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A Metathetical Cycloaddition–Cycloreversion Approach to the Formation of Furan Scaffold Libraries

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Abstract—A general cycloaddition–cycloreversion metathesis procedure for the selective formation of a furan-based template-directed scaffold is described. In addition, features relative to library construction, such as the chemoselective nature of dipole formation, are discussed. Through the investigation of the temperature sensitive cleavage step, the furan synthesis was found to be accelerated by aqueous medium at physiological temperature leading to pure product from the solid-phase under biologically relevant conditions. The chemoselective nature of the rhodium(II) mediated cycloaddition allowed the selective formation of a key dipole intermediate, in the presence of a number of carbene-active functional groups, to facilitate the split-pool combinatorial synthesis of a small library of compounds.

Introduction

The generation and evaluation of novel scaffolds for drug design has recently become an area of extensive research interest, largely due to the emergence of automated synthesis and high-throughput screening techniques.[1–3] One popular example is a template-directed scaffold that possesses a central core from which functionality can radiate in a random and diverse nature.[4–6] In these structures, the central core plays a major role in the presentation of functionality, but is generally not thought to play a direct role in binding. Therefore, desirable criteria for this type of scaffold are: (1) facile, preferably convergent, synthesis, (2) compatibility with a diverse set of functionalities, and (3) the ability to present this functionality in a geometrically meaningful manner. Herein, we report the design, synthesis and analysis of a scaffold-based, template-directed library for the presentation of diverse functionality around a central furan core (**1**). Cycloaddition reactions have long been a powerful method of forming ring-containing compounds and are becoming increasingly popular as a diversity strategy in the development of combinatorial libraries.[7–11] Although the key step in our synthetic approach, the rhodium(II) mediated 1,3-dipolar cycloaddition reaction on solid-phase has only recently been reported,[12,13] we believe that by fully exploring this reaction on solid support, we can gain access to a high level of diversity. This is dependent, however, on the correct choice of rhodium(II) catalyst to control carbenoid reactivity.[14] Once selectivity is established, the reactivity of rhodium(II) carbenes could prove very useful in diverse library generation.

In this example, the reaction of acetylenes with isomünchnones is presented as a general methodology for the combinatorial formation of a furan based library (Fig. 1). The central core can be rapidly assembled by a heterocyclic 1,3-dipolar cycloaddition reaction. The cycloaddition of isomünchnones with dimethylacetylene dicarboxylate (DMAD) gives a transient cycloadduct,

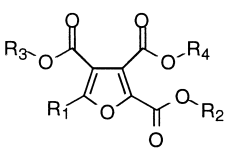

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Figure 1. Schematic representation of furan scaffold.

Key words: Combinatorial library; cycloaddition–cycloreversion; furans; solid-phase synthesis; solvent effects.
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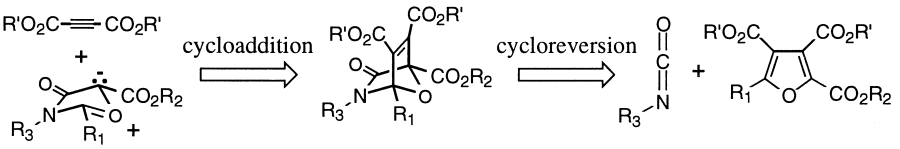


Figure 2. Conceptual analysis of the tandem cycloaddition–cycloreversion metathesis.

which can subsequently undergo a facile cycloreversion to a tetra-substituted furan and an isocyanate (Fig. 2).[15] This metathetical process, from an alkyne and 1,3-dipole to an isocyanate and furan, is the central theme of this approach. Through the development of the novel thermolytic cleavage step, the furan synthesis yields pure product from the solid phase in a temperature dependent manner.

The thermolytic cycloreversion of diactivated alkyne cycloadducts has been described as a one-pot procedure at elevated temperatures.[16–19] However, to take full advantage of this cycloreversion on solid-phase, the initial cycloadduct is synthesized and isolated at ambient temperature, with a subsequent discrete cleavage step under thermally controlled conditions (Fig. 3). This approach is advantageous since the unreacted starting materials are removed by filtration prior to the cycloreversion cleavage step, thus eliminating the need for purification of the furan. Only pure product is obtained, regardless of cycloaddition yield since the isocyanate and any unreacted synthetic intermediates remain attached to the solid-phase resin.

The following aspects of this scaffold system have been evaluated and are discussed: (1) the chemoselective control of carbonyl ylide formation, (2) the temperature dependence of the cycloreversion, (3) the feasibility of the cycloaddition–cycloreversion protocol on a solid phase resin, and (4) the reliability of the synthetic procedure under split and pool conditions.

Chemoselectivity of Rhodium Catalyzed Carbonyl Ylide Formation

In order to apply this reaction to library synthesis, the chemoselectivity of the intermediate rhodium carbenoid must be controlled. It is shown in previous systems that C-H insertion five atom centers away from the diazo function is a preferred process.[19] For this reason, a number of different catalysts were investigated for their ability to chemoselectively form carbonyl ylide over C-H insertion products.

The first model system investigated was diazo imide **4**, which was selected based on the presence of both a carbonyl group and a tertiary C-H bond within five atoms of the diazo group (Scheme 1). The synthesis of diazo imide **4** began with the acetylation of isobutyl amine **2** to amide **3**. Standard imide formation with methyl malonyl chloride lead cleanly to imide, which upon treatment with 4-acetamido-benzenesulfonyl azide[20] gave diazo imide **4**.

