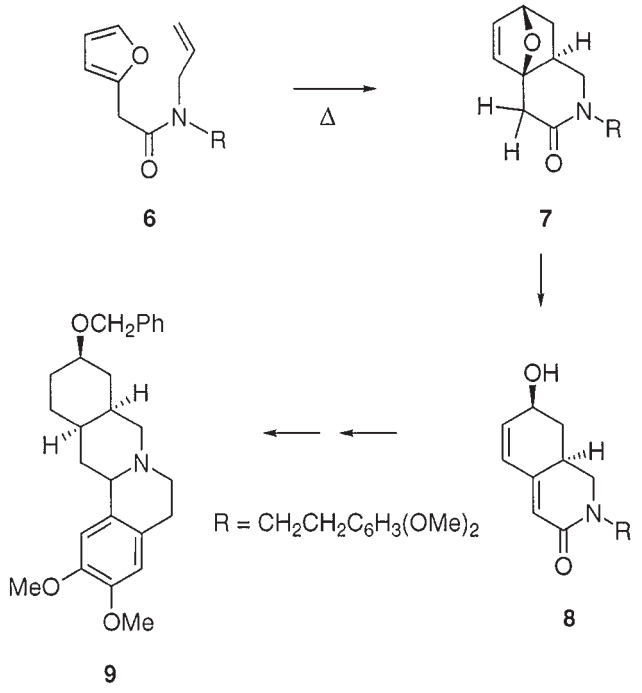
Scheme 1.



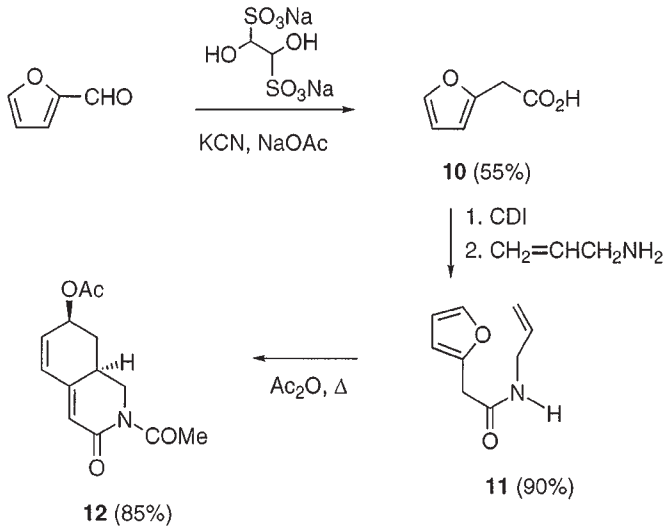
Scheme 2.



nature of the substituent group attached to the π-bond (i.e., R_1) (Scheme 1).

One of the most attractive features of this reaction sequence is the propensity for nitrogen assisted ring-opening and subsequent iminium ion formation of the oxabicyclic cycloadducts (i.e., **2** → **3**). The majority of work carried out by other investigators on the IMDAF reaction utilizing nitrogen containing tethers was done with furfurylamine derived substrates whose cycloadducts are not predisposed to spontaneous ring-opening (27–29). As an extension of our earlier work in this area, we believed that related furanyl amides such as **6** should also be excellent substrates for intramolecular Diels–Alder cycloaddition and oxabicyclic

Scheme 3.



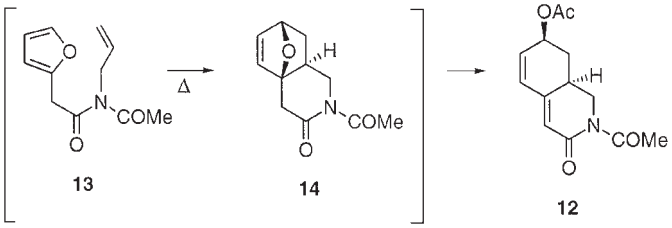
ring-opening as a consequence of the acidic nature of the protons adjacent to the oxygen bridge (Scheme 2). To the best of our knowledge, amides derived from 2-furylacetic acid have not been utilized in Diels–Alder chemistry. A study to examine the synthesis of furans such as **6** and their subsequent cycloaddition and ring-opening chemistry was initiated with the intention of using this method as an entry into the berberine alkaloid family (30). The biological activity that these molecules display varies widely and includes anti-inflammatory, antimicrobial and antileukemic, as well as antitumor, properties (30). In the light of these properties and due to the general challenge that the construction of complex alkaloids offers, the development of new methods for the stereoselective synthesis of these nitrogen heterocycles is of considerable interest. In this paper we report the results of our IMDAF studies dealing with *N*-allyl 2-furan-2-yl-acetamides.

