Efficient Synthesis of 1,4-Dihydro-2*H*-isoquinoline-3,5,8-triones via Cyclobutene Ring Expansion

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The thermal ring expansion and subsequent cyclization of squaric acid derivatives has received much attention as a valuable tool in organic synthesis over the past few years.[1,2] The versatility of this method is based on readily available squaric acid derivatives and the plethora of synthetic routes for alkynes.[3] The squaric acid approach has been used to construct many carbo- and heterocyclic ring systems, such as hydroquinones, quinones, cyclopentenones, piperidinoquinones, dihydrophenanthridines, and benzophenanthridines.[4] The facility of the electrocyclic ring opening is due to the release of strain present in the cyclobutenone. The reaction is believed to involve a ketene intermediate, generated by the cyclobutenone ring opening, followed by a ring closure with the alkyne moiety and further annulation depending on the R^1 group (Figure 1).[1b] The cascade of C,C-bond formations is usually initiated at moderate temperatures (xylenes or toluene, reflux) and occurs in satisfactory to excellent yields.[1]

As part of our program directed toward the synthesis of isoquinoline-containing natural products, we needed an efficient method to construct an isoquinoline-3,5,8-trione ring system. The squaric acid ring expansion methodology was an attractive strategy for us since it would allow access to this heterocycle in a convergent manner. Xiong and Moore reported the preparation of a related piperidinoquinone in 1996.[5] However, this methodology has not been extended to prepare the isoquinoline-3,5,8-trione ring system **1** (Figure 2). Herein, we report our studies toward the preparation of a variety of heterocycles **1** in four steps from commercially available carboxylic acids, **5**, amines, **4**, and squarates, **3**.

Results and Discussion

Acylation with 3,3-dimethylacrylolyl chloride- (for **6a**) or isobutyl chlorofomate-promoted coupling[6] of carboxylic acids **5b**−**d** with propargylamine provided the α,β-unsaturated amides **6b**−**d** in 61−77% yield (Scheme 1).[7]

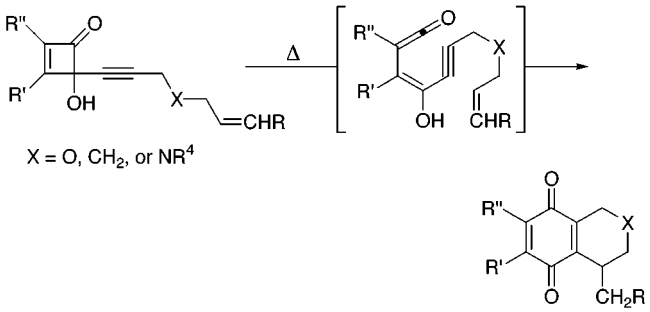


Figure 1.

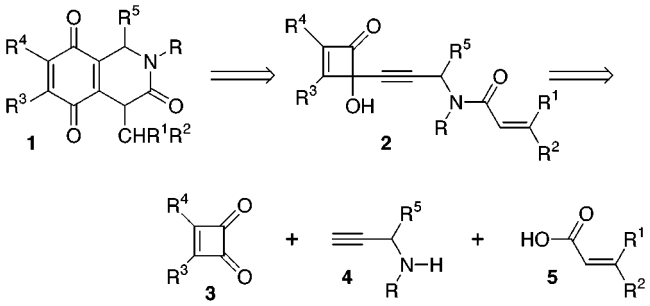
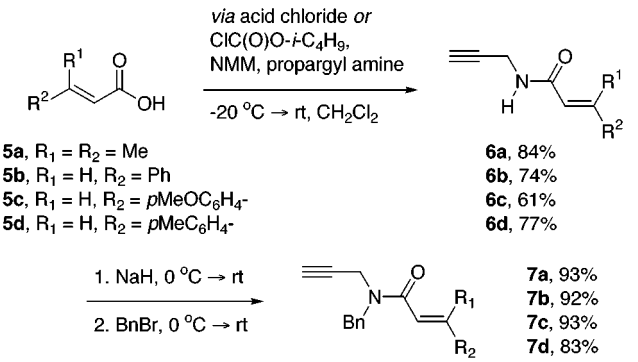
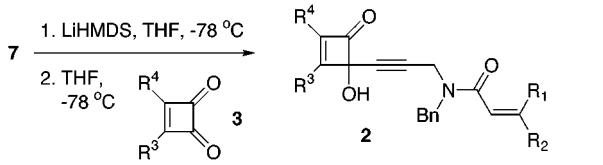


Figure 2.

Scheme 1



Scheme 2



Amides **6a**−**d** were N-benzylated (BnBr, NaH, THF, 0 °C) to give the tertiary amides **7a**−**d**. The desired cyclization precursors were subsequently obtained by treatment of the alkynyl amides with LHMDS (−78 °C, THF) followed by addition to a low-temperature solution (−78 °C, THF) of the appropriate squarate **3**[8,9] to yield the cyclobutenones **2a**−**f** in 47−87% yield (Scheme 2, Table 1). α,β-Unsaturated amides with substituents R^1 = H gave slightly lower yields due to product decomposition on silica gel during purification (Table 1, entries

(1) For recent reviews pertaining to this ring expansion, see: (a) Decker, O. H. W.; Moore, H. W. *Chem. Rev.* **1986**, *86*, 821. (b) Yerxa, B. R.; Moore, H. W. *ChemTracts* **1992**, 273. (c) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053. (d) Paquette, L. A.; Morwick, T. M.; Negri, J. T.; Rogers R. D. *Tetrahedron* **1996**, *52*, 3075. (e) Danheiser R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

(2) For an example carried out on solid support, see: Tempest, P. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7607.

(3) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.

(4) Moore, H. W.; Yerxa, B. R. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: London, 1995; Vol. 4, p 81.

(5) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168.

(6) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1967**, *89*, 5012.

(7) Amide **6a** was obtained in 84% yield.

(8) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477.

(9) Squarates **3b** and **3d** were prepared in two steps from the commercially available diisopropoxy squarate according to ref 8.

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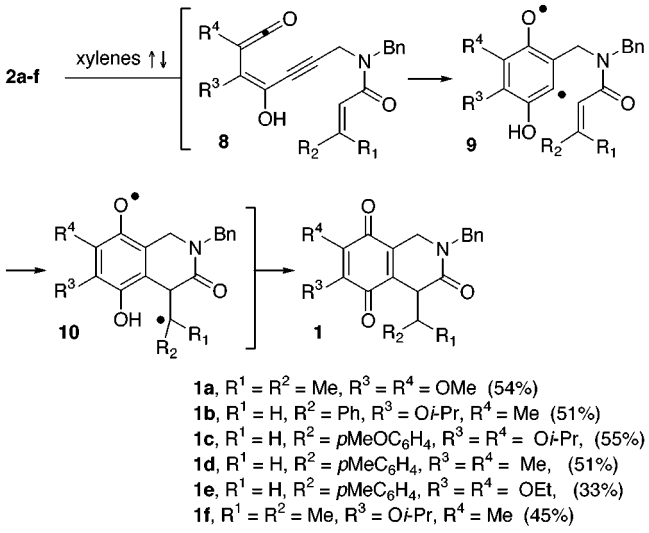
Table 1. Addition of Lithiated Amide Alkynes 7 to Squarates 3 According to Scheme 2

entry	squarate			cyclobutenone					yield
no.	no.	R^3	R^4	no.	R^1	R^2	R^3	R^4	(%)
1	**3a**	OMe	OMe	**2a**	Me	Me	OMe	OMe	72
2	**3b**	O-*i*-Pr	Me	**2b**	H	Ph	O-*i*-Pr	Me	61
3	**3c**	O-*i*-Pr	O-*i*-Pr	**2c**	H	*p*-MeO-C_6H_4	O-*i*-Pr	O-*i*-Pr	55
4	**3d**	Me	Me	**2d**	H	*p*-Me-C_6H_4	Me	Me	47
5	**3e**	OEt	OEt	**2e**	H	*p*-Me-C_6H_4	OEt	OEt	ND[a]
6	**3b**	O-*i*-Pr	Me	**2f**	Me	Me	O-*i*-Pr	Me	87

[a] This compound was directly used in the ring-opening cycloisomerization reaction without prior purification by chromatography.

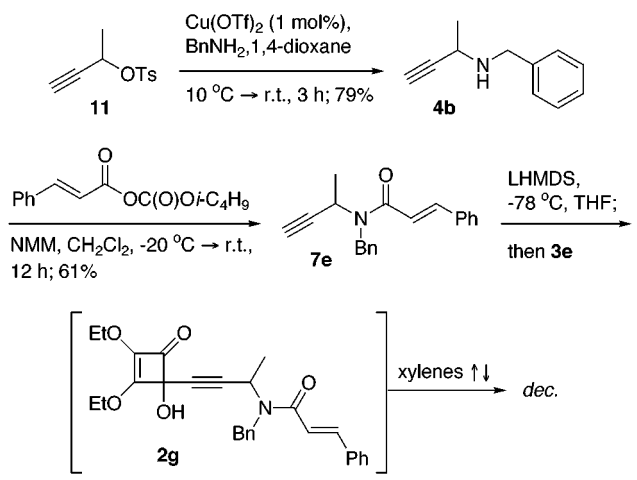
Scheme 3



2−5). In general, substrates **2a**−**f** were stable for a few days if kept under nitrogen in a freezer at −25 °C. However, further conversions of these intermediates were generally carried out shortly after preparation.

