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Cu(I)-Catalyzed Intramolecular Cyclization of Alkynoic Acids in Aqueous Media: A "Click Side Reaction"

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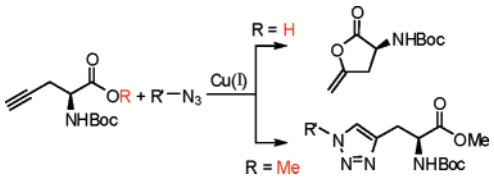
Received September 15, 2007



Alkynoic acids, in particular, 4-pentynoic acid derivatives, undergo intramolecular cyclizations to enol lactones under reaction conditions typically applied for the Cu(I)-catalyzed cycloaddition of terminal alkynes and azides (click chemistry). Starting from appropriate alkynoic acid derivatives, either enol lactones or 1,2,3-triazole click products can be obtained selectively by Cu(I) catalysis in aqueous media.

Propargyl glycines are versatile synthetic building blocks[1] which have recently also found application as multifunctional substrates for "click chemistry", the copper(I)-catalyzed [3 + 2] cycloaddition of terminal alkynes and azides.[2] For example, propargyl glycine (HPraOH, **1f**) and derivatives thereof have been employed for the synthesis of triazole-linked amino acid and peptide glycosides[3] and cyclic peptides.[4] We have reported the use of propargyl glycines as click substrates for the assembly of novel triazole-based metal chelating systems while simultaneously attaching them to (bio)molecules for imaging applications.[5] In the course of our investigations, we observed that click reactions of some alkynoic acid derivatives with azides provided the desired triazole products in considerably lower yields than typically achieved by this chemistry. For instance, reaction of *N*(α)-Boc-protected L-propargyl glycine (BocPraOH, **1a**), 2-acetoxy-4-pentynoic acid (**1b**),[6] and (4)-pentynoic acid (**1c**) with benzyl azide **2** gave triazoles **3a**−**c** in less than 50% yield (Scheme 1). On the other hand, related alkyne substrates HPraOMe **1d**, BocPraOMe **1e**, HPraOH **1f**, and 2-acetoxy-4-pentynoic acid methyl ester (**1g**) quantitatively yielded the corresponding products **3d**−**g**.[7] Examination of the product mixture obtained from the click reactions of alkynes **1a**−**c** revealed the formation of unexpected side products, enol lactones **4** and/or their hydrolysis products **5**, respectively.[8]

These results spurred our interest for two reasons. (1) As illustrated by numerous accounts on click chemistry, the Cu(I)-catalyzed reaction of azides and terminal alkynes generally provides 1,4-disubstituted 1,2,3-triazoles selectively and in high yields. Examples of the formation of click side products are scarce,[9] and to the best of our knowledge, structural limitations of acetylenic substrates have not yet been reported in this context. Because propargyl glycines are currently the only commercial alkynyl-functionalized amino acids available, evaluation of their utility as click substrates is of particular importance. (2) The transition-metal-catalyzed intramolecular cyclization of alkynoic acids provides an efficient entry to enol lactones,[10] a class of densely functionalized small heterocycles useful as synthetic precursors and intermediates.[11] However, reported syntheses usually require water-free conditions and employ precious metal catalysts (e.g., based on Pd or Rh), organic solvents, and elevated temperatures. A protocol that provides enol lactones from alkynoic acids in aqueous media at room temperature employing inexpensive catalysts would represent an economically and ecologically attractive alternative.

We thus set out to study the cyclization of alkynoic acids under aqueous click chemistry conditions, in general, and of propargyl glycine derivatives, in particular. It soon became apparent that the azide substrate employed in the initial click reaction (Scheme 1) was not involved in the cyclization of BocPraOH **1a**. The same ratio of enol lactone **4a** and hydrolysis product **5a** was obtained in combined yields of 80% in the absence of the azide. On the other hand, addition of catalytic amounts of copper(I) (CuCl, CuBr, or 1:2 mixtures of $Cu(OAc)_2$/sodium ascorbate) proved to be essential. No reaction was observed in the absence of Cu(I) or when Cu(II) salts ($CuCl_2$, $Cu(OAc)_2$, $CuSO_4$) were employed. Addition of base (e.g., K_2CO_3), extended reaction time, or elevated temperature resulted in hydrolysis of enol lactone **4a**, and *N*(α)-Boc-protected 4-oxo norvaline **5a** was isolated as the major product.[12] Substitution of the cosolvent ^{t}BuOH by other alcohols (e.g., MeOH) resulted in the quantitative formation of the corresponding esters of

(1) See for example: (a) Wolf, L. B.; Tjen, K. C. M. F.; ten Brink, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 70−83. (b) van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791−1795.

(2) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064. For a recent review of click chemistry, see: (c) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249−1262.

(3) (a) Dondoni, A.; Giovannini, P. P.; Massi, A. *Org. Lett.* **2004**, *6*, 2929−2932. (b) Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. B. R.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123−3126.

(4) Punna, S.; Kuzelka, J.; Wang, Q.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2215−2220.

(5) Mindt, T. L.; Struthers, H.; Brans, L.; Anguelov, T.; Schweinsberg, C.; Maes, V.; Tourwe, D.; Schibli, R. *J. Am. Chem. Soc.* **2006**, *128*, 15096−15097.

(6) Prepared from racemic HPraOH *rac*-**1f** by a reported procedure (Cahiez, G.; Metais, E. *Tetrahedron Lett.* **1995**, *36*, 6449−6452).

(7) Click reactions of BocPraOMe **1e** have been reported (ref 3b). For triazoles **3a** and **3f** as well as for additional examples of click reactions with propargyl glycines, see ref 5.

(8) For compound **5a**, see: Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1993**, *34*, 4485−4488.