Results and discussion

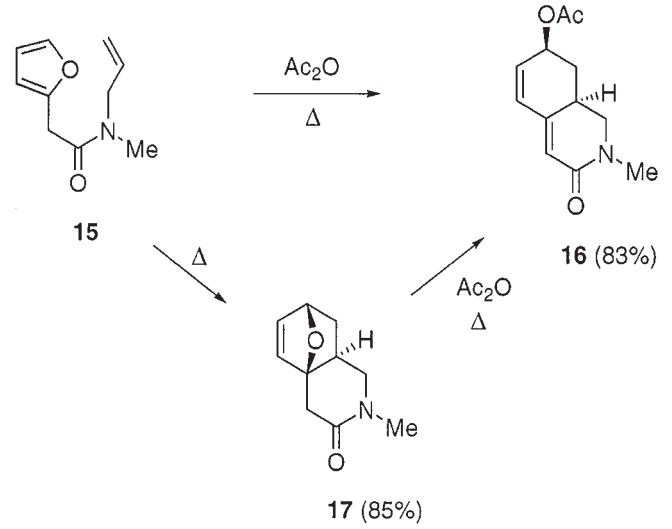
As an entry into furanyl amides such as **6**, 2-furylacetic acid (**10**) was required as the key starting material. In our hands, the most reliable synthesis corresponds to the one-pot reaction between 2-furaldehyde and potassium cyanide (31). Reaction of these two reagents in the presence of sodium carbonate and glyoxal (sodium bisulfite addition compound hydrate) in a 20:1 water:dioxane solution reproducibly gave **10** in 55% yield. Carboxylic acid **10** was converted to the *N*-allyl amide **11** in 90% yield by reaction with 1,1-carbonyldiimidazole (CDI) followed by quenching with allylamine (Scheme 3). The attempted Diels–Alder cycloaddition of **11** in refluxing toluene or xylene led only to recovered starting material. This result is perfectly consistent with the earlier reports of Jung (27) and Parker (28) who found that related furans containing secondary amide tethers failed to undergo the Diels–Alder reaction. Cycloaddition could be effected, however, by heating **11** in refluxing acetic anhydride.[2] Under these conditions, the initial formation of imide **13** presumably

[2] The role of acetic anhydride in this reaction is to promote the [4+2]-cycloaddition by acylation at nitrogen as well as to assist in the subsequent oxa-bridge cleavage.

Scheme 4.



Scheme 5.

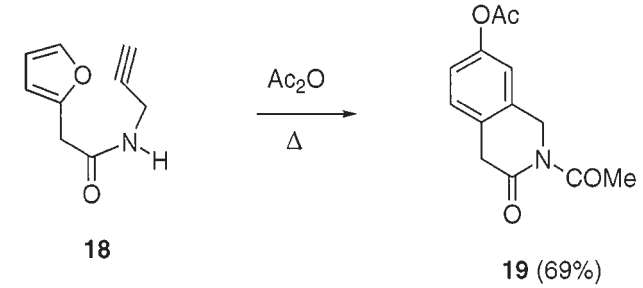


facilitates the Diels–Alder reaction to give the oxabicyclic intermediate **14**. The cycloadduct was not isolated as it undergoes spontaneous ring-opening and O-acetylation to furnish **12** as a single diastereomer in 85% yield (Scheme 4).

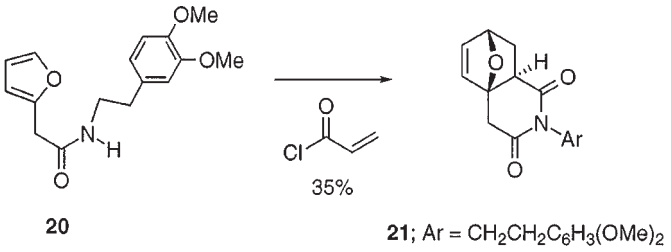
The *trans* relationship between the acetate and the bridgehead hydrogen is derived from the presumed cycloadduct **14** which results from *exo* orientation of the tether during the cycloaddition. This mode of cyclization for the IMDAF reaction of substrates containing nitrogen in the tether is analogous to that reported by others for related furanyl systems possessing short tethers (32, 33). The ring-opened acetate **12** is thus derived from an IMDAF cycloaddition where the side arm of the tethered alkenyl group is oriented *syn* (*exo*) with respect to the oxygen bridge. Products resulting from an *endo* side arm transition state were neither detected nor isolated. This result is not so surprising since, in these mobile cycloaddition equilibria, the *exo* adducts are expected to be thermodynamically more favored. Indeed, semi-empirical AM1 calculations show that the *exo*-cycloadduct is 11 kcal lower in energy than the corresponding *endo* (with respect to the tether) adduct and, presumably, some of this energy difference is reflected in the transition state for cycloaddition.