With the desired cyclization precursors **2** in hand, we turned our attention to the thermal rearrangement reaction.[1−4] We investigated several solvents (toluene, acetonitrile, α,α,α-trifluorotoluene, xylenes) at various temperatures with **2a** as the test substrate and determined that the optimal conditions involved the use of degassed xylenes at reflux temperatures and moderate dilution conditions (0.01−0.02 M concentrations). Accordingly, cyclobutenones **2a**−**f** were dissolved in degassed xylenes and slowly added (20−30 min) to refluxing xylenes. Shortly after the addition was complete, the reaction flask was cooled to room temperature, and column chromatography on SiO_2 provided the triones **1a**−**f** in 45−55% yields as the only clearly identifiable products (Scheme 3).[10] It is possible that the moderate yield of these thermal conversions is due to a 1,5-hydrogen abstraction of the aryl radical in the putative intermediate **9** from the benzylic carbon of the *N*-benzyl substituent.[5,11] In particular, this side reaction would be of considerable concern in the *trans*-amide rotamer of **9** (vide infra). However, we were unable to isolate any stable product derived from a 1,5-hydrogen atom shift, and our further studies indicated that 1,5-hydrogen abstraction is unlikely to be the major source of side reactions in this cascade pathway.

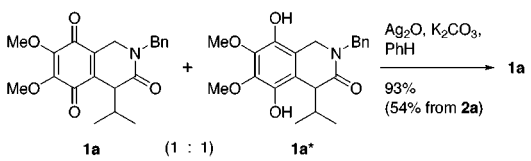
Scheme 4



To further explore the scope of this novel isoquinoline-3,5,8-trione synthesis, we turned our attention to derivatives of the heterocyclic core **1** with $R^5 \neq$ H, e.g., with branching at the C(1)-position. Thus, the tosyl-protected alcohol **11**,[12] derived from but-3-yn-2-ol, was converted in 79% yield to the secondary amine **4b** using benzylamine in the presence of catalytic $Cu(OTf)_2$ (Scheme 4).[13,14] This amine was subsequently coupled with in situ activated *trans*-cinnamic acid mixed anhydride[6] to afford the tertiary amide **7e** in 61% yield. After deprotonation of the alkyne moiety of **7e** with LHMDS (−78 °C, THF), addition to diethyl squarate **3e** generated the cyclobutenone **2g**, which was immediately subjected to the cyclization conditions. However, this compound did not undergo the desired thermal ring expansion to the isoquinoline trione skeleton, and only decomposition of the starting material was observed. Since substrate **2g** is likely to favor an amide rotamer with a trans disposition between the branched *N*-propargyl substituent and the styryl moiety, a conformation suitable for annulation as shown for **9** is energetically disfavored. The presence of the methyl group at the crucial propargylic position in **2g** is therefore likely to promote side reactions leading to product decomposition under the reaction conditions.

The correlation between the relative population of favorable (cis) and unfavorable (trans) amide rotamers in intermediates **9** derived from cyclobutenones **2**, and the ultimate success of the ring expansion strategy is speculative but supported by our data from three subsequent experiments. The *N*-*tert*-butyl-protected cyclization precursor **2h** can be expected to favor the amide

(10) Quinone **1a** was isolated along with the reduced hydroquinone species **1a*** in 58% yield. However, following Moore's protocol,[5,8] the mixture was readily oxidized to the quinone (Ag_2O, PhH, K_2CO_3) in 54% overall yield from **2a**.



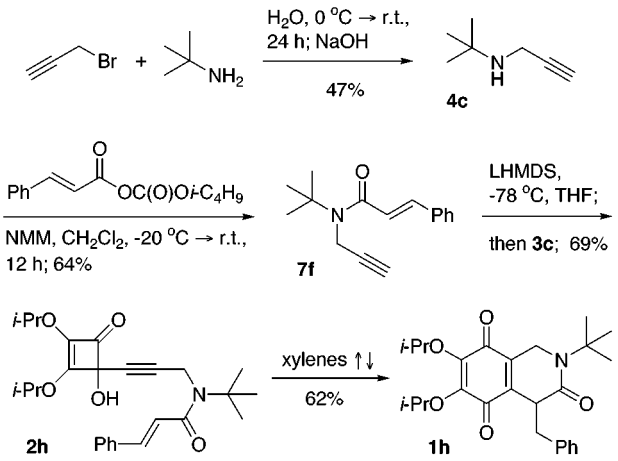
(11) However, use of an *N*-methyl group in place of the *N*-benzyl function in **2a** provided equivalent yields in the ring-opening rearrangement reaction.

(12) Tanabe, Y.; Yamamoto, H.; Yoshida, Y.; Miyawaki, T.; Utsumi, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 297.

(13) Imada, Y.; Yuasa, M.; Ishin, N.; Murahashi, S. I. *J. Org. Chem.* **1994**, *59*, 2282.

(14) Wipf, P.; Uto, Y. Unpublished results.

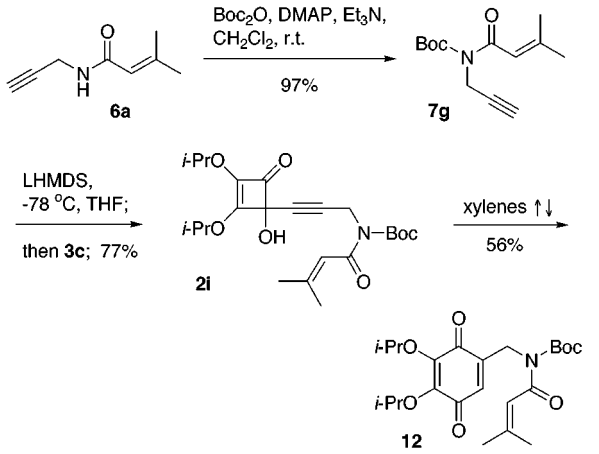
Scheme 5



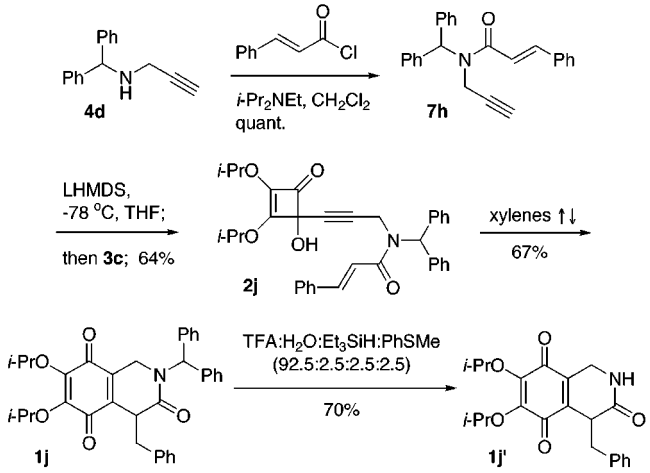
rotamer distribution in a sense opposite to that of substrate **2g**, with the steric bulk of the *N*-*tert*-butyl group locking the amide into a cis orientation of alkene and alkyne substituents (Scheme 5).[15] Cyclobutenone **2h** was prepared in three steps from *tert*-butylamine, propargyl bromide, cinnamate, and squarate **3c**.[16] This substrate was then subjected to the cyclization conditions (xylenes, reflux) to afford the trione **1h** in an isolated yield of 62%. This example illustrates that a sterically hindered amide is well suited for ring annulation *if* the amide conformation is favorable for the interconversion of the formal diradicals **9** and **10**. Since the isolated yields with cyclobutenones **2a**−**f** were in the 45−55% range, whereas the conformationally strongly biased *tert*-butyl amide **2h** provided a slightly higher yield, we further suggest that the cis arrangement of alkyne and alkene moieties in the substrate is necessary for isoquinoline formation but that there are also other decomposition pathways for intermediates **8**−**10** that lead to intractable material.