Upon treatment of diazo imide **4** with rhodium(II) acetate [$Rh_2(OAc)_4$], rhodium(II) trifluoroacetate [$Rh_2(TFA)_4$] or rhodium(II) perfluorobutyramidate [$Rh_2(pfbm)_4$], isomünchnone was cleanly formed, and in the presence of DMAD, lead to cycloadduct **5** (Scheme 2). The absence of side products via C-H insertion was unexpected and also noted for diazo imide **7** which gave only cycloadduct **8** with all three catalysts. This preference for cycloaddition is most likely due to an unfavorable ring-closure geometry for the C-H insertion, rather than an electronic preference of the catalyst, since both $Rh_2(OAc)_4$ and $Rh_2(TFA)_4$ have been shown to be efficient insertion catalysts.[14]

In examples where cyclopropanation was a potential side reaction, catalyst selective for formation of the scaffold became much more important (Scheme 3). When diazo imide **10** was treated with $Rh_2(OAc)_4$ at room temperature, in the presence of excess DMAD, an equimolar mixture of cycloadduct **11** and cycloheptatriene **12** was formed, presumably through a tandem

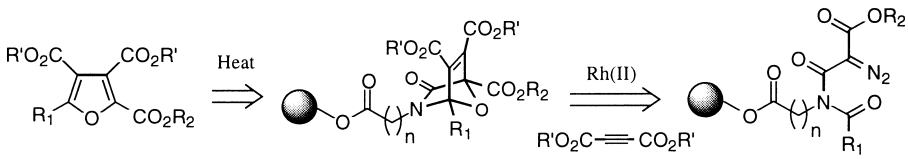
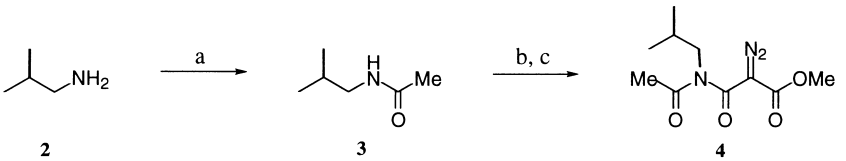
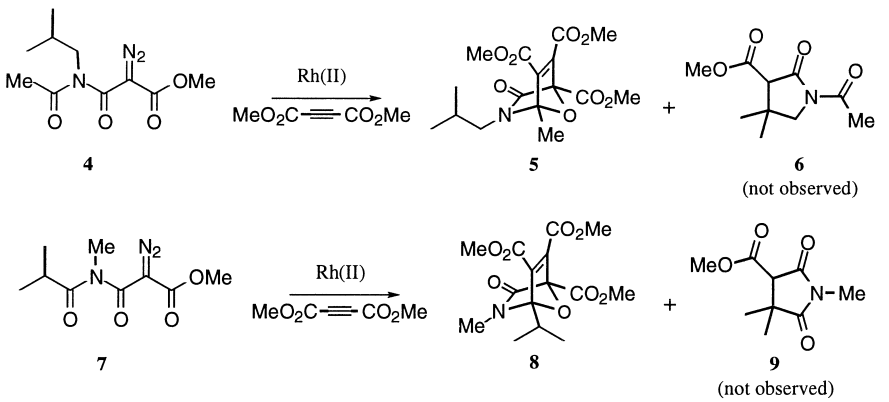


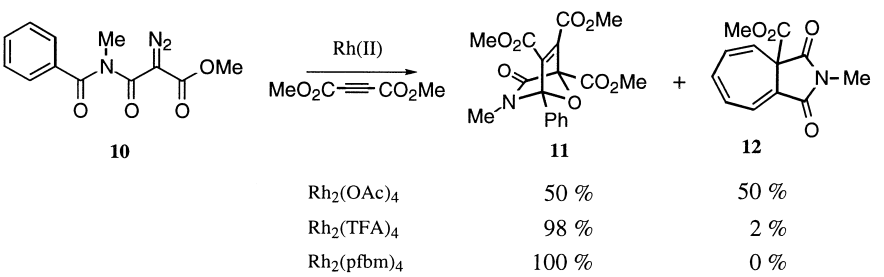
Figure 3. Solid-phase retrosynthesis of furan utilizing the cycloaddition–cycloreversion metathesis of isomünchnone cycloaddition with acetylenic dipolarophiles.



Scheme 1. Formation of diazo imide **4**. (a) Ac_2O, Et_3N, 0 °C; (b) $MeCOCH_2COCl$, benzene, 80 °C; (c) 4-AcNH-benzenesulfonyl azide, Et_3N.



Scheme 2. Observed selectivity for carbonyl ylide formation over insertion.



$Rh_2(OAc)_4$	50 %	50 %
$Rh_2(TFA)_4$	98 %	2 %
$Rh_2(pfbm)_4$	100 %	0 %

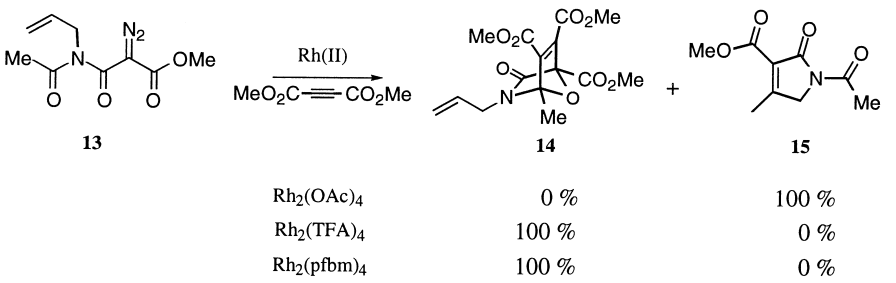
Scheme 3. Observed selectivity for carbonyl ylide formation over cyclopropanation.

cyclopropanation/Cope rearrangement. Similar treatment of α-diazo imide **10** with $Rh_2(TFA)_4$ lead to a marked improvement in carbonyl ylide selectivity. Finally, treatment with $Rh_2(pfbm)_4$ lead exclusively to cycloadduct **11** with no observable cyclopropanation side product. For diazo imide **13**, which possesses an allylamine moiety, an alternative reaction leading to the unsaturated lactam **15** was observed (Scheme 4). The mechanism leading to compound **15** is not easily discerned since it has been shown that this compound can be formed either thermally or through a cyclopropanation-ring opening process.[21,22] In either case, formation of this undesired product was completely suppressed with either $Rh_2(pfbm)_4$ or $Rh_2(TFA)_4$, giving only the desired cycloadduct **14**. Interestingly, treatment of **13** with $Rh_2(OAc)_4$ lead exclusively to lactam **15**.