We next turned our attention to determining whether a tertiary amide linkage between the furan and alkene would allow the cycloaddition to proceed. Amide **15** was prepared in 94% yield by reaction of carboxylic acid **10** with CDI followed by quenching with *N*-methylallylamine. Upon thermolysis of **15** in acetic anhydride, the expected ring-opened and acetylated lactam **16** was isolated in 83% yield as a single diastereomer. The formation of **16** proceeds by a

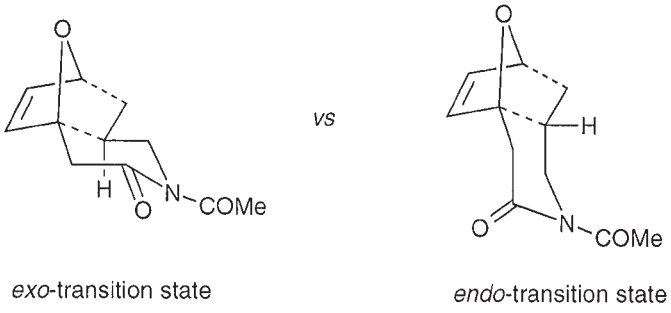
Scheme 6.



Scheme 7.



Structure 1.

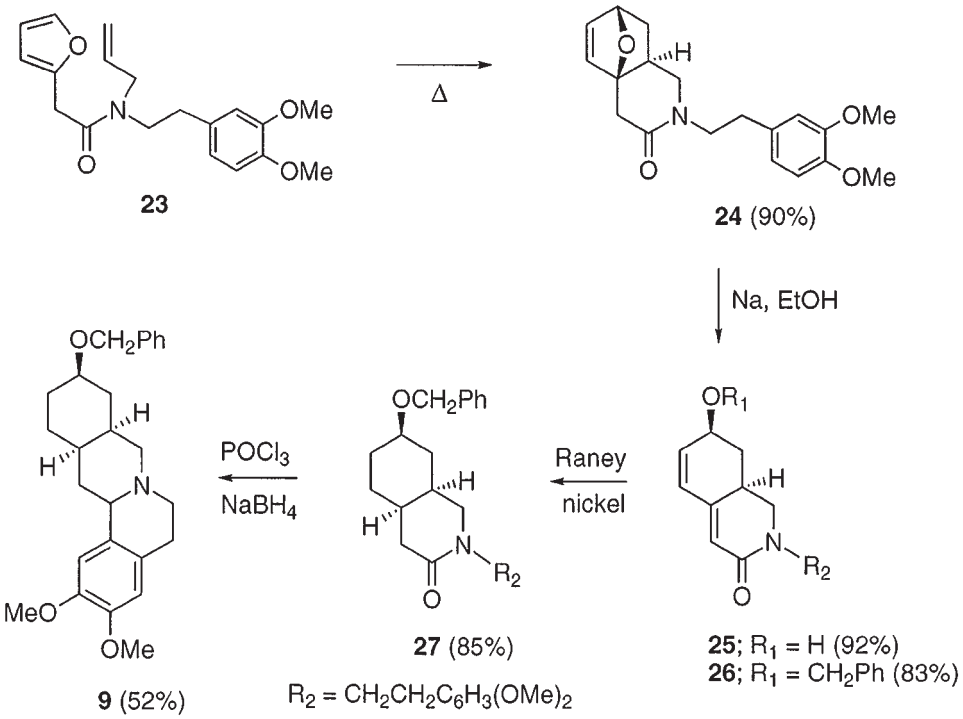


similar pathway to that described for **13**. Interestingly, when amide **15** was heated in refluxing toluene, the primary cycloadduct **17** was obtained in 85% yield, also as a single diastereomer, and could be quantitatively converted to **16** by heating in acetic anhydride (Scheme 5).

To further examine the scope of this cycloaddition with respect to the dienophile, furan **18** containing an alkyne tether was prepared in 86% yield. Heating a sample of **18** in acetic anhydride gave the isoquinoline derivative **19** in 69% yield (Scheme 6).

We next turned our attention to substrates bearing both a dienophile and an electron-rich aromatic group connected to the amide nitrogen (i.e., **23**). It was envisioned that a Bischler–Napieralski type cyclization (vide infra) could be effected on the Diels–Alder cycloaddition product. To this end, amide **20** was prepared in 87% yield by the usual reaction of 2-furylacetic acid with CDI and quenching with 3,4-dimethoxyphenethylamine. Unfortunately, all of our attempts to alkylate **20** with allyl bromide using a variety of bases (Cs_2CO_3 (DMF); NaH (THF); NaOH, K_2CO_3, Bu_4NHSO_4) failed to give any product. Imide formation with acryloyl chloride at room temperature in the presence of 4 Å molecular sieves did produce cycloadduct **21**, but only in 35% yield (Scheme 7).

Scheme 8.