We were also interested in extending the scope of this methodology to include readily removable protective groups at the ring nitrogen. Since our working hypothesis for successful cyclization demanded bulky groups at that position, we first introduced a Boc function on amide **6a** (Scheme 6). Alkylation of cyclobutenone **3c** proceeded uneventfully, but the thermal ring expansion−cyclization cascade stopped at an intermediate stage and provided quinone **12** in 56% yield. We were unable to detect any isoquinoline ring products in the crude reaction mixture. While this novel result could be due to the unusual conformational properties of the alkenimide moiety, we believe that the lack of intramolecular radical addition to the alkenimide function is due to the increased unfavorable electronic polarization of the alkene moiety. Even at relatively high dilution (0.015 M), intermolecular hydrogen migration in **9** now successfully competes with the radical annulation process.[17] This mechanistically intriguing but for us synthetically undesirable result was readily improved upon by replacement of the Boc substituent with another acid-labile amide protective group. The benzhydryl-protected cyclobutenone **2j** was prepared

Scheme 6



Scheme 7



in three steps from amine **4d**, cinnamoyl chloride, and squarate **3c** (Scheme 7). In this case, ring expansion−cyclization proceeded uneventfully to give the desired isoquinoline trione **1j**, which was N-deprotected in a mixture of trifluoroacetic acid, water, triethylsilane, and thioanisole (92.5:2.5:2.5:2.5). The yield obtained in the cascade step with the very bulky benzhydryl amide was the highest (67%) observed so far, and no monocyclic quinone derived from an intramolecular 1,5-hydrogen abstraction[5] or intermolecular migration was detected.

In conclusion, our study extends the scope of the thermal ring expansion and cyclization of squaric acid derived cyclobutenones toward an efficient and convergent synthesis of the highly substituted 1,4-dihydro-2*H*-isoquinoline-3,5,8-trione ring system. Previous routes to these heterocycles often involve low-yielding multistep annulations and linear arene functionalizations.[18] The cyclobutenone ring expansion proceeds in yields up to 67% from readily available precursors and tolerates different substitution patterns on the alkene moiety (aryl or alkyl) as well as the four-membered ring (dialkyl, dialkoxy, monoalkyl/mono-alkoxy). Our work also provides compelling evidence that the amide conformational preference and the electronic polarization of the acceptor

(15) The *trans*-amide conformation shown for **7e** is favored by ca. 2 kcal/mol over the cis conformation according to MacroModel MM2* calculations. In contrast, the *trans*-amide conformation shown for **7f** is favored by ca. 9 kcal/mol.

(16) Ben-Efraim, D. A. *Tetrahedron* **1973**, *29*, 4111.

(17) Xia, H.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 3765.

(18) For alternative preparations of related isoquinoline triones, see: (a) Fukumi, H.; Kurihara, H.; Hata, T.; Tamura, C.; Mishima, H.; Kubo, A.; Arai, T. *Tetrahedron Lett.* **1977**, 3825. (b) Fukumi, H.; Kurihara, H.; Mishima, H. *Chem. Pharm. Bull.* **1978**, *26*, 2175. (c) Fukumi, H.; Kurihara, H. *J. Heterocycl. Chem.* **1978**, *15*, 569. (d) Parker, K. A.; Casteel, D. A. *J. Org. Chem.* **1988**, *53*, 2847. (e) Nakahara, S.; Tanaka, Y.; Kubo, A. *Heterocycles* **1996**, *43*, 2113.

ene can be a crucial factor in the success of the ring expansion-cyclization cascade. Bulky R groups on cyclobutenones **2** are advantageous, and the benzhydryl function allows a convenient N-deprotection under acidic conditions.

Experimental Section

General Methods. All moisture-sensitive reactions were performed under an atmosphere of N_2 or Ar, and all glassware was dried in an oven at 140 °C prior to use. THF and Et_2O were dried by distillation over Na/benzophenone and LAH under a nitrogen atmosphere, respectively. Dry CH_2Cl_2 and toluene were obtained by distillation from CaH_2. Unless otherwise stated, solvents or reagents were used without further purification. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F-254 plates (particle size 0.040−0.055 mm, 230−400 mesh). NMR spectra were recorded at either 300 MHz/75 MHz (^{1}H/^{13}C NMR) or 500 MHz/125 MHz (^{1}H/^{13}C NMR) in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) are reported in parts per million, and the residual solvent peak was used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), integration, and coupling constants.

3-Methyl-but-2-enoic Acid Prop-2-ynylamide (6a). A solution of 3,3-dimethylacryloyl chloride (6.6 mL, 7.0 g, 59 mmol) in 100 mL of Et_2O was cooled to 0 °C and after 15 min treated with propargylamine (5.0 g, 90 mmol) dropwise over a 20 min period. After the addition was complete, the reaction mixture was allowed to stir for 1 h at 0 °C, the precipitate was filtered, and the Et_2O solution was washed with 1 N HCl, $NaHCO_3$ solution, and water. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 6.84 g (49.9 mmol, 84%) of amide **6a** as a colorless solid: mp 87.2−88.8 °C; IR 3307, 1636, 1530, 754 cm^{-1}; ^{1}H NMR δ 5.71 (br. s, 1 H), 5.56 (s, 1 H), 4.1−4.03 (m, 2 H), 2.21 (t, 1 H, J = 2.4 Hz), 2.16 (s, 3 H), 1.84 (s, 3 H); ^{13}C NMR δ 166.9, 152.1, 117.9, 80.1, 71.2, 28.8, 27.3, 20.0; MS (EI) m/z (rel intensity) 137 (M^+, 16), 83 (100), 79 (41); HRMS (EI) m/z calcd for $C_8H_{11}NO$ 137.0841, found 137.0845.

General Procedure A for the Coupling of Acids with Propargylamine (6b−d, 7e,f). 3-Phenyl-*N*-prop-2-ynylacrylamide (6b). A solution of *trans*-cinnamic acid (785.1 mg, 5.299 mmol), recrystallized from benzene, and *N*-methylmorpholine (0.82 mL, 0.75 g, 7.46 mmol) in dry CH_2Cl_2 (50 mL) was cooled to −20 °C and treated dropwise with 0.72 mL of isobutyl chloroformate (0.76 g, 5.6 mmol). After 15 min, a solution of propargylamine (0.5 mL; 401.5 mg; 7.288 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was warmed to room temperature over 2 h and then washed with 1 M NaH_2PO_4, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting colorless solid was recrystallized (hexanes/EtOAc) to afford 731.0 mg (3.950 mmol, 74%) of the desired amide **6b** as a colorless solid: mp 102.1−102.9 °C; IR 3307, 2360, 1662, 1625 cm^{-1}; ^{1}H NMR δ 7.68 (d, 1 H, J = 15.6 Hz), 7.50−7.45 (m, 3 H), 7.35−7.27 (m, 3 H), 6.80−6.70 (m, 1 H), 6.54 (d, 1 H, J = 15.7 Hz), 4.23−4.18 (m, 2 H), 2.26 (t, 1 H, J = 2.3 Hz); ^{13}C NMR δ 166.1, 141.9, 134.7, 130.0, 129.0, 128.0, 120.1, 79.7, 71.8, 29.6; MS (EI) m/z (rel intensity) 185 (M^+, 21), 142 (61), 131 (100), 103 (79); HRMS (EI) m/z calcd for $C_{12}H_{11}NO$ 185.0840, found 185.0849.

3-(4-Methoxyphenyl)-*N*-prop-2-ynylacrylamide (6c). According to general procedure A, 1.070 g (6.006 mmol) of 4-methoxy-*trans*-cinnamic acid and 449.7 mg (8.163 mmol) of propargylamine provided 789.5 mg (61%) of **6c** as colorless needles: mp 122.6−123.5 °C; IR 3280, 3254, 2255, 1651, 1630, 1598 cm^{-1}; ^{1}H NMR δ 7.62 (d, 1 H, J = 15.6 Hz), 7.44 (d, 2 H, J = 8.7 Hz), 6.86 (d, 2 H, J = 8.7 Hz), 6.32 (d, 1 H, J = 15.6 Hz), 6.25−6.15 (m, 1 H), 4.22−4.17 (m, 2 H), 3.82 (s, 3 H), 2.26 (t, 1 H, J = 2.6 Hz); ^{13}C NMR δ 166.4, 161.1, 141.6, 129.6, 127.5, 117.7, 114.4, 79.8, 71.8, 55.5, 29.6; MS (EI) m/z (rel intensity) 215 (M^+, 11), 214 ([M−H]$^+$, 14), 178 (76), 161 (100); HRMS (EI) m/z calcd for $C_{13}H_{13}NO_2$ 215.0946, found 215.0942.

***N*-Prop-2-ynyl-3-*p*-tolylacrylamide (6d).** According to general procedure A, 902.6 mg (5.565 mmol) of 4-methyl-*trans*-cinnamic acid and 417.6 mg (7.580 mmol) of propargylamine provided 857.6 mg (77%) of **6d** as a colorless solid: mp 127.3−128.6 °C; IR 3223, 1650, 1603, 729 cm^{-1}; ^{1}H NMR δ 7.65 (d, 1 H, J = 15.6 Hz), 7.38 (d, 2 H, J = 7.9 Hz), 7.14 (d, 2 H, J = 7.8 Hz), 6.5−6.4 (m, 1 H), 6.45 (d, 1 H, J = 15.5 Hz), 4.22−4.18 (m, 2 H), 2.35 (s, 3 H), 2.26 (t, 1 H, J = 2.5 Hz); ^{13}C NMR δ 166.1, 141.8, 140.2, 131.9, 129.6, 127.9, 118.9, 79.7, 71.7, 29.5, 21.5; MS (EI) m/z (rel intensity) 199 (M^+, 17), 198 ([M^+ − H], 19), 156 (74), 145 (100); HRMS (EI) m/z calcd for $C_{13}H_{13}NO$ 199.0997, found 199.1000.