The observed reactivity of the cycloaddition with perfluorinated catalysts provided the chemoselectivity required to proceed with library synthesis. In practice, $Rh_2(pfbm)_4$ was found to be much more soluble in organic solvents than $Rh_2(TFA)_4$, leading to faster reaction rates, and was therefore selected for all future manipulations. With chemoselectivity in hand, we next sought to explore the temperature selectivity of the cycloreversion step.

Temperature Sensitivity of Cycloreversion

Initial studies suggested that polar protic solvents accelerated the cycloreversion over nonpolar solvents at similar temperatures.[13] This solvent effect was intriguing,



Scheme 4. Selectivity for carbonyl ylide over alkene formation.

because it suggested that compound cleavage may be facilitated in aqueous media. Therefore, the thermal cleavage reaction of cycloadduct **5** was investigated in a range of solvents at 37 °C, to give isocyanate **16** and the trimethyl methylfuran tricarboxylate **17** (Scheme 5).

Initial cycloreversion data, summarized in Table 1, indicate that solvent polarity does not seem to be the major factor in the rate of cycloreversion. Interestingly, a moderate rate enhancement was noted in methanol at ambient temperatures. This prompted us to investigate the rate of cycloreversion in a number of additional solvents at a physiologically relevant temperature (37 °C).

Furan cleavage was carried out in nonpolar (benzene), polar aprotic (chloroform, acetonitrile, dimethyl sulfoxide) and polar protic (methanol and water) deuterated solvents. While the furan product does have moderate water solubility,[23] the starting cycloadduct was not sufficiently soluble in water to detect a signal in ^{1}H NMR, thus the cycloreversion was performed in D_2O with 10% DMSO-d_6. Figure 4 shows both the data points and a first-order curve fit for both ^{1}H NMR measured disappearance of starting material and appearance of product with respect to time.

From analysis of the first order curve fit for the percent starting material over time, we can establish a half-life for the cycloreversion as a function of solvent (Table 2). The rate of cycloreversion does not correlate with solvent polarity (e.g. acetonitrile and benzene), however, it does appear to be dependent on the availability of a hydrogen bond donor.

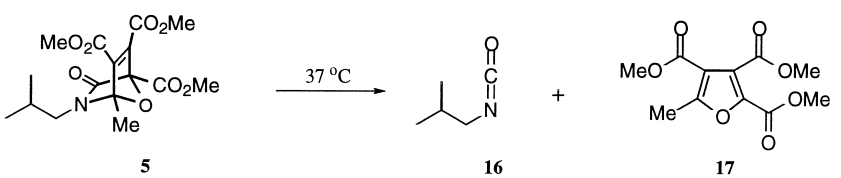
This remarkable rate acceleration in water can be used, to great measure, by coupling the cycloreversion step with a cell-based biological assay. Most biological assays are tolerant of up to 1% DMSO, a level which would allow up to millimolar concentrations of furan product. We envision a bead-based assay, performed in aqueous media and involving cell viability, since cycloreversion can take place within the time frame of cell growth, under cell growth conditions.

Solid-phase Synthesis of Furan Molecules

The solid-phase library synthesis began from the esterification of Wang resin with *N*-acyl protected aminocaproic acid **18** to give amide **19** (Scheme 6). The acylation of **19** with methylmalonyl chloride in benzene, at reflux temperature, provided the imide **20**, which was followed immediately by diazotransfer to result in the formation of diazoester **21**. Decomposition of the diazoester **21** with $Rh_2(pfbm)_4$ and subsequent cycloaddition of the resultant 1,3-dipole with DMAD, at room temperature, afforded the cycloadduct **22** on the solid support[24] without any observable cycloreversion product.

Table 1. Solvent and temperature dependence of the cycloreversion of compound **5**

Solvent	Temp.	50% Complete
Chloroform-*d*	23 °C	5.5 days
Chloroform-*d*	37 °C	24 h
Methanol-d_4	37 °C	12 h
Benzene-d_6	37 °C	22 h
Benzene-d_6	79 °C	< 1 h



Scheme 5. Thermal cycloreversion of cycloadduct **5**.

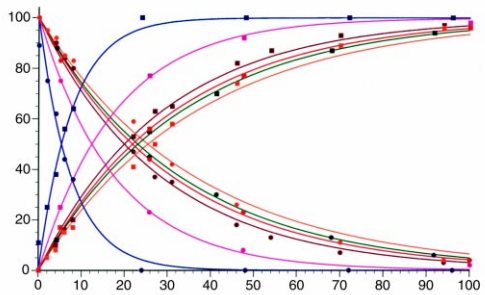


Figure 4. NMR analysis of the cycloreversion of compound **5** in a number of deuterated solvents. Data and curve: acetonitrile (orange); chloroform (green); benzene (red); dimethyl sulfoxide (brown); methanol (purple); water/dimethyl sulfoxide (blue).

Table 2. Experimental half-life for the cycloreversion of cycloadduct **5** in various solvents at 37 °C

Solvent	Half-life ($t_{1/2}$, h)
Acetonitrile-d_3	23.3
Chloroform-d	23.0
Benzene-d_6	21.8
DMSO-d_6	19.9
Methanol-d_4	12.3
D_2O / 10% DMSO-d_6	5.3

Furan **17** was subsequently cleaved from the solid support, in a thermolytic fashion, in 70% yield based on the initial loading, and isolated in over 98% purity (HPLC chromatography, NMR spectroscopy and GC/MS analysis), directly from the resin.