As an alternative route to **23**, the known secondary amine allyl-[2-(3,4-dimethoxyphenethylamine)] (**22**) (34) was prepared and used to generate the desired tertiary amide directly. Thus, the reaction of carboxylic acid **10** with CDI followed by addition of amine **22** gave the desired cyclization precursor **23** in 77% yield. Upon heating **23** in refluxing xylene, cycloadduct **24** was isolated in 90% yield as a single diastereomer. A variety of bases were examined to induce ring-opening of **24** to the allylic alcohol **25**. Triethylamine, sodium hydride, and potassium *tert*-butoxide were all successful, but the use of the sodium in ethanol gave the highest yield (92%) and cleanest reaction. We then attempted a Bischler–Napieralski cyclization of the aromatic ring onto the amide carbonyl of **25** but this gave only a complex mixture of unidentifiable products. Instead, the alcohol was protected as its benzyl ether with sodium hydride and benzyl bromide in 83% yield. Compound **26** was then reduced to the decahydroisoquinoline **27** with Raney nickel in 85% yield. This compound was formed as a single diastereomer and there is literature precedence for a similar transformation in which Raney nickel reduction occurs from the *exo* face of a bicyclic structure to yield a *cis* ring junction (35). The Bischler–Napieralski cyclization of **27** was effected with $POCl_3$ followed by $NaBH_4$ and furnished **9** in 52% yield (Scheme 8). The appearance of two singlets in the aromatic region of the ^{1}H-NMR spectrum of **9** was indicative that the desired cyclization had taken place. This reaction proved to be very sensitive to the experimental conditions and, unfortunately, even the use of freshly distilled $POCl_3$ offered no advantage in terms of reaction yield. Nevertheless, the tetracyclic compound **9** containing the core skeleton of the berberine alkaloids was readily accessible in just five steps from relatively simple cyclization precursors.

In conclusion, the intramolecular Diels–Alder reaction of furanyl amides derived from 2-furylacetic acid proceeds smoothly and in high yield. The cyclization precursors are easily synthesized from readily available starting materials. The cycloaddition can be carried out under a variety of conditions to yield either the primary cycloadduct or the ring-opened and acetylated product. Consistent with previous studies, only compounds bearing imide or tertiary amide linkages between the furan and tethered dienophile were suitable substrates for cycloaddition. Overall, this methodology represents an efficient route to functionalized members of the tetrahydroisoquinolinone ring system in various oxidation states which could serve as intermediates to members of the berberine alkaloid family. Applications toward specific natural products and the further development of the IMDAF are currently underway and will be reported in due course.

Experimental section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate – hexane mixture as the eluent unless specified otherwise.

N-*Allyl-2-furan-2-yl-acetamide (**11**)*: To a solution containing 1.4 g (11 mmol) of furan-2-yl-acetic acid (**10**) (31) in 25 mL of CH_2Cl_2 was added 2.0 g (12.6 mmol) of 1,1′-carbonyldiimidazole. After stirring at room temperature for 1.5 h, 1.3 g (22 mmol) of allylamine was added and the mixture was stirred for an additional 1 h. The mixture was concentrated under reduced pressure and the crude product was purified by silica gel chromatography to give 1.6 g (90%) of

11 as a pale yellow liquid; IR (neat) ν: 3290, 1652, 1545, 1418, and 1246 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.64 (2H, s), 3.85–3.89 (2H, m), 5.08–5.14 (2H, m), 5.75–5.85 (1H, m), 5.95 (1H, brs), 6.24 (1H, d, *J* = 3.2 Hz), 6.36 (1H, dd, *J* = 3.2 and 1.6 Hz), and 7.39 (1H, d, *J* = 1.6 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.1, 41.8, 108.5, 110.7, 116.0, 133.8, 142.4, 148.6, and 168.4 ppm; HRMS calcd for $C_9H_{11}NO_2$: 165.0790; found: 165.0787.

*7-Acetoxy-2-acetyl-1,7,8,8a-tetrahydro-2*H-*isoquinoline-3-one (**12**)*: A solution containing 0.3 g (1.7 mmol) of **11** in 10 mL of acetic anhydride was heated at reflux for 20 h. The solution was concentrated under reduced pressure and the crude product was purified by silica gel chromatography to give 0.36 g (85%) of **12** as a white solid, mp 160–161°C; IR (neat): 1734, 1676, 1467, 1371, and 1289 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.46 (1H, dd, *J* = 12.8 and 11.6 Hz), 2.11 (3H, s), 2.30–2.35 (1H, m), 2.56 (3H, s), 2.69–2.76 (1H, m), 2.99 (1H, t, *J* = 12.8 Hz), 4.75 (1H, dd, *J* = 12.8 and 4.8 Hz), 5.55–5.59 (1H, m), 5.83 (1H, d, *J* = 2.0 Hz), 6.20 (1H, d, *J* = 10.0 Hz), and 6.35 (1H, dd, *J* = 10.0 and 2.0 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.0, 27.2, 31.9, 45.8, 68.6, 120.0, 127.3, 138.6, 151.0, 165.9, 170.2, and 172.8 ppm. Anal. calcd. for $C_{13}H_{15}NO_4$: C 62.64, H 6.07, N 5.62; found: C 62.52, H 6.09, N 5.54.