***N*-Benzyl-*N*-(1-methyl-prop-2-ynyl)-3-phenylacrylamide (7e).** According to general procedure A, 378.6 mg (2.556 mmol) of *trans*-cinnamic acid and 404.3 mg (2.548 mmol) of propargylamine **4b** provided 437.6 mg (61%) of **7e** as a light yellow oil: IR 3307, 1649, 1600, 733 cm^{-1}; ^{1}H NMR δ 7.76 (d, 1 H, J = 15.3 Hz), 7.43−7.27 (m, 10 H), 6.63 (d, 1 H, J = 15.3 Hz), 5.86−5.75 (m, 1 H), 4.91, 4.79 (AB, 2 H, J = 17.8 Hz), 2.28 (s, 1 H), 1.39 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 166.9, 143.8, 138.7, 135.2, 129.9, 128.9, 128.0, 127.5, 126.4, 118.1, 83.2, 72.5, 47.8, 42.6, 20.8; MS (EI) m/z (rel intensity) 289 (M^+, 9), 236 (17), 131 (100); HRMS (EI) m/z calcd for $C_{20}H_{19}NO$ 289.1467, found 289.1469.

***N*-*tert*-Butyl-3-phenyl-*N*-prop-2-ynylacrylamide (7f).** According to general procedure A, 740.6 mg (5.000 mmol) of *trans*-cinnamic acid and 789.4 mg (7.098 mmol) of propargylamine **4c** provided 770.5 mg (64%) of **7f** as a colorless solid: mp 103.9−105.5 °C; IR 3306, 2246, 1651, 1611, 732 cm^{-1}; ^{1}H NMR δ 7.60 (d, 1 H, J = 15.5 Hz), 7.53−7.49 (m, 2 H), 7.43−7.27 (m, 3 H), 6.94 (d, 1 H, J = 15.4 Hz), 4.14 (d, 2 H, J = 2.4 Hz), 2.37 (t, 1 H, J = 2.2 Hz), 1.55 (s, 9 H); ^{13}C NMR δ 168.3, 141.9, 135.5, 129.6, 128.9, 127.9, 121.5, 81.3, 72.6, 58.0, 35.3, 28.8; MS (EI) m/z (rel intensity) 241 (M^+, 30), 240 ([M − H], 45), 131 (100), 103 (46); HRMS (EI) m/z calcd for $C_{16}H_{18}NO$ (M − H) 240.1388, found 240.1382.

General Procedure B for the N-Benzylation of Amides (7a−d). *N*-Benzyl Propargyl 3,3-Dimethylacrylamide (7a). A solution of the amide **6a** (2.875 g, 20.98 mmol) in dry THF (30 mL) was transferred, via cannula, over a 10 min period to a cooled (0 °C) suspension of NaH (1.078 g, 60% in oil, 26.95 mmol) in THF (30 mL). The reaction mixture was warmed to room temperature for 1 h and then recooled to 0 °C and treated with neat benzyl bromide (6.2 mL, 52 mmol). The solution was stirred overnight at room temperature and quenched by addition of H_2O (20 mL). The organic layer was washed with water and brine. The aqueous layer was then extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (hexanes/EtOAc 7:3) to yield 4.42 g (19.5 mmol, 93%) of the benzylated amide **7a** as a yellow oil: IR 3231, 1626, 1483, 953, 694 cm^{-1}; ^{1}H NMR δ 7.39−7.21 (m, 5 H), 5.93, 5.89 (2 s, 1 H), 4.74, 4.70 (2 s, 2 H), 4.20 (d, 1 H, J = 2 Hz), 3.97 (d, 1 H, J = 2 Hz), 2.30, 2.21 (2 s, 1 H), 2.02, 1.99 (2 s, 3 H), 1.89, 1.84 (2 s, 3 H); ^{13}C NMR δ 168.0, 149.2, 148.2, 137.0, 136.4, 128.9, 128.6, 128.4, 127.7, 127.5, 127.0, 117.5, 117.2, 79.1, 78.6, 73.0, 72.0, 50.5, 47.3, 36.8, 33.3, 26.5, 26.4, 20.4; MS (EI) m/z (rel intensity) 227 (M^+, 22), 91 (62), 83 (100); HRMS (EI) m/z calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1309.

***N*-Benzyl-3-phenyl-*N*-prop-2-ynylacrylamide (7b).** According to general procedure B, 676.5 mg (3.655 mmol) of propargyl amide **6b** provided 942.5 mg (92%) of **7b** as a yellow oil: IR 3291, 3233, 1651, 1604, 978, 768, 694 cm^{-1}; ^{1}H NMR δ 7.82 (d, 1 H, J = 15.4 Hz), 7.57−7.27 (m, 10 H), 6.99, 6.87 (2 d, 1 H, J = 15.4 Hz), 4.84 (s, 1 H), 4.34, 4.09 (2 s, 2 H), 2.36, 2.26 (2 s, 1 H); ^{13}C NMR δ 166.8, 144.3, 144.0, 136.9, 136.5, 135.1, 130.0, 129.1, 129.0, 128.6, 128.1, 126.9, 117.0, 79.0, 78.7, 73.2, 72.2, 50.4, 49.1, 36.7, 35.0; MS (EI) m/z (rel intensity) 275 (M^+, 16), 184 (37), 131 (100), 91 (66), 61 (70); HRMS (EI) m/z calcd for $C_{19}H_{17}NO$ 275.1310, found 275.1304.

***N*-Benzyl-3-(4-methoxyphenyl)-*N*-prop-2-ynylacrylamide (7c).** According to general procedure B, 667.1 mg (3.101 mmol) of propargyl amide **6c** provided 868.4 mg (93%) of **7c** as a light yellow oil: IR 3291, 3233, 1730, 1646, 1604, 826, 736 cm^{-1}; ^{1}H NMR δ 7.78 (d, 1 H, J = 15.3 Hz), 7.52−7.27 (m, 7 H), 6.93−6.75 (m, 3 H), 4.83 (s, 2 H), 4.33, 4.08 (2 s, 2 H), 3.82 (s, 3 H), 2.33, 2.24 (2 s, 1 H); ^{13}C NMR δ 167.0, 161.0, 143.8, 143.6, 136.9, 136.5, 129.6, 129.0, 128.7, 128.4, 127.8, 127.7, 126.8, 114.5, 114.2, 79.0, 78.7, 73.0, 72.1, 55.3, 50.2, 49.0, 36.6, 34.8; MS (EI)

m/*z* (rel intensity) 305 (M^+, 27), 172 (68), 161 (100); HRMS (EI) *m*/*z* calcd for $C_{20}H_{19}NO_2$ 305.1416, found 305.1404.

***N*-Benzyl-*N*-prop-2-ynyl-3-*p*-tolylacrylamide (7d).** According to general procedure B, 815.7 mg (4.097 mmol) of propargyl amide **6d** provided 987.8 mg (83%) of **7d** as a light yellow oil: IR 3291, 3227, 2119, 1735, 1649, 1609, 810, 694 cm^{-1}; ^1H NMR δ 7.80 (d, 1 H, J = 15.3 Hz), 7.49−7.15 (m, 9 H), 6.94, 6.83 (2 d, 1 H, J = 15.3 Hz), 4.84 (s, 2 H), 4.33, 4.09 (2 s, 2 H), 2.36−2.25 (m, 4 H); ^{13}C NMR δ 167.0, 144.3, 144.0, 140.3, 136.5, 132.4, 129.7, 129.1, 128.8, 128.6, 128.1, 128.0, 127.8, 126.9, 126.7, 116.1, 115.8, 79.1, 73.1, 72.2, 50.4, 49.0, 36.7, 34.9, 21.6; MS (EI) *m*/*z* (rel intensity) 289 (M^+, 9), 156 (41), 145 (100); HRMS (EI) *m*/*z* calcd for $C_{20}H_{19}NO$ 289.1467, found 289.1460.

4-Isopropoxy-3-methylcyclobut-3-ene-1,2-dione (3b).[8] To a cold (−20 °C) suspension of commercially available diisopropoxy squarate (1.190 g, 6.004 mmol) in dry THF (20 mL) was added 4.4 mL of MeMgBr (1.5 M solution, 6.6 mmol, 1.1 equiv). After 75 min, 20 mL of a saturated NH_4Cl solution was added, and the layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The resulting orange liquid was purified by column chromatography on SiO_2 (hexanes/EtOAc 7:3) to yield an inseparable mixture of the mono- and disubstituted products (961.3 mg). This mixture (1.265 g) was dissolved in dry CH_2Cl_2 (26 mL) and treated with six drops of concentrated HCl. After 1 h, TLC analysis showed product and **3d**, and the mixture was diluted with CH_2Cl_2, dried (K_2CO_3), and concentrated. The resulting orange liquid was purified using column chromatography on SiO_2 (hexanes/EtOAc 7:3) to afford 642.8 mg (4.170 mmol, 69%) of the desired methyl isopropoxy squarate **3b** as a yellow liquid: ^1H NMR δ 5.29 (hept, 1 H, J = 6.3 Hz), 2.12 (s, 3 H), 1.38 (d, 6 H, J = 6.3 Hz).