Synthesis of a Combinatorial Furan Library

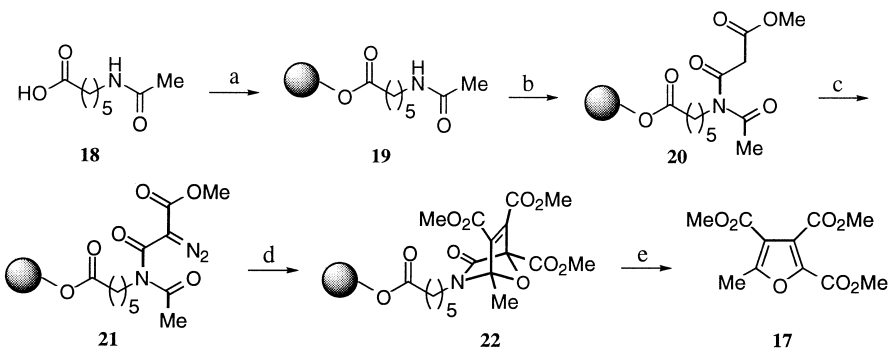
This solid-phase chemistry has been extended to a split-pool synthesis of a small, exemplary combinatorial furan library (3×3×2). Starting from commercially available starting materials, diversity was incorporated into the amides (R_1 = Me, *i*-Pr, and Ph), esters (R_2 = Me, Et, and *t*-Bu) of the diazo imide and the cycloaddition dipolarophiles (E = CO_2Me and CO_2Et). The final cycloaddition reactions were not recombined, yielding two nine-member pools (**27a** and **27b**) (Scheme 7).

The use of the rhodium(II) perfluorobutyramidate catalyst in the library synthesis allows for the incorporation of both alkyl- and aryl-substituted furans, as can be seen by the formation of the benzamide (R_1 = Ph) and isopropyl (R_1 = *i*-Pr) library members, a pathway that would be otherwise excluded with the use of an unselective rhodium(II) catalyst.

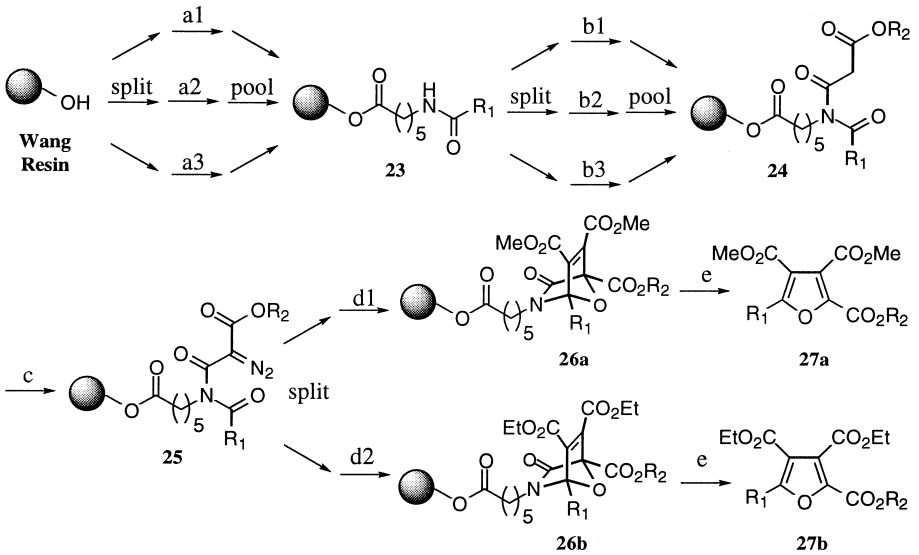
The cleaved product pools were analyzed individually using analytical HPLC chromatography. For pool **27a**, the retention times were: t = 2.98, 3.25, 3.53, 3.67, 3.74, 3.94, 4.08, 4.24, and 4.77, for pool **27b**, the retention times were: t = 3.52, 3.74, 3.96, 4.07, 4.13, 4.28, 4.40, 4.52, and 4.84. In each chromatograph, broad peaks corresponding to column degradation material were noted (t > 4.9, Figs 5 and 6). Nine compound peaks were observed in each chromatograph, yielding a total of 18 compounds, which is the expected diversity (3×3×2 = 18). In addition, only nine compounds were cleaved from the resin, even though the total conversion for the library construction was not quantitative. This exemplifies the power of a selective resin cleavage step.

Conclusion

In summary, we have developed a convergent synthesis of a furan-based scaffold molecule for the selective formation of combinatorial libraries in pure and diverse form. In addition, we have shown the importance of chemoselectivity in the application of this technique to chemical diversity and the potential for development of an in vitro assay system utilizing the temperature selectivity between cycloaddition and cycloreversion.



Scheme 6. Solid-phase synthesis of furan scaffold. (a) Wang resin, BOP, HOBt, DIPEA; (b) $MeCOCH_2COCl$, benzene, 80 °C; (c) methanesufonyl azide, Et_3N; (d) $Rh_2(pfbm)_4$, DMAD, benzene; (e) 70 °C.



Scheme 7. Solid-phase synthesis of furan library. (a1) $MeCO_2H$, BIOP, DIPEA; (a2) *i*-$PrCO_2H$, BOP, HOBt, DIPEA; (a3) $PhCO_2H$, BOP, HOBt, DIPEA; (b1) $MeCOCH_2COCl$, benzene, 80 °C; (b2) $EtCOCH_2COCl$, benzene, 80 °C; (b3) *t*-$BuCOCH_2COCl$, benzene, 80 °C; (c) methanesulfonyl azide, Et_3N; (d1) $Rh_2(pfbm)_4$, DMAD, benzene; (d2) $Rh_2(pfbm)_4$, DEAD, benzene; (e) 70 °C.