N-*Allyl-2-furan-2-yl*-N-*methyl-acetamide (**15**)*: To a solution of 0.6 g (4.8 mmol) of furan-2-yl-acetic acid (**10**) in 20 mL of CH_2Cl_2 was added 1.0 g (6.4 mmol) of 1,1′-carbonyldiimidazole. After stirring for 1 h at room temperature, 0.7 g (9.6 mmol) of *N*-methylallylamine was added and the mixture was stirred for an additional 1 h. The solution was concentrated under reduced pressure and the crude product was purified by silica gel chromatography to yield 0.8 g (94%) of **15** as a pale yellow oil which contained a mixture of amide rotamers in solution; IR (neat) ν: 1652, 1477, 1396, and 1147 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.94 (3H, s) and 3.00 (3H, s), 3.71 (2H, s) and 3.76 (2H, s), 3.97 (2H, m) and 4.01 (2H, m), 5.11–5.24 (2H, m), 5.68–5.79 (1H, m), 6.19–6.20 (1H, m), 6.31–6.33 (1H, m), and 7.34–7.35 (1H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 33.5, 33.6, 34.0, 34.9, 50.0, 52.4, 107.4, 110.4, 116.7, 117.2, 132.2, 132.5, 141.5, 141.6, 148.6, 148.7, 168.3, and 168.7 ppm; HRMS calcd. for $C_{10}H_{13}NO_2$: 179.0946; found: 179.0939.

*7-Acetoxy-2-methyl-1,7,8,8a-tetrahydro-2*H-*isoquinoline-3-one (**16**)*: A solution containing 0.2 g (1.1 mmol) of furan **15** in 10 mL of acetic anhydride was heated at reflux for 20 h. The solution was concentrated under reduced pressure and the crude solid was purified by silica gel chromatography to give 0.21 g (83%) of **16** as a white solid, mp 104–105 °C; IR (neat) ν: 1730, 1652, 1590, and 1232 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.38–1.47 (1H, m), 2.10 (3H, s), 2.24–2.30 (1H, m), 2.82–2.85 (1H, m), 3.01 (3H, s), 3.26–3.36 (2H, m), 5.52–5.55 (1H, m), 5.77 (1H, d, *J* = 1.6 Hz), 6.02 (1H, d, *J* = 10.0 Hz), and 6.29 (1H, dd, *J* = 10.0 and 1.6 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.9, 31.2, 31.8, 34.2, 52.9, 68.6, 119.8, 127.9, 135.3, 145.4, 165.4, and 170.2 ppm. Anal. calcd. for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33; found: C 65.38, H 6.91, N 6.47.

*4-Methyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-3-one (**17**)*: A solution containing 1.6 g (8.8 mmol) of furan **15** in 15 mL of toluene was heated at reflux for 20 h. The solution was concentrated under reduced pressure and the crude solid was purified by silica gel chromatography to give 1.3 g (85%) of **17** as a white solid, mp 89–90°C; IR (neat) ν: 1646, 1495, 1394, and 1315 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44–1.51 (2H, m), 1.85–1.91 (1H, m), 2.94 (1H, d, J = 18.8 Hz), 3.00 (3H, s), 3.14 (1H, d, *J* = 18.8 Hz), 3.31–3.34 (2H, m), 4.94 (1H, dd, *J* = 4.0 and 1.6 Hz), 6.14 (1H, d, *J* = 6.0 Hz), and 6.40 (1H, dd, *J* = 6.0 and 1.6 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.6, 35.0, 35.2, 35.5, 52.9, 78.1, 85.6, 137.3, 137.4, and 168.4 ppm. Anal. calcd. for $C_{10}H_{13}NO_2$: C 67.02, H 7.31, N 7.82; found: C 66.75, H 7.24, N 7.73.

2-Furan-2-yl-N-*prop-2-ynyl-acetamide (**18**)*: To a solution containing 0.8 g (6.4 mmol) of furan-2-yl-acetic acid (**10**) in 25 mL of CH_2Cl_2 was added 1.4 g (8.6 mmol) of 1,1′-carbonyldiimidazole. After stirring at room temperature for 1.5 h, 0.6 mL (8.7 mmol) of propargylamine was added and the mixture was stirred for an additional 1 h. The solution was concentrated under reduced pressure and the crude product was purified by silica gel chromatography to give 0.9 g (86%) of **18** as a white solid, mp 75–76°C; IR (neat) ν: 3286, 1648, 1552, 1424, and 1240 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.23 (1H, t, *J* = 2.4 Hz), 3.63 (2H, s), 4.02 (2H, dd, *J* = 2.8 and 2.4 Hz), 6.23 (1H, d, *J* = 2.8 Hz), 6.34–6.36 (1H, m), 6.50 (1H, brs), and 7.38 (1H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.1, 35.7, 71.4, 79.2, 108.4, 110.6, 142.3, 148.2, and 168.4 ppm. Anal. calcd. for $C_9H_9NO_2$: C 66.25, H 5.56, N 8.58; found: C 66.16, H 5.49, N 8.61.