General Procedure C for the Addition of the Lithiated Alkyne to Cyclobutenediones (2a−d,f,h−j). 3-Methylbut-2-enoic Acid Benzyl[3-(1-hydroxy-2,3-dimethoxy-4-oxocyclobut-2-enyl)prop-2-ynyl]amide (2a). A solution of the benzylated amide **7a** (911.7 mg, 4.014 mmol) in 30 mL of dry THF was cooled to −78 °C and treated dropwise with 6.0 mL of LiHMDS (1.0 M solution in hexanes, 6.0 mmol). The resulting alkynyllithium reagent was stirred for 10 min at −78 °C and transferred, via cannula, to a cold (−78 °C) solution of dimethyl squarate **3a** (857.1 mg, 6.033 mmol) in 30 mL of dry THF. The reaction mixture was allowed to stir for 2 h at −78 °C and quenched with 50 mL of saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (hexanes/EtOAc; 1:1) to yield 1.06 g (2.87 mmol, 72%) of **2a** as a viscous yellow oil: IR 3250, 2351, 1755, 1605, 721 cm^{-1}; ^1H NMR δ 7.36−7.19 (m, 5 H), 5.89, 5.87 (2 br. s, 1 H), 4.71, 4.67 (2 s, 2 H), 4.28 (d, 1 H, J = 1.7 Hz), 4.15 (2 s, 3 H), 4.07 (s, 1 H), 3.97, 3.96 (2 s, 3 H), 3.62, 3.58 (2 s, 1 H), 2.00, 1.98 (2 s, 3 H), 1.88, 1.83 (2 s, 3 H); ^{13}C NMR δ 181.0, 168.5, 165.2, 150.1, 148.8, 136.9, 136.3, 135.4, 135.3, 128.9, 128.6, 128.5, 127.7, 127.6, 127.0, 117.3, 116.8, 84.3, 83.4, 79.2, 78.4, 60.2, 60.1, 58.7, 58.6, 50.9, 47.7, 37.4, 34.1, 26.7, 26.4, 20.5; MS (FAB) *m*/*z* (rel intensity) 392 ([M + Na]$^+$, 80), 369 (M^+, 45), 352 (100).

***N*-Benzyl-*N*-[(3-(1-hydroxy-2-isopropoxy-3-methyl-4-oxocyclobut-2-enyl)prop-2-ynyl]-3-phenylacrylamide (2b).** According to general procedure C, 697.5 mg (2.535 mmol) of propargyl amide **7b** and 330.2 mg (2.142 mmol) of squarate **3b** provided 545.0 mg (61%) of **2b** as an orange solid: mp 59.3−60.9 °C; IR 3278, 2250, 1761, 1647, 1611 cm^{-1}; ^1H NMR δ 7.76 (d, 1 H, J = 15.4 Hz), 7.55−7.23 (m, 10 H), 6.93, 6.81 (2 d, 1 H, J = 15.3 Hz), 5.2−4.9 (m, 2 H), 4.8−4.7 (m, 2 H), 4.37, 4.13 (2 s, 2 H), 1.62 (s, 3 H), 1.44−1.26 (m, 6 H); ^{13}C NMR δ 187.7, 180.4, 180.3, 166.9, 144.4, 144.2, 136.8, 136.4, 135.0, 130.0, 129.0, 128.9, 128.8, 128.6, 128.1, 127.9, 127.7, 126.9, 124.4, 117.0, 116.8, 84.8, 84.2, 83.0, 79.6, 78.9, 78.4, 50.4, 49.2, 37.2, 35.3, 23.0, 22.8, 6.7; MS (FAB) *m*/*z* (rel intensity) 430 (M + H$^+$, 10), 131 (100).

***N*-Benzyl-*N*-[3-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)prop-2-ynyl]-3-(4-methoxyphenyl)acrylamide (2c).** According to general procedure C, 455.2 mg (1.492 mmol) of propargyl amide **7c** and 290.0 mg (1.463 mmol) of squarate **3c** provided 415.4 mg (55%) of **2c** as an orange, waxy solid: IR 3295, 1774, 1631 cm^{-1}; ^1H NMR δ 7.75 (d, 1 H, J = 15.3 Hz), 7.42−7.24 (m, 7 H), 6.90−6.84 (m, 3 H), 4.89−4.76 (m, 4 H), 4.40 (d, 1 H, J = 5.0 Hz), 4.14 (s, 1 H), 3.81 (s, 3 H), 1.4−1.25 (m, 6 H), 1.3−1.15 (m, 6 H); ^{13}C NMR δ 180.8, 167.2, 164.7, 161.1, 144.2, 143.9, 137.0, 136.6, 133.9, 129.7, 129.0, 128.7, 128.6, 127.8, 127.6, 126.9, 114.3, 83.8, 83.3, 79.9, 79.1, 78.5, 78.0, 74.1, 55.4, 50.4, 49.2, 37.2, 35.3, 22.8, 22.6; MS (FAB) *m*/*z* (rel intensity) 526 ([M + Na]$^+$, 100), 504 ([M + H]$^+$, 22), 486 (45), 161 (97), 91 (81).

***N*-Benzyl-*N*-[3-(1-hydroxy-2,3-dimethyl-4-oxocyclobut-2-enyl)prop-2-ynyl]-3-*p*-tolylacrylamide (2d).** According to general procedure C, 451.7 mg (1.562 mmol) of propargyl amide **7d** and 226.2 mg (2.054 mmol) of squarate **3d** provided 298.7 mg (47%) of **2d** as a tan, waxy solid: IR 3306, 1767, 1644, 1604 cm^{-1}; ^1H NMR δ 7.77 (d, 1 H, J = 15.3 Hz), 7.44−7.15 (m, 9 H), 6.89−6.75 (m, 1 H), 4.79, 4.73 (2 s, 2 H), 4.47−4.17 (m, 2 H), 2.36 (s, 3 H), 2.12, 2.06 (2 s, 3 H), 1.73 (s, 3 H); ^{13}C NMR δ 177.0, 167.2, 150.8, 144.6, 144.2, 140.5, 136.5, 132.3, 131.9, 129.7, 129.3, 129.1, 128.9, 128.6, 128.2, 127.0, 126.8, 115.6, 86.0, 84.8, 79.2, 50.8, 35.6, 21.6, 10.8, 8.1; MS (FAB) *m*/*z* (rel intensity) 422 ([M + Na]$^+$, 41), 400 ([M + H]$^+$, 36), 368 (70), 154 (100), 91 (64).

3-Methylbut-2-enoic Acid Benzyl[3-(1-hydroxy-2-isopropoxy-3-methyl-4-oxocyclobut-2-enyl)prop-2-ynyl]amide (2f). According to general procedure C, 564.6 mg (2.486 mmol) of propargyl amide **7a** and 343.5 mg (2.228 mmol) of squarate **3b** provided 733.7 mg (87%) of **2f** as an orange oil: IR 3272, 2251, 1764, 1616 cm^{-1}; ^1H NMR δ 7.34−7.18 (m, 5 H), 5.88, 5.85 (2 s, 1 H), 5.01 (hept, 1 H, J = 6.1 Hz), 4.7−4.65 (m, 2 H), 4.26 (s, 1 H), 4.03 (s, 1 H), 1.98, 1.96 (2 s, 3 H), 1.86, 1.82 (2 s, 3 H), 1.66, 1.64 (2 s, 3 H), 1.47−1.42 (m, 6 H); ^{13}C NMR δ 187.8, 180.4, 168.3, 149.7, 148.7, 137.0, 136.4, 128.9, 128.7, 128.6, 127.8, 127.6, 127.1, 124.3, 117.4, 117.1, 84.9, 84.1, 83.0, 79.4, 78.5, 78.3, 50.7, 47.5, 37.4, 33.8, 26.7, 26.5, 23.0, 22.8, 20.5, 6.7, 6.6; MS (FAB) *m*/*z* (rel intensity) 382 ([M + H]$^+$, 100), 338 (76), 300 (77), 190 (75), 151 (85).