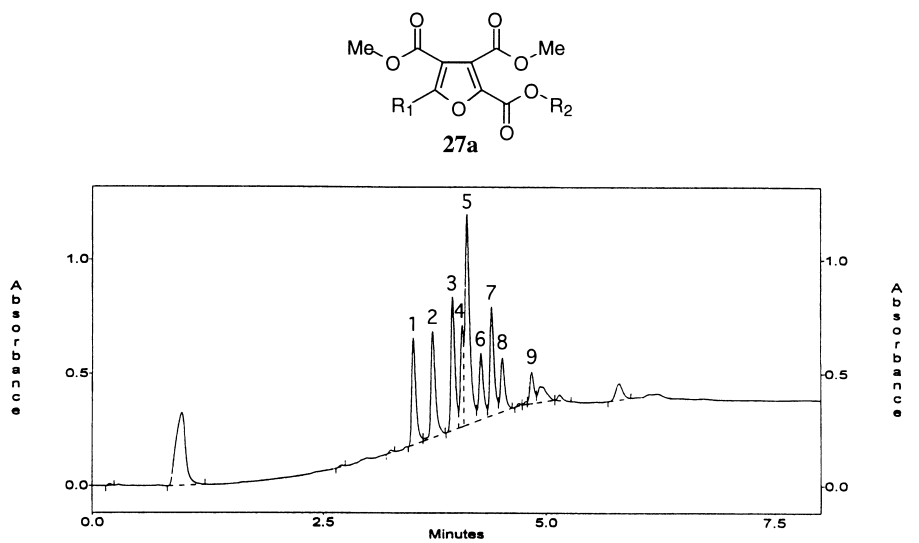


Figure 5. HPLC analysis of furan library; pool **27a** (R_1 = Me, *i*-Pr, Ph; R_2 = Me, Et, *t*-Bu).

Experimental

Synthesis of methyl 3-[acetyl(isobutyl)amino]-2-diazo-3-oxopropanoate (4)

In a round bottom flask, isobutylamine (**2**) (12.6 mL, 127 mmol), triethylamine (26.4 mL, 190 mmol) and 500 mL methylene chloride were combined. The mixture was then cooled to 0 °C and acetic anhydride (10.0 mL, 106 mmol) was added slowly. The reaction mixture was warmed to room temperature and sonicated for 30 min. An additional aliquot of acetic anhydride (1.0 mL) was added and the solution was sonicated for a further 5 min followed by dilution with methylene chloride. The solution was washed twice with 0.2 M HCl, twice with water and once with saturated brine. Following the washing, the organic layer was dried over magnesium sulfate, filtered and concentrated. Upon azeotropic removal of any remaining acetic acid, with toluene, the material was dried in vacuo. *N*-Isobutylacetamide (**3**) was isolated as a clear oil (9.96 g, 86 mmol, 81%). IR (neat,

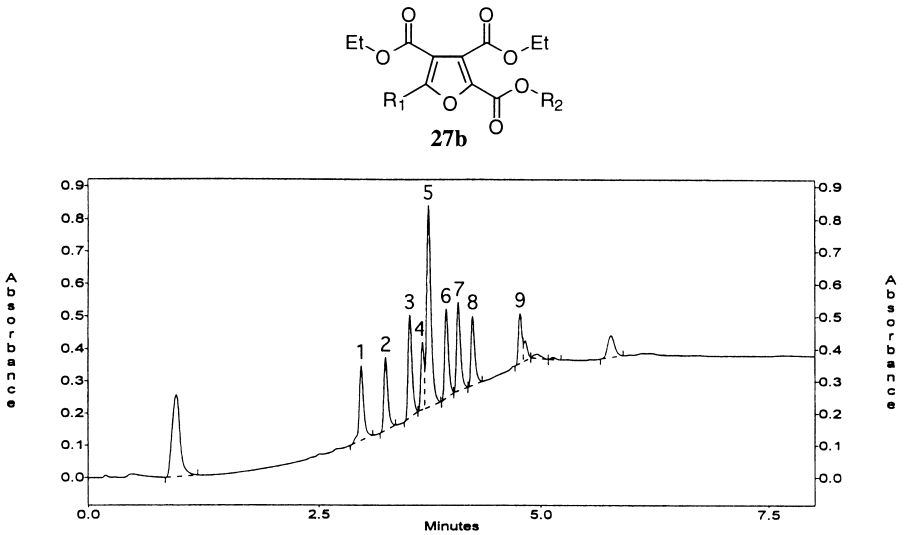


Figure 6. HPLC analysis of furan library, pool **27b** (R_1 = Me, *i*-Pr, Ph; R_2 = Me, Et, *t*-Bu).

cm^{-1}) 3294, 3090, 2969, 1653; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 6 Hz, 6H), 1.77 (m, 1H), 2.00 (s, 3H), 3.08 (t, J = 6 Hz, 2H), 5.63 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 23.2, 28.4, 47.0, 170.4.

N-Isobutylacetamide (**3**) (1.0 g, 8.7 mmol) and 80 mL dry benzene were combined in a flame dried round bottom flask under an atmosphere of nitrogen. The solution was then heated to reflux while nitrogen was bubbled through the solution and methyl malonyl chloride (1.2 mL, 12 mmol) was added dropwise to the refluxing solution. Heating was continued for an additional 3 h, with continued nitrogen bubbling, to remove hydrogen chloride. After this time the reaction was cooled to room temperature and concentrated in vacuo. Methyl 3-[acetyl(isobutyl)amino]-3-oxopropanoate was isolated by column chromatography (1/1, EtOAc/hexanes, silica gel) in 98% as a clear pale-yellow oil. IR (neat, cm^{-1}) 2961, 2874, 1748, 1698, 1470, 1437, 1377, 1339, 1234, 1213; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J = 9 Hz, 6H), 1.98 (m, 1H), 2.35 (s, 3H), 3.56 (d, J = 9 Hz, 2H), 3.73 (s, 3H), 3.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 25.3, 28.5, 46.3, 51.6, 52.2, 167.9, 168.7, 173.8.