*2-Acetyl-7-acetoxy-1,4-dihydro-2*H-*isoquinolin-3-one (**19**)*: A solution containing 0.2 g (1.4 mmol) of furan **18** in 10 mL of acetic anhydride was heated at reflux for 24 h. The solution was concentrated under reduced pressure and the crude residue was purified by silica gel chromatography to give 0.24 g (69%) of **19** as a pale yellow oil; IR (neat) ν: 1760, 1705, 1498, 1367, and 1208 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.32 (3H, s), 2.58 (3H, s), 3.74 (2H, s), 4.92 (2H, s), 7.02–7.05 (1H, m), 7.05 (1H, s), and 7.22–7.26 (1H, m) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.0, 27.2, 40.8, 45.3, 119.2, 121.2, 127.5, 129.5, 133.5, 149.4, 169.2, 170.8, and 172.1 ppm; HRMS (FAB) calcd. for $C_{13}H_{13}NO_4Li$ (M + Li): 254.1005; found: 254.1006.

N-*[2-(3,4-Dimethoxyphenethyl)]-2-furan-2-yl-acetamide (**20**)*: To a solution containing 0.86 g (6.8 mmol) of furan-2-yl-acetic acid (**10**) in 25 mL of CH_2Cl_2 was added 1.5 g (9.0 mmol) of 1,1′-carbonyldiimidazole. After stirring for 1 h at room temperature, 1.9 g (10.3 mmol) of 3,4-dimethoxyphenethylamine was added and the mixture was stirred for an additional 1 h. The solution was concentrated under reduced pressure and the crude product was purified by silica gel chromatography to give 1.7 g (87%) of **20** as a white solid, mp 78–79°C; IR (neat) ν: 3293, 1648, 1511, and 1258 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.72 (3H, t, *J* = 6.8 Hz), 3.46 (2H, dt, *J* = 6.8 and 6.0 Hz), 3.57 (2H, s), 3.84 (3H, s), 3.85 (3H, s), 5.85 (1H, brs), 6.15–6.16 (1H, m), 6.31–6.33 (1H, m), 6.63–6.67 (2H, m), 6.76–6.78 (1H, m),

and 7.32–7.33 (1H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 34.9, 36.1, 40.7, 55.6, 55.7, 108.3, 110.6, 111.1, 111.7, 120.4, 131.0, 142.2, 147.4, 148.6, 148.8, and 168.3 ppm; Anal. calcd. for $C_{16}H_{19}NO_4$: C 66.42, H 6.62, N 4.84; found: C 66.40, H 6.60, N 4.89.

*4-[2-(3,4-Dimethoxyphenethyl)]-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}] undec-9-ene-3,5-dione (**21**)*: To a solution containing 0.5 g (1.7 mmol) of amide **20** in 15 mL of CH_2Cl_2 was added 1.7 g of powdered molecular sieves (4 Å) followed by 0.46 g (5.1 mmol) of acryloyl chloride and the mixture was stirred at room temperature for 20 h. The solution was filtered through a pad of celite and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give 0.2 g (35%) of **21** as a pale yellow solid, mp 170–171°C; IR (neat) ν: 1730, 1680, 1515, and 1365 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.74 (1H, dd, *J* = 12.0 and 4.8 Hz), 2.26–2.32 (1H, m), 2.75–2.78 (3H, m), 3.24 (1H, d, *J* = 16.8 Hz), 3.46 (1H, d, *J* = 16.8 Hz), 3.86 (3H, s), 3.88 (3H, s), 3.91–4.06 (2H, m), 5.09 (1H, dd, *J* = 4.8 and 2.0 Hz), 5.78 (1H, d, *J* = 5.6 Hz), 6.56 (1H, d, *J* = 5.6 Hz), and 6.75–6.81 (3H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.6, 33.4, 40.5, 41.5, 47.1, 55.7, 55.8, 80.3, 82.1, 111.0, 112.0, 120.9, 130.6, 131.6, 141.7, 147.6, 148.7, 170.0, and 171.0 ppm; Anal. calcd. for $C_{19}H_{21}NO_5$: C 66.46, H 6.16, N 4.08; found: C 66.39, H 6.14, N 4.06.