***N*-*tert*-Butyl-*N*-[3-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)prop-2-ynyl]-3-phenylacrylamide (2h).** According to general procedure C, 661.0 mg (2.743 mmol) of propargyl amide **7f** and 491.8 mg (2.481 mmol) of squarate **3c** provided 762.7 mg (69%) of **2h** as a yellow sticky solid: IR 3295, 2251, 1774, 1626, 733 cm^{-1}; ^1H NMR δ 7.59−7.42 (m, 3 H), 7.39−7.26 (m, 3 H), 6.88 (d, 1 H, J = 15.4 Hz), 4.92, 4.82 (2 hept, 2 H, J = 6.1 Hz), 4.26−4.03 (m, 3 H), 1.51 (s, 9 H), 1.36 (t, 6 H, J = 6.5 Hz), 1.25 (t, 6 H, J = 6.1 Hz); ^{13}C NMR δ 180.8, 168.4, 164.7, 142.1, 135.4, 133.8, 129.6, 128.9, 128.0, 121.3, 85.7, 79.4, 78.6, 78.1, 74.3, 58.0, 35.8, 28.9, 22.8, 22.7, 22.6; MS (FAB) *m*/*z* (rel intensity) 439 (M^+, 20), 282 (25), 131 (100).

[3-(1-Hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)-prop-2-ynyl]-(3-methylbut-2-enoyl)carbamic Acid *tert*-Butyl Ester (2i). According to general procedure C, 571.4 mg (2.408 mmol) of propargyl amide **7g** and 601.4 mg (3.034 mmol) of squarate **3c** provided 806.2 mg (77%) of **2i** as a yellow oil: IR 3411, 2981, 2253, 1776, 1736, 1632 cm^{-1}; ^1H NMR δ 6.44−6.40 (m, 1 H), 4.93, 4.85 (2 hept, 2 H, J = 6.1 Hz), 4.52 (2s, 2 H), 2.98 (s, 1 H), 2.08 (2s, 3 H), 1.93 (2s, 3 H), 1.53 (s, 9 H), 1.40 (d, 6 H, J = 6.1 Hz), 1.29 (d, 3 H, J = 6.1 Hz), 1.27 (d, 3 H, J = 6.1 Hz); ^{13}C NMR δ 179.9, 167.6, 163.9, 154.0, 119.6, 85.2, 83.6, 78.6, 76.7, 74.4, 33.7, 28.1, 27.6, 22.7, 22.5, 21.0; MS (FAB) *m*/*z* (rel intensity) 435 (M^+, 20), 318 (40), 276 (87), 234 (100).

***N*-Benzhydryl-*N*-[3-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)prop-2-ynyl]-3-phenylacrylamide (2j).** According to general procedure C, 654.9 mg (1.865 mmol) of propargyl amide **7h** and 499.7 mg (2.521 mmol) of squarate **3c** provided 654.7 mg (64%) of **2j** as an orange amorphous solid: IR 3305, 3060, 2980, 2360, 1775, 1631 cm^{-1}; ^1H NMR δ 7.56−7.02 (br. m, 18 H), 4.9−4.7 (m, 2 H), 4.21 (br. s, 2 H), 2.62 (2 br. s, 1 H), 1.38 (d, 6 H, J = 6.2 Hz), 1.35 (d, 3 H, J = 6.1 Hz), 1.29 (d, 6 H, J = 6.2 Hz); ^{13}C NMR δ 180.0, 167.1, 164.1, 144.3, 143.8, 138.6, 135.1, 133.9, 129.9, 129.1, 128.9, 128.7, 128.1, 127.8, 117.8, 84.5, 79.3, 78.3, 76.8, 74.1, 65.7, 64.5, 61.7, 60.5, 35.4, 22.7, 22.6, 22.5; MS (FAB) *m*/*z* (rel intensity) 167 (100), 131 (21).

2-Benzyl-4-isopropyl-6,7-dimethoxy-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1a). A solution of **2a** (1.019 g, 2.762 mmol) in 15 mL of freshly degassed xylenes was added via syringe pump over a 30 min period to 130 mL of refluxing degassed xylenes. The solution was heated at reflux for an additional 30 min, cooled to room temperature, and concentrated in vacuo leaving a dark red oil. The residue was purified by

column chromatography on SiO_2 (hexanes/EtOAc 1:1) to yield 599.1 mg (1.623 mmol, 58%) of a ca. 1:1 mixture of the oxidized and reduced compounds **1a** and **1a*** as a red oil. A solution of the combined mixture of **1a** and **1a*** (486.1 mg, 1.317 mmol), Ag_2O (1.503 g, 6.486 mmol), and potassium carbonate (906.3 mg, 6.557 mmol) in benzene (15 mL) was stirred at room temperature overnight, passed through a small plug of SiO_2, and concentrated in vacuo to afford 447.0 mg (1.211 mmol; 93%) of the quinone **1a** as a red oil. A portion of this material (100.4 mg) was further purified by rotary chromatography on SiO_2 (hexanes/EtOAc/CH_2Cl_2 7:5:3) to yield 47.2 mg (47%) of pure **1a** as a red oil: IR 3053, 1672, 1657, 1623, 738 cm^{-1}; ^1H NMR δ 7.34−7.30 (m, 5 H), 4.86 (d, 1 H, J = 14.4 Hz), 4.56 (d, 1 H, J = 14.4 Hz), 4.24 (dd, 1 H, J = 19.9, 1.3 Hz), 4.06 (dd, 1 H, J = 19.9, 2.8 Hz), 4.03 (s, 6 H), 3.66−3.62 (m, 1 H), 2.18−2.12 (m, 1 H), 1.15 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 182.1, 181.7, 168.0, 145.1, 144.6, 139.1, 136.4, 134.2, 128.9, 128.7, 128.0, 61.5, 50.3, 45.6, 45.4, 34.4, 21.4, 19.3; MS (EI) *m/z* (rel intensity) 367 ([M − H_2]$^+$, 46), 276 (52), 91 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{21}NO_5$ (M − H_2) 367.1420, found 367.1407.

General Procedure D for Ring Expansion of Cyclobutenone Precursors (1b−d,f,h,j). 2,4-Dibenzyl-6-isopropoxy-7-methyl-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1b). A solution of the alcohol **2b** (306.8 mg, 0.7148 mmol) in freshly degassed xylenes (10 mL) was added dropwise over a 20 min period to 40 mL of refluxing, degassed xylenes. After the addition was complete, the reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting red oil was purified by column chromatography on SiO_2 (hexanes/EtOAc/CH_2Cl_2 6:1:3) to afford 154.6 mg (0.3602 mmol, 51%) of the desired isoquinolinone **1b** as an orange-red oil: IR 3030, 2981, 2251, 1643, 909, 734, 649 cm^{-1}; ^1H NMR δ 7.32−6.84 (m, 10 H), 4.76 (hept, 1 H, J = 6.1 Hz), 4.68 (d, 1 H, J = 14.3 Hz), 4.37 (d, 1 H, J = 14.3 Hz), 4.08−4.0 (m, 1 H), 3.86 (dd, 1 H, J = 19.8, 2.0 Hz), 3.46 (dd, 1 H, J = 13.4, 5.0 Hz), 3.07 (dd, 1 H, J = 13.3, 4.6 Hz), 2.84 (dd, 1 H, J = 19.9, 3.5 Hz), 1.92 (s, 3 H), 1.34, (d, 3 H, J = 6.1 Hz), 1.32 (d, 3 H, J = 6.1 Hz); ^{13}C NMR δ 185.3, 181.6, 168.7, 154.9, 137.1, 136.7, 136.5, 135.8, 130.7, 129.7, 129.0, 128.9, 128.3, 128.0, 127.2, 76.7, 50.3, 45.0, 41.4, 38.8, 23.1, 9.2; MS (EI) *m/z* (rel intensity) 429 (M$^+$, 46), 172 (86), 161 (100), 133 (39), 91 (70); HRMS (EI) *m/z* calcd for $C_{27}H_{27}NO_4$ 429.1940, found 429.1944.

2-Benzyl-6,7-diisopropoxy-4-(4-methoxybenzyl)-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1c). According to general procedure D, 292.5 mg (0.5812 mmol) of cyclobutenone **2c** provided 161.4 mg (55%) of **1c** as a red oil: IR 2978, 1653, 1604 cm^{-1}; ^1H NMR δ 7.32−7.27 (m, 5 H), 6.71 (d, 2 H, J = 8.6 Hz), 6.49 (d, 2 H, J = 8.6 Hz), 4.81, 4.75 (2 hept, 2 H, J = 6.1 Hz), 4.56, 4.49 (AB, 2 H, J = 14.3 Hz), 4.0−3.9 (m, 1 H), 3.84 (dd, 1 H, J = 19.7, 2.1 Hz), 3.69 (s, 3 H), 3.43 (dd, 1 H, J = 13.6, 4.4 Hz), 2.96 (dd, 1 H, J = 13.6, 4.7 Hz), 2.82 (dd, 1 H, J = 19.7, 3.4 Hz), 1.36−1.26 (m, 12 H); ^{13}C NMR δ 182.8, 182.0, 168.5, 158.7, 145.9, 145.4, 137.3, 135.9, 135.1, 130.7, 129.2, 128.8, 128.3, 128.0, 113.5, 76.5, 76.4, 55.3, 50.4, 44.8, 41.6, 38.0, 22.8, 22.7; MS (EI) *m/z* (rel intensity) 503 (M$^+$, 33), 121 (100), 91 (60); HRMS (EI) *m/z* calcd for $C_{30}H_{33}NO_6$ 503.2308, found 503.2302.