Methyl 3-[acetyl(isobutyl)amino]-3-oxo propanoate (719 mg, 3.3 mmol) was combined with 4-acetamidobenzenesulfonyl azide (967 mg, 4.0 mmol) and triethylamine (1.4 mL, 10 mmol) in 40 mL THF. The reaction was stirred for 48 h at room temperature. After this time, the reaction was concentrated and the material was adsorbed onto silica gel. Methyl 3-[acetyl(isobutyl)-amino]-2-diazo-3-oxopropanoate (**4**) was isolated by column chromatography (2/1, hexanes/EtOAc, silica gel) as a clear yellow oil (670 mg, 2.8 mmol, 86%). IR (neat, cm^{-1}) 2961, 2874, 2140, 1727, 1653, 1437, 1374, 1330, 1230; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 7 Hz, 6H), 2.05 (m, 1H), 2.28 (s, 3H), 3.49 (d, J = 7 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 24.0, 28.6, 52.5, 53.7, 87.8, 160.9, 166.7, 172.7.

Synthesis of methyl 3-[acetyl(allyl)amino]-2-diazo-3-oxo-propanoate (13). Triethylamine (15.8 mL, 114 mmol) was added to a stirred solution of allyl amine (5.00 g, 87.7 mmol) in Et_2O (100 mL). The solution was cooled to 0 °C and acetic anhydride (9.89 mL, 105 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature and stirring was continued for 2 h. The precipitate was filtered through a silica plug using Et_2O to elute the resulting amide. Evaporation of the solvent afforded *N*-allyl acetamide as a clear oil; yield: 8.30 g (96%); IR (neat, cm^{-1}) 3288, 3082, 3012, 2920, 1654, 1552; ^1H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H), 3.75 (t, J = 6 Hz, 2H), 5.02 (d, J = 10 Hz, 1H), 5.08 (d, J = 17 Hz, 1H), 5.67–5.80 (m, 1H), 6.76 (br t, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 42.0, 116.0, 134.3, 170.5.

Methyl malonyl chloride (1.30 mL, 12.1 mmol) was added to a solution of allyl acetamide (1.00 g, 10.1 mmol), heated to reflux in dry benzene (25 mL). Dry nitrogen was bubbled through the solution to drive the hydrogen chloride from the reaction mixture. Reflux was maintained for 30 min, until TLC showed complete conversion. The mixture was then cooled to room temperature, Et_2O (25 mL) was added and the mixture was washed with saturated $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic phase was dried (Na_2SO_4)

and concentrated to yield methyl 3-[acetyl(allyl)amino]-3-oxopropanoate as a clear oil; yield: 1.90 g (95%); IR (neat, cm^{-1}) 3009, 2955, 1745, 1699, 1374, 1338, 1222; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.69 (s, 3H), 3.81 (s, 2H), 4.33 (d, $J=5$ Hz, 2H), 5.15 (d, $J=8$ Hz, 1H), 5.20 (s, 1H), 5.75–5.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 46.1, 46.7, 52.3, 116.5, 132.3, 167.8, 168.1, 173.3.

Triethylamine (2.09 mL, 15.1 mmol) was added to a stirred solution of methyl 3-[acetyl(allyl)amino]-3-oxopropanoate (1.00 g, 5.03 mmol) and methanesulfonyl azide (0.93 g, 7.54 mmol) in Et_2O (15 mL). The solution was stirred at room temperature for 5 h until complete conversion (TLC control). The mixture was then concentrated under reduced pressure and chromatographed on silica gel (25% ethyl acetate in hexanes) to afford methyl 3-[acetyl(allyl)amino]-2-diazo-3-oxopropanoate (**13**) as a pale-yellow oil; yield: 1.03 g (91%); IR (neat, cm^{-1}) 3012, 2952, 2140, 1717, 1653, 1559, 1437, 1373, 1280; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 3H), 3.11 (s, 3H), 3.96 (d, $J=5$ Hz, 2H), 4.89 (dd, $J=1$, 10 Hz, 1H), 5.15 (dd, $J=1$, 17 Hz), 5.53–5.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 47.6, 51.4, 52.7, 86.5, 116.3, 133.3, 160.7, 165.3, 172.1.

Synthesis of methyl 3-[isobutyryl(methyl)amino]-2-diazo-3-oxopropanoate (7). Methyl chloroformate (4.39 mL, 56.8 mmol) was added dropwise to a chilled solution of isobutyric acid (5.00 g, 56.8 mmol) and triethylamine (8.61 mL, 61.9 mmol) in Et_2O (100 mL). The reaction mixture was allowed to warm to room temperature and stirred for additional 20 min after which it was placed in an ice bath and aqueous methylamine (40% w/w solution, 6.67 mL, 77.4 mmol) was slowly added. The mixture was stirred at 25 °C for 2 h and the resulting suspension was filtered through a silica gel plug. Concentration of the filtrate yielded *N*-methyl isobutyramide as a clear oil; yield: 5.30 g (92%); IR (neat, cm^{-1}) 3293, 3090, 2960, 1655; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, $J=7$ Hz, 6H), 2.34 (m, 1H), 2.70 (d, $J=4$ Hz, 2H), 6.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 26.1, 35.4, 178.0.

As described in the synthesis of compound **4**, methyl 3-[isobutyryl(methyl)amino]-3-oxopropanoate was prepared and isolated as a clear oil (90%); IR (neat, cm^{-1}) 2977, 1747, 1696, 1467, 1437, 1343, 1062; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, $J=7$ Hz, 6H), 3.03 (m, 1H), 3.25 (s, 3H), 3.69 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 31.4, 34.1, 46.1, 52.3, 167.8, 169.0, 180.3.

As described in the synthesis of compound **4**, methyl 3-[isobutyryl(methyl)amino]-2-diazo-3-oxopropanoate (**7**) was prepared as a pale-yellow oil (89%); IR (neat, cm^{-1}) 2976, 2140, 1728, 1700, 1653, 1472, 1437, 1333, 1062; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, $J=7$ Hz, 6H), 3.02 (m, 1H), 3.15 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 33.6, 33.9, 52.5, 86.7, 160.7, 166.8, 179.7.