N-*Allyl-[2-(3,4-dimethoxyphenethyl)]-2-furan-2-yl-acetamide (**23**)*: To a solution containing 0.2 g (1.7 mmol) of furan-2-yl-acetic acid (**10**) in 8 mL of CH_2Cl_2 was added 0.4 g (2.5 mmol) of 1,1′-carbonyldiimidazole. After stirring at room temperature for 1 h, 0.5 g (2.4 mmol) of allyl-[2-(3,4-dimethoxyphenethyl)]amine (**22**) (34) was added and the mixture was stirred for an additional 2 h. The solution was concentrated under reduced pressure and the crude product was purified by silica gel chromatography to give 0.4 g (77%) of **23** as a clear oil which contained a mixture of amide rotamers in solution; IR (neat) ν: 1651, 1515, 1457, and 1260 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.74 (2H, t, *J* = 7.2 Hz) and 2.82 (2H, t, *J* = 7.2 Hz), 3.51–3.56 (2H, m), 3.70 (1H, s), 3.82–3.83 (2H, m), 3.84 (3H, s) and 3.85 (3H, s), 3.86 (3H, s) and 3.87 (3H, s), 4.02 (1H, d, *J* = 6.0 Hz), 5.13–5.21 (2H, m), 5.71 (1H, m) and 5.81 (1H, m), 6.14–6.18 (1H, m), 6.31–6.34 (1H, m), 6.65–6.83 (3H, m), and 7.33–7.36 (1H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 33.4, 33.5, 33.7, 34.5, 48.0, 48.6, 49.2, 51.1, 55.7, 55.8, 55.9, 107.4, 107.5, 110.4, 110.5, 111.1, 111.4, 111.8, 111.9, 116.6, 117.1, 120.6, 120.7, 130.5, 131.6, 132.7, 133.1, 141.6, 141.7, 147.4, 147.8, 148.7, 148.8, 168.3, and 168.7 ppm; Anal. calcd. for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 4.17; found: C 68.98, H 7.04, N 4.22.

*4-[2-(3,4-Dimethoxyphenethyl)]-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}] undec-9-en-3-one (**24**)*: A solution containing 0.17 g (5.2 mmol) of furan **23** in 10 mL of xylene was heated at reflux for 20 h. The solution was concentrated under reduced pressure and the crude solid was purified by silica gel chromatography to give 0.15 g (90%) of **24** as a white solid, mp 119–120°C; IR (neat) ν: 1644, 1513, 1449, and 1154 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39–1.44 (2H, m), 1.71–1.75 (1H, m), 2.79–2.83 (2H, m), 2.92 (1H, d, *J* = 18.8 Hz), 3.15 (1H, d, *J* = 18.8 Hz), 3.18–3.22 (2H, m), 3.51–3.58 (1H, m), 3.66–3.73 (1H, m), 3.86 (3H, s), 3.88 (3H, s), 4.89 (1H, dd, *J* = 4.0 and 1.6 Hz), 6.14 (1H, d, *J* = 5.6 Hz), 6.37 (1H, dd, *J* = 5.6 and 1.6 Hz), and 6.75–6.81 (3H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.3, 33.5, 35.9, 36.0, 50.0, 51.6, 55.7, 55.8, 78.1, 85.6, 111.1, 111.8, 120.6, 131.4, 137.3, 137.4, 147.4, 148.7, and 168.6 ppm; Anal. calcd. for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 4.25; found: C 69.11, H 7.09, N 4.21.

*2-[2-(3,4-Dimethoxyphenethyl)]-7-hydroxy-1,7a,8,8a-tetrahydro-2*H*-isoquinoline-3-one (**25**)*: To a solution containing 0.24 g (10 mmol) of sodium metal in 25 mL of EtOH was added 1.0 g (3.0 mmol) of cycloadduct **24** at 0 °C. After stirring for 1 h at room temperature, 20 mL of water was added and the solution was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and the crude product was purified by silica gel chromatography to give 0.9 g (92%) of **25** as a white solid, mp 137–139°C; IR (neat) ν: 3348, 1641, 1511, 1478, and 1244 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21–1.30 (1H, m), 1.91 (1H, d, *J* = 6.6 Hz, exchangeable with D_2O), 2.08–2.13 (1H, m), 2.57–2.60 (1H, m), 2.80–2.85 (2H, m), 3.17 (1H, s), 3.20 (1H, d, *J* = 3.6 Hz), 3.51–3.73 (2H, m), 3.86 (3H, s), 3.87 (3H, s), 4.41 (1H, dd, *J* = 10.0 and 4.8 Hz), 5.71 (1H, d, *J* = 1.6 Hz), 6.17 (2H, dd, *J* = 18.8 and 10.0 Hz), and 6.76–6.83 (3H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 31.8, 33.5, 35.4, 49.0, 51.9, 55.6, 55.7, 65.9, 111.2, 111.9, 118.3, 120.6, 126.0, 131.3, 141.1, 147.4, 148.7, and 165.8 ppm; Anal. calcd. for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 4.25; found: C 69.14, H 7.05, N 4.20.