2-Benzyl-6,7-dimethyl-4-(4-methyl-benzyl)-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1d). According to general procedure D, 249.2 mg (0.6243 mmol) of cyclobutenone **2d** provided 126.6 mg (51%) of **1d** as an orange-red oil: IR 2923, 1650 cm^{-1}; ^1H NMR δ 7.36−7.20 (m, 5 H), 6.83 (d, 2 H, J = 7.6 Hz), 6.73 (d, 2 H, J = 7.7 Hz), 4.69 (d, 1 H, J = 14.4 Hz), 4.34 (d, 1 H, J = 14.4 Hz), 4.02−3.95 (m, 1 H), 3.82 (d, 1 H, J = 19.6 Hz), 3.46 (dd, 1 H, J = 13.4, 4.6 Hz), 2.98 (dd, 1 H, J = 13.3, 4.2 Hz), 2.77 (dd, 1 H, J = 19.5, 3.1 Hz), 2.24 (s, 3 H), 2.08, 2.01 (2 s, 6 H); ^{13}C NMR δ 185.2, 184.5, 168.7, 141.5, 140.8, 138.8, 136.7, 136.6, 135.9, 133.3, 129.7, 128.9, 128.8, 127.9, 50.2, 44.8, 41.7, 38.4, 21.2, 12.6, 12.3; MS (EI) *m/z* (rel intensity) 399 (M$^+$, 53), 306 (58), 266 (100), 91 (68); HRMS (EI) *m/z* calcd for $C_{26}H_{25}NO_3$ 399.1834, found 399.1838.

2-Benzyl-6,7-diethoxy-4-(4-methylbenzyl)-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1e). To a cooled (−78 °C) solution of the benzylated amide **7d** (459.3 mg, 1.588 mmol) in dry THF (12 mL) was added 1.8 mL of LHMDS (1.0 M solution in THF, 1.8 mmol). After 15 min, the alkynyllithium reagent was transferred via cannula to a cold (−78 °C) solution of the squarate **3e** (276.0 mg, 1.622 mmol) in dry THF (12 mL). After 45 min, the reaction mixture was quenched by addition to 40 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting dark red oil (695.9 mg) was carried on without further purification. A solution of the crude alcohol in freshly degassed xylenes (20 mL) was added over a 35 min period to 90 mL of degassed, refluxing xylenes. After the addition was complete, the mixture was cooled to room temperature and concentrated. The resulting red oil was purified by column chromatography on SiO_2 (hexanes/EtOAc/CH_2Cl_2, 6:2:2) to afford 241.6 mg (0.5261 mmol, 33% based on **7d**) of the desired trione **1e** as a red oil: IR 2981, 1652, 1605 cm^{-1}; ^1H NMR δ 7.34−7.21 (m, 5 H), 6.83 (d, 2 H, J = 7.8 Hz), 6.73 (d, 2 H, J = 8.0 Hz), 4.66 (d, 1 H, J = 14.4 Hz), 4.37 (d, 2 H, J = 14.3 Hz), 4.39−4.20 (m, 4 H), 4.00−3.93 (m, 1 H), 3.81 (dd, 1 H, J = 19.7, 2.1 Hz), 3.44 (dd, 1 H, J = 13.4, 4.7 Hz), 2.99 (dd, 1 H, J = 13.4, 4.7 Hz), 2.78 (dd, 1 H, J = 19.7, 3.6 Hz), 2.23 (s, 3 H), 1.42 (t, 3 H, J = 7.1 Hz), 1.37 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 182.3, 181.6, 168.4, 144.8, 144.4, 137.3, 136.7, 135.8, 135.0, 133.2, 129.7, 129.6, 128.9, 128.8, 128.0, 70.0, 69.9, 50.2, 44.7, 41.5, 38.4, 21.2, 15.7; MS (EI) *m/z* (rel intensity) 459 (M$^+$, 66), 356 (43), 326 (100), 91 (34); HRMS (EI) *m/z* calcd for $C_{28}H_{29}NO_5$ 459.2046, found 459.2051.

2-Benzyl-6-isopropoxy-4-isopropyl-7-methyl-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1f). According to general procedure D, 299.3 mg (0.7852 mmol) of cyclobutenone **2f** provided 134.7 mg (45%) of **1f** as an orange oil: IR 2970, 2253, 1661, 1642, 909, 732 cm^{-1}; ^1H NMR δ 7.33−7.27 (m, 5 H), 4.83−4.78 (m, 2 H), 4.58 (d, 1 H, J = 14.4 Hz), 4.24 (dd, 1 H, J = 20.2, 1.6 Hz), 4.05 (dd, 1 H, J = 20.1, 2.8 Hz), 3.64−3.60 (m, 1 H), 2.2−2.05 (m, 1 H), 1.93 (s, 3 H), 1.32 (d, 3 H, J = 6.1 Hz), 1.29 (d, 3 H, J = 6.2 Hz), 1.08 (d, 3 H, J = 6.8 Hz), 0.85 (d, 3 H, J = 7.0 Hz); ^{13}C NMR δ 185.7, 181.8, 168.3, 155.0, 139.0, 136.5, 135.9, 130.4, 128.9, 128.7, 128.0, 76.6, 50.3, 45.7, 45.5, 34.3, 23.1, 21.4, 19.4, 9.1; MS (EI) *m/z* (rel intensity) 381 (M$^+$, 100), 339 (26), 296 (65), 91 (29); HRMS (EI) *m/z* calcd for $C_{23}H_{27}NO_4$ 381.1940, found 381.1941.

2-*tert*-Butyl-4-benzyl-6,7-diisopropoxy-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1h). According to general procedure D, 350.7 mg (0.7984 mmol) of cyclobutenone **2h** provided 218.0 mg (62%) of **1h** as a red oil: IR 2979, 1653, 1603 cm^{-1}; ^1H NMR δ 7.16−7.14 (m, 3 H), 6.94−6.91 (m, 2 H), 4.77 (hept, 2 H, J = 6.3 Hz), 4.08 (dd, 1 H, J = 19.7, 1.6 Hz), 3.85−3.80 (m, 1 H), 3.44 (dd, 1 H, J = 13.3, 4.6 Hz), 2.98 (dd, 1 H, J = 13.3, 4.8 Hz), 2.76 (dd, 1 H, J = 19.8, 3.6 Hz), 1.39 (s, 9 H), 1.35−1.29 (m, 12 H); ^{13}C NMR δ 182.9, 182.3, 169.2, 145.9, 145.5, 137.1, 136.9, 135.6, 130.0, 128.2, 127.2, 76.5, 76.4, 58.6, 43.6, 42.1, 38.9, 28.2, 22.8, 22.7; MS (EI) *m/z* (rel intensity) 439 (M$^+$, 61), 397 (35), 340 (50), 256 (90), 91 (100); HRMS (EI) *m/z* calcd for $C_{26}H_{33}NO_5$ 439.2359, found 439.2354.

2-Benzhydryl-4-benzyl-6,7-diisopropoxy-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1j). According to general procedure D, 310.0 mg (0.5644 mmol) of cyclobutenone **2j** provided 207.7 mg (67%) of **1j** as a red oil: IR 2980, 2935, 2252, 1654 cm^{-1}; ^1H NMR δ 7.40−7.19 (m, 10 H), 7.05−6.95 (m, 2 H), 6.85−6.72 (m, 3 H), 4.85, 4.73 (2 hept, 2 H, J = 6.1 Hz), 4.15−4.08 (m, 1 H), 3.90 (dd, 1 H, J = 19.7, 1.7 Hz), 3.52 (dd, 1 H, J = 13.4, 4.3 Hz), 3.08 (dd, 1 H, J = 13.5, 5.0), 2.47 (dd, 1 H, J = 19.7, 3.7 Hz), 1.38 (d, 3 H, J = 6.2 Hz), 1.35 (d, 3 H, J = 6.1 Hz), 1.29 (d, 6 H, J = 6.2 Hz); ^{13}C NMR δ 182.8, 181.9, 169.1, 146.1, 145.4, 137.7, 137.4, 137.3, 136.4, 135.6, 130.4, 129.6, 129.0, 128.9, 128.8, 128.3, 128.1, 127.6, 127.5, 127.0, 126.1, 76.6, 76.5, 59.8, 42.1, 41.2, 38.7, 23.1, 22.9, 22.8, 22.7; MS (EI) *m/z* (intensity) 549 (M$^+$, 75), 437 (35), 167 (100); HRMS (EI) *m/z* calcd for $C_{35}H_{35}NO_5$ 549.2515, found 549.2510.