Synthesis of methyl 3-[benzoyl(methyl)amino]-2-diazo-3-oxopropanoate (10). 1,1-Carbonyl diimidazole (3.98 g 24.6 mmol) was added to a solution of benzoic acid (3.00 g, 24.6 mmol) in methylene chloride (50 mL) at room temperature. The reaction mixture was stirred until gas evolution was complete (20 min) and an aqueous solution of methylamine (40% w/w solution, 2.89 mL, 33.5 mmol) was added. The mixture was stirred at room temperature for 2 h after which it was partitioned between Et_2O (50 mL) and water (50 mL). The ether phase was washed with 1 M HCl (50 mL), saturated $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated to yield *N*-methyl benzamide as a white crystalline solid; mp 71–72 °C; yield: 3.20 (96%); IR (KBr, cm^{-1}) 3345, 3054, 2962, 1641, 1556; ^1H NMR (300 MHz, $CDCl_3$) δ 2.96 (d, $J=5$ Hz, 3H), 6.74 (m, 1H), 7.36–7.79 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 127.0, 128.5, 131.3, 134.6, 168.5.

As described in the synthesis of compound **4**, methyl 3-[benzoyl(methyl)amino]-3-oxopropanoate was prepared and isolated as a thick, clear oil (89%), IR (neat, cm^{-1}) 3003, 2955, 1746, 1688, 1448, 1320, 1216, 1019; ^1H NMR (300 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.67 (s, 3H), 3.85 (s, 2H), 7.42–7.61 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.2, 44.6, 52.4, 128.4, 128.8, 132.4, 134.3, 167.9, 168.9, 174.1.

As described in the synthesis of compound **4**, methyl 3-[benzoyl(methyl)amino]-2-diazo-3-oxopropanoate (**10**) was prepared as a yellow crystalline solid (89%), mp 95–96 °C; IR (neat, cm^{-1}) 3003, 2956, 2137, 1721, 1646, 1432, 1304, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 3H), 3.66 (s, 3H), 7.40–7.64 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.2, 52.5, 92.5, 128.4, 129.0, 132.2, 135.0, 161.0, 166.4, 173.0.

Synthesis of trimethyl 2-isobutyl-1-methyl-3-oxo-7-oxa-2-azabicyclo[2.2.1]hept-5-ene-4,5,6-tricarboxylate (5). Methyl 3-[acetyl(isobutyl)amino]-2-diazo-3-oxopropanoate (**4**) (1.77 g, 7.3 mmol) was combined with dimethyl acetylenedicarboxylate (DMAD) (5.40 mL, 44.0 mmol) and a catalytic amount (1.0 mol%) of rhodium perfluorobutyramidate in 15 mL benzene in a flame dried round bottom flask under nitrogen. The reaction was stirred at room temperature for 6 h and reaction progress was monitored by TLC (hexanes/EtOAc, 2/1). Trimethyl 2-isobutyl-1-methyl-3-oxo-7-oxa-2-azabicyclo-[2.2.1]hept-5-ene-4,5,6-tricarboxylate (**5**) was isolated by

column chromatography (hexanes/EtOAc, 3/1) as a crystalline white solid (2.10 g, 5.9 mmol, 81%). IR (KBr, cm^{-1}) 2959, 2361, 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (dd, $J=6.6$, 20.1 Hz, 6H), 1.93 (m, 1H), 1.99 (s, 3H), 2.99 (d, $J=7.5$ Hz, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.81, 19.85, 20.07, 28.61, 49.57, 52.93, 53.17, 53.61, 90.25, 98.96, 144.88, 147.09, 161.50, 162.30, 171.18.

Synthesis of trimethyl 5-methyl-2,3,4-furantricarboxylate (17). Compound **4** (70 mg, 0.29 mmol) was added to a solution containing rhodium (II) perfluorobutyramidate (1 mg) and dimethyl acetylenedicarboxylate (50 μL, 0.43 mmol) in benzene-d_6 (0.6 mL). The reaction mixture was allowed to stand at room temperature for 5 h until ^1H NMR showed disappearance of the diazo compound. The mixture was heated to reflux for 20 min to ensure complete cycloreversion. Flash column chromatography afforded trimethyl 5-methyl-2,3,4-furantricarboxylate (**17**) as a white solid; mp 94–95 °C; yield: 70 mg (95%), IR (KBr, cm^{-1}) 3006, 2956, 1715, 1608, 1559, 1443, 1288, 1224; ^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 52.1, 52.6, 53.1, 114.0, 126.2, 138.9, 157.6, 162.0, 162.3, 163.6.

Synthesis of trimethyl 5-phenyl-2,3,4-furantricarboxylate from cycloadduct (11). As described for **17** trimethyl 5-phenyl-2,3,4-furantricarboxylate was prepared and isolated as a white solid (92%), mp 63–64 °C; IR (KBr, cm^{-1}) 3005, 2954, 1733, 1606, 1446, 1235; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.93 (s, 3H), 3.99 (s, 3H), 7.42–7.52 (m, 3H), 7.90–7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4, 52.7, 53.2, 127.4, 127.9, 128.2, 124.4, 129.1, 131.0, 139.7, 157.7, 159.7, 161.8, 163.5.

Synthesis of trimethyl 5-isopropyl-2,3,4-furantricarboxylate from cycloadduct (8). As described for **17** trimethyl 5-isopropyl-2,3,4-furantricarboxylate was prepared and isolated as a clear thick oil (89%); IR (neat, cm^{-1}) 2955, 2878, 1728, 1607, 1558, 1443; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, $J=7$ Hz, 6H), 3.78 (m, 1H) 3.81 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 27.7, 52.1, 52.5, 53.1, 112.2, 126.1, 138.9, 157.7, 162.0, 163.9, 170.1.