*7-Benzyloxy-2-[2-(3,4-dimethoxyphenethyl)]-1,7a,8,8a-tetrahydro-2*H*-isoquinolin-3-one (**26**)*: To a 5 mL solution of THF was added 0.04 g (1.0 mmol) of NaH (60% dispersion) which had been rinsed with hexane. After cooling to 0°C, 0.13 g (0.4 mmol) of alcohol **25** in 10 mL of THF was added and the mixture was warmed to room temperature. After stirring for 2 h, 0.24 g of benzyl bromide was added and the solution was heated at 60°C for 15 h. The reaction was cooled to 0°C and 10 mL of water was added slowly. The mixture was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude mixture by silica gel chromatography gave 0.12 g (83%) of **26** as a white solid, mp 118–119°C; IR (neat) ν: 1647, 1510, 1453, and 1260 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25–1.38 (1H, m), 2.14–2.19 (1H, m), 2.50–2.58 (1H, m), 2.81–2.85 (2H, m), 3.11–3.21 (2H, m), 3.52–3.73 (2H, m), 3.85 (3H, s), 3.87 (3H, s), 4.21 (1H, dd, *J* = 10.4 and 5.2 Hz), 4.62 (2H, s), 5.74 (1H, d, *J* = 2.4 Hz), 6.22 (2H, s), 6.75–6.81 (3H, m), and 7.30–7.36 (5H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 31.8, 32.7, 33.7, 49.0, 52.1, 55.7, 55.8, 70.5, 73.2, 111.1, 111.9, 119.4, 120.6, 126.9, 127.6, 127.8, 128.4, 131.6, 137.9, 146.6, 147.4, 148.8, and 165.2 ppm; Anal. calcd. for $C_{26}H_{29}NO_4$: C 74.44, H 6.97, N 3.34; found: C 74.28, H 6.90, N 3.31.

*7-Benzyloxy-2-[2-(3,4-dimethoxyphenethyl)]-octahydroisoquinolin-3-one (**27**)*: To a solution of 0.05 g (0.13 mmol) of **26** in 8 mL of EtOH was added a slight excess of Raney nickel. After stirring at room temperature for 15 h, the mixture was filtered through Celite with ethyl acetate. The

solution was concentrated under reduced pressure and the crude product was purified by silica gel chromatography to give 0.047 g (85%) of **27** as a clear oil; IR (neat) ν: 1636, 1511, 1452, and 1264 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.49–1.69 (5H, m), 1.83–1.91 (2H, m), 2.07–2.11 (2H, m), 2.27–2.47 (2H, m), 2.76–2.85 (2H, m), 3.07 (1H, dd, *J* = 12.0 and 2.8 Hz), 3.33–3.43 (3H, m), 3.68–3.75 (1H, m), 3.84 (3H, s), 3.87 (3H, s), 4.54 (2H, d, *J* = 2.4 Hz), 6.73–6.77 (3H, m), and 7.25–7.35 (5H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 26.3, 26.7, 30.8, 31.4, 32.3, 32.6, 33.1, 49.1, 52.9, 55.7, 55.8, 69.8, 76.1, 111.1, 112.0, 120.7, 127.3, 127.4, 128.3, 131.6, 138.7, 147.4, 148.8, and 168.9 ppm; HRMS calcd. for $C_{26}H_{33}NO_4$: 423.2410; found: 423.2397.

*10-Benzyloxy-2,3-dimethoxy-5,8,8a,9,10,11,12,12a,13,13a-decahydro-6*H*-isoquino[3,2-a]isoquinoline (**9**)*: To a solution of 0.3 g (0.6 mmol) of **27** in 10 mL of benzene was added 0.2 g (1.3 mmol) of phosphorous oxychloride. After heating at reflux for 2 h, the solvent was removed under reduced pressure and the crude product was taken up in 10 mL of methanol. To this solution was added 0.05 g (1.3 mmol) of sodium borohydride and the mixture was stirred for an additional 2 h. The solvent was removed under reduced pressure and the crude material was purified by silica gel chromatography to give 0.15 g (52%) of **9** as a yellow foam; IR (neat) ν: 1601, 1510, and 1270 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32–1.45 (1H, m), 1.56–2.04 (9H, m), 2.39 (1H, dt, *J* = 11.6 Hz and 3.6 Hz), 2.50–2.57 (2H, m), 2.72 (1H, dd, *J* = 11.6 and 1.6 Hz), 2.81–2.85 (1H, m), 3.02–3.11 (2H, m), 3.34–3.42 (1H, m), 3.84 (3H, s), 3.85 (3H, s), 4.55 (2H, dd, *J* = 23.6 and 12.4 Hz), 6.57 (1H, s), 6.68 (1H, s), and 7.24–7.33 (5H, m) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.0, 29.4, 29.5, 32.0, 32.3, 34.3, 35.1, 52.6, 55.7, 55.9, 62.0, 63.3, 69.3, 78.0, 108.0, 111.3, 127.0, 127.1, 127.3, 128.2, 130.5, 139.3, 147.0, and 147.1 ppm; HRMS calcd. for $C_{26}H_{33}NO_3$: 408.2539; found: 408.2526.

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