4-Benzyl-6,7-diisopropoxy-1,4-dihydro-2*H*-isoquinoline-3,5,8-trione (1j′). A solution of quinone **1j** (36.8 mg; 0.0670 mmol) in 2 mL of a mixture of TFA/Et_3SiH/thioanisole/H_2O (92.5:2.5:2.5:2.5) was heated at 50 °C overnight. The reaction mixture was cooled to room temperature. The red, oily residue was purified by chromatography on SiO_2 (hexanes/EtOAc 1:1) to yield 18.9 mg (0.0493 mmol, 70%) of **1j′** as a orange/red oil: IR 3410, 2982, 2253, 1666 cm^{-1}; ^1H NMR δ 7.22−7.10 (m, 3 H), 7.00−6.95 (m, 2 H), 6.01 (br. s, 1 H), 4.80 (hept, 2 H, J = 6.0 Hz), 4.00−3.90 (2 m, 2 H), 3.46 (dd, 1 H, J = 13.4, 4.4 Hz), 3.06 (dd, 1 H, J = 13.4, 5.0 Hz), 2.93 (dd, 1 H, J = 19.5, 3.3 Hz), 1.38−

1.26 (m, 12 H); ^{13}C NMR δ 182.7, 181.9, 170.8, 137.1, 136.4, 135.2, 129.7, 128.3, 127.2, 76.6, 76.3, 40.7, 40.2, 38.3, 22.7, 22.6; MS (EI) *m*/*z* (intensity) 385 (M + H_2, 35), 294 (21), 252 (81), 210 (100); HRMS (EI) *m*/*z* calcd for $C_{22}H_{27}NO_5$ (M + H_2) 385.1889, found 385.1890.

Benzyl(1-methyl-prop-2-ynyl)amine (4b).[13] A solution of $Cu(OTf)_2$ (28.7 mg, 0.0794 mmol) in 6.0 mL of 1,4-dioxane was cooled to 10 °C and treated with 1.2 mL of benzylamine (1.2 g, 11 mmol). After 15 min, a solution of the tosyl alcohol **11** (1.17 g, 5.22 mmol) in 1,4-dioxane (6.0 mL) was slowly added. The reaction mixture was warmed to room temperature, stirred for 3 h, and extracted with 1 N HCl. The aqueous layer was neutralized with NaOH and then extracted with EtOAc. The organic extracts were dried (Na_2SO_4) and concentrated. The resulting greenish oil was purified by column chromatography on SiO_2 (hexanes/EtOAc 8:2) to afford 652.8 mg (4.099 mmol, 79%) of the desired secondary amine **4b** as a yellow liquid: ^{1}H NMR δ 7.41−7.28 (m, 5 H), 4.05 (d, 1 H, J = 12.8 Hz), 3.84 (d, 1 H, J = 12.8 Hz), 3.52 (dq, 1 H, J = 6.8, 2.0 Hz), 2.36 (d, 1 H, J = 1.9 Hz), 1.79 (br s, 1 H), 1.42 (d, 3 H, J = 7.0 Hz).

***tert*-Butylprop-2-ynylamine (4c).**[16] To a cold (0 °C) solution of *tert*-butylamine (13.6 mL, 9.47 g; 129 mmol) in H_2O (7 mL) was added 2.4 mL of propargyl bromide (80% in $PhCH_3$, 22 mmol) over a 40 min period. The reaction mixture was slowly warmed to room temperature and stirred overnight. After addition of 1 g of NaOH pellets, the mixture was extracted with Et_2O, and the organic extract was washed with brine, dried (K_2CO_3), and concentrated to afford 1.118 g (10.05 mmol, 47%) of the desired secondary amine **4c** along with the dipropargylated tertiary amine as a 10:1 ratio of products: ^{1}H NMR δ 3.33 (d, 2 H, J = 2.1 Hz), 2.15 (t, 1 H, J = 2.7 Hz), 1.08 (s, 9 H).

Benzhydrylprop-2-ynylamine (4d).[19] A solution of diphenylmethylamine (3.0 mL; 3.2 g; 17 mmol) in 40 mL of dry ether was treated with 1.35 mL of propargyl bromide (80% in toluene; 12.2 mmol) and a catalytic amount of NaI. This mixture was heated at reflux for 16 h, cooled to room temperature, washed with water, and concentrated, leaving an orange oil. The residue was purified using column chromatography on SiO_2 (hexanes/EtOAc 95:5) to afford 1.14 g (5.14 mmol; 42%) of the desired amine **4d** as a pale yellow solid: ^{1}H NMR δ 7.47−7.21 (m, 10 H), 5.13 (s, 1 H), 3.39 (d, 2 H, J = 2.4 Hz), 2.28 (t, 1 H, J = 2.3 Hz), 1.80 (br s, 1 H).

(3-Methylbut-2-enoyl)prop-2-ynylcarbamic Acid *tert*-Butyl Ester (7g). A solution of amide **6a** (340.2 mg; 2.482 mmol) in dry CH_2Cl_2 (8 mL) was treated under N_2 with Boc_2O (1.044 g; 4.784 mmol), DMAP (91.0 mg; 0.745 mmol), and Et_3N (0.35 mL; 250 mg; 2.5 mmol). The reaction mixture was stirred at room temperature for 6 h, diluted with ether, and washed with aqueous HCl, saturated $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$), and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc 8:2) to yield 571.4 mg (2.408 mmol, 97%) of the desired Boc-amide **7g** as a light yellow oil: IR 3275, 2979, 1732, 1677 cm^{-1}; ^{1}H NMR δ 6.42−6.38 (m, 1 H), 4.43 (d, 2 H, J = 2.6 Hz), 2.13 (t, 1 H, J = 2.6 Hz), 2.08 (s, 3 H), 1.92 (s, 3 H), 1.53 (s, 9 H); ^{13}C NMR δ 167.8, 154.0, 152.5, 119.8, 83.6, 80.0, 70.2, 33.7, 28.2, 27.7, 21.1; MS (EI) *m*/*z* (rel intensity) 181 (M^+, 21), 83 (91), 57 (100); HRMS (EI) *m*/*z* calcd for $C_9H_{11}NO_3$ 181.0739, found 181.0736.

***N*-Benzhydryl-3-phenyl-*N*-prop-2-ynylacrylamide (7h).** To a solution of the amine **4d** (881 mg; 3.98 mmol) and Hünig's base (0.84 mL; 620 mg; 4.8 mmol) in 6 mL of dry CH_2Cl_2 was added a solution of cinnamoyl chloride (942 mg; 5.67 mmol) in dry CH_2Cl_2, and the mixture was stirred overnight. After addition of water, the organic fraction was washed with brine, dried ($MgSO_4$), and concentrated leaving a dark oil. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc 8:2) to afford 1.397 g (100%) of the desired amide **7h** as a yellow oil: IR 3303, 3029, 2245, 1651, 1608 cm^{-1}; ^{1}H NMR δ 7.82−7.27 (m, 18 H), 4.15 (d, 2 H, J = 2.1 Hz), 2.14 (br. s, 1 H); ^{13}C NMR δ 167.1, 144.0, 138.9, 135.2, 129.9, 129.0, 128.9, 128.7, 128.4, 128.1, 127.8, 127.5, 118.1, 79.8, 72.6, 61.9, 35.0; MS (EI) *m*/*z* (rel intensity) 351 (M^+, 65), 312 (90), 182 (86), 131 (100); HRMS (EI) *m*/*z* calcd for $C_{25}H_{21}NO$: 351.1623, found 351.1622.

(4,5-Diisopropoxy-3,6-dioxocyclohex-1,4-dienylmethyl)-(3-methylbut-2-enoyl)carbamic Acid *tert*-Butyl Ester (12). A solution of cyclobutenone **2i** (339.3 mg; 0.7796 mmol) in freshly degassed xylenes (10 mL) was added dropwise over a 20 min period to 40 mL of refluxing, degassed xylenes. After an additional 30 min, the reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting red oil was purified by chromatography on SiO_2 (hexanes/EtOAc 8:2) to afford 188.4 mg (0.4329 mmol, 56%) of the monocyclized product **12** as a red oil: IR 3020, 2981, 1730, 1657, 1597 cm^{-1}; ^{1}H NMR δ 6.47−6.45 (m, 1 H), 6.15 (t, 1 H, J = 1.8 Hz), 4.84, 4.75 (2 hept, 2 H, J = 6.1 Hz), 4.68 (d, 2 H, J = 2.0 Hz), 2.07 (d, 3 H, J = 1.1 Hz), 1.94 (2, 3 H, J = 0.9 Hz), 1.44 (s, 9 H), 1.29 (d, 6 H, J = 6.2 Hz), 1.28 (d, 6 H, J = 6.3 Hz); ^{13}C NMR δ 184.5, 184.1, 168.1, 154.7, 152.4, 145.5, 143.4, 128.3, 119.4, 83.7, 76.2, 76.1, 42.2, 28.0, 27.6, 22.7, 21.0; MS (EI) *m*/*z* (rel intensity) 435 (M^+, 7), 295 (17), 83 (100); HRMS (EI) *m*/*z* calcd for $C_{23}H_{33}NO_7$ 435.2257, found 435.2240.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **6a**−**d**, **7a**−**h**, **2a**−**d**,**f**,**h**−**j**, **1a**−**f**,**h**,**j**,**j′**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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