Synthesis of methyl 1-acetyl-4-methyl-2-oxo-2,5-dihydro-1*H*-3-pyrrolecarboxylate (15). Diazo imide **13** (56 mg, 0.25 mmol) was added to a solution of rhodium (II) acetate (1 mg) and dimethylacetylene dicarboxylate (DMAD) (46 μL, 0.38 mmol) in benzene-d_6 (0.6 mL). The reaction mixture was allowed to stand at room temperature for 2 days until ^1H NMR showed complete disappearance of the diazo compound. Flash column chromatography afforded methyl 1-acetyl-4-methyl-2-oxo-2,5-dihydro-1*H*-3-pyrrolecarboxylate (**15**) as a white solid; mp 105–106 °C; yield: 50 mg (88%); IR (KBr, cm^{-1}) 2954, 1701, 1627, 1330; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 2.56 (s, 3H), 3.89 (s, 3H), 4.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 25.5, 53.1, 53.2, 125.2, 163.1, 166.7, 169.1, 171.0.

Synthesis of methyl 2-methyl-1,3-dioxo-1,2,3,3*a*-tetrahydrocyclohepta[*c*]pyrrole-3*a*-carboxylate (12). Diazo imide **10** (32 mg, 0.12 mmol) was added to a solution containing rhodium (II) acetate (1 mg) and dimethyl acetylenedicarboxylate (DMAD) (23 μL, 0.18 mmol) in benzene-d_6 (0.6 mL). The reaction mixture was allowed to stand at room temperature until ^1H NMR showed complete disappearance of the diazo compound. Flash column chromatography afforded methyl 2-methyl-1,3-dioxo-1,2,3,3*a*-tetrahydrocyclohepta[*c*]pyrrole-3*a*-carboxylate (**12**) as a viscous yellow oil; yield: 12 mg (42%); IR (neat, cm^{-1}) 3028, 2954, 1775, 1750, 1706, 1650, 1434, 1379, 1283; ^1H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.63 (s, 3H), 5.90 (d, $J=10$ Hz, 1H), 6.51–6.79 (m, 3H), 7.31 (d, $J=6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 53.2, 58.1, 124.4, 127.7, 128.0, 129.4, 135.8, 166.2, 167.4, 172.3.

Kinetic evaluation of the cycloreversion of trimethyl 2-isobutyl-1-methyl-3-oxo-7-oxa-2-azabicyclo[2.2.1]hept-5-ene-4,5,6-tricarboxylate (5). This reaction was conducted in a number of solvents and monitored by ^1H NMR spectroscopy. A sample of the cycloadduct was dissolved in the appropriate deuterated solvent and placed in an incubator set to the desired temperature. Periodically the samples were removed and proton spectra were acquired. The samples were then placed back in the incubator. ^1H NMR of trimethyl 5-methyl-2,3,4-furantricarboxylate (**17**) (300 MHz, $CDCl_3$) δ 2.67 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.18, 52.12, 52.55, 53.05, 114.02, 126.15, 138.93, 157.59, 162.01, 162.29, 163.58; IR (neat, cm^{-1}) 3005, 2956, 2850, 2362, 2338, 1749.

Solid-phase synthesis of trimethyl 5-methyl-2,3,4-furantricarboxylate (17). Wang resin (1.0 g, 0.80 mmol/g loading) was combined with 6-(acetylamino)hexanoic acid (0.26 g, 1.48 mmol), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) (0.66 g, 1.48 mmol), *N*-hydroxybenzotriazole monohydrate (HOBt) (0.20 g, 1.48 mmol) and *N*,*N*′-diisopropylethylamine (DIPEA) (0.39 mL, 2.22 mmol) in methylene chloride (5 mL). The resin mixture was agitated for 8 h at 25 °C. The resin was washed with DMF, methylene chloride yielding 1.21 g of air dried Wang resin 6-(acetylamino)hexanoate (**19**); IR (KBr, cm^{-1}) 3291, 1733, 1653.

As described in the solution phase synthesis of compound **4**, Wang resin 6-[acetyl(3-methoxy-3-oxopropanoyl)-

amino]hexanoate (**20**) was prepared and isolated as the pale yellow resin; IR (KBr, cm^{-1}) 1740, 1698.

As described in the solution phase synthesis of compound **4**, Wang resin 6-[acetyl(2-diazo-3-methoxy-3-oxopropanoyl)amino]hexanoate (**21**) was prepared and isolated as the deep-yellow resin; IR (KBr, cm^{-1}) 2140, 1729, 1653.

Wang resin 6-[acetyl(2-diazo-3-methoxy-3-oxopropanoyl)-amino]hexanoate (**21**) (100 mg) was combined with DMAD (0.20 mL) in dry benzene (3 mL). Rhodium (II) perfluorobutyramidate (3 mg) was added to the suspension and the mixture was agitated for 8 h at 25 °C. The brown resin was washed extensively with DMF and methylene chloride and dried in vacuo to yield trimethyl 2-[6-(Wang resin)-6-oxohexyl]-1-methyl-3-oxo-7-oxa-2-azabicyclo[2.2.1]hept-5-ene-4,5,6-tricarboxylate (**22**). IR (KBr, cm^{-1}) 1730, 1699.

Trimethyl 2-[6-(Wang resin)-6-oxohexyl]-1-methyl-3-oxo-7-oxa-2-azabicyclo[2.2.1]hept-5-ene-4,5,6-tricarboxylate (**22**) (108 mg) was suspended in dry benzene in a sealed vial and heated at 70 °C for 30 min. The dark-brown resin was extensively washed with benzene and methylene chloride. The washings were concentrated to yield 11 mg (63% yield for five steps) of GC pure crystalline trimethyl 5-methyl-2,3,4-furantricarboxylate (**17**), which was identical, in all spectroscopic detail, with the previously synthesized material, prepared in solution phase.

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23. The furan compounds were soluble in the range of 8–12 mg/mL, while the cycloadduct precursors were soluble at approximately 2–4 mg/mL. Neither compound was soluble enough for a reproducible signal in the ^1H NMR spectrum, however, these solubilities are high enough for most biological assays.

24. The degree of reaction completion was determined via direct IR spectroscopy of the resin material, ground into a KBr disk, and monitored at 2100 cm^{-1} (diazo stretch).