(9) The formation of bistriazole side products has been reported for Cu(I)-catalyzed Huisgen cycloadditions (Angell, Y.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3649−3651).

(10) Negishi, E.-I.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707−6738.

(11) See for example: *Progress in Heterocyclic Chemistry*; Gribble G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, UK, 2000.

10.1021/jo702030e CCC: $37.00
Published on Web 11/29/2007

SCHEME 1. Click Reaction of Some Alkynoic Acids Yields Product Mixtures

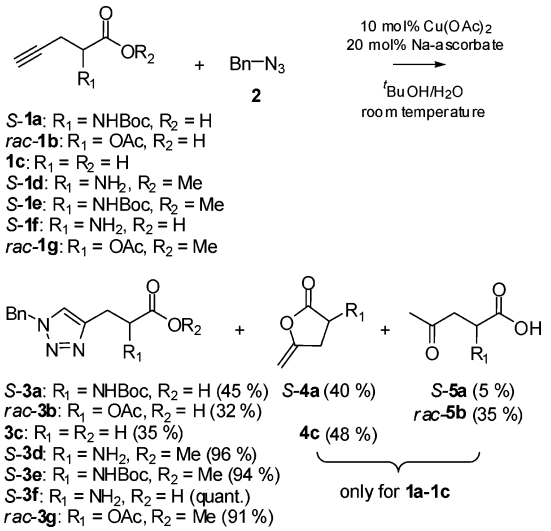
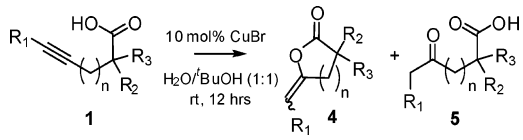


TABLE 1. Cu(I)-Catalyzed Cyclization of Alkynoic Acids



entry	alkyne **1**	*n*	R_1	R_2	R_3	lactone[a] **4**	ketone[a] **5**
1	(*S*)-**1a**	1	H	H	NHBoc	(*S*)-**4a**: 91%	–
2	(*S*)-**1a**	1	H	H	NHBoc	(*S*)-**4a**: 88%[b]	–
3	*rac*-**1b**	1	H	H	OAc	–	*rac*-**5b**: 68%
4	**1c**	1	H	H	H	**4c**: 90%	–
5	(*S*)-**1f**	1	H	H	NH_2	–	–
6	(*S*)-**1h**	1	H	H	NHFmoc	(*S*)-**4h**: 82%	–
7	(*S*)-**1i**	1	H	H	NHAdoc[18]	(*S*)-**4i**: 84%	–
8	**1j**	1	H	propargyl	NHBoc	*rac*-**4j**: 85%	–
9	*rac*-**1k**	1	CH_3	H	NHBoc	*rac*-**4k**: 51%	–
10	(*S*)-**1l**	1	H	H	NHTs	(*S*)-**4l**: 80%[b,c]	(*S*)-**5l**: 75%
11	(*S*)-**1m**	1	H	H	NHAc	–	(*S*)-**5m**: 65%
12	(*S*)-**1n**	1	H	H	NH*n*hexyl	–	–
13	**1o**	2	H	H	H	**4o**: 78%[b,c]	–
14	*rac*-**1p**	2	H	H	NHBoc	*rac*-**4p**: 65%[b,c]	–
15	**1q**	3	H	H	H	–	–

[a] Yields of isolated and purified products. [b] Reaction performed in CH_3CN. [c] Reaction in the presence of 10 mol % of K_2CO_3.

acyclic product **5a**.[13] Of all aqueous procedures tested,[14] best results were achieved by stirring a mixture of BocPraOH **1a** and 5−10 mol % of CuBr in water/*t*BuOH (1:1) at room temperature for 12 h (Table 1, entry 1). These conditions precluded the formation of side products[15] and provided the desired enol lactone **4a**[16] in yields comparable or improved to those reported for related metal-catalyzed cyclizations of alkynoic acids.[17]

To investigate the scope of the aqueous preparation of enol lactones by the Cu(I)-catalyzed cyclization reaction, we subjected a variety of alkyne substrates to the optimized reaction conditions (Table 1). 4-Pentynoic acid (**1c**), FmocPraOH **1h**, AdocPraOH **1i**,[18] and C(α)-disubstituted BocPraOH derivative **1j**[19] converted cleanly to the corresponding enol lactones **4c**[20] and **4h**−**j** (entries 4 and 6−8). Substrate **1k** with an internal alkyne yielded cyclization product **4k** as a mixture of *E*/*Z* isomers (1.5:1) in satisfying yields (entry 9).[21] Enol lactones derived from TsPraOH **1l**,[22] AcPraOH **1m**, and 2-acetoxy-4-pentynoic acid (**1b**) were not stable under aqueous conditions, and the corresponding hydrolysis products **5l**,**m** and **5b**, respectively, were obtained (entries 3, 10, and 11). In the case of TsPraOH **1l**, changing to organic solvents (CH_3CN) and addition of base (10 mol % of K_2CO_3) provided the cyclization product **4l** in good yields.[23] No reaction was observed with HPraOH **1f** or *n*hexyl-PraOH **1n** (entries 5 and 12), and employing alkynoic acid ester (HPraOMe **1d** and BocPraOMe **1e**) or acetylenic alcohol substrates (e.g., 4-pentynol) did not provide detectable amounts of cyclization products (data not shown). Attempted cyclization of homologue alkynoic acid substrates **1o** and **1p**[24] in water did not yield six-membered ring enol lactones. Again, cyclization of these substrates to enol lactones **4o**[25] and **4p** could be achieved in CH_3CN in the presence of K_2CO_3 (entries 13 and 14). No reaction was observed with 6-heptynoic acid (**1q**) neither in aqueous media nor organic solvents (entry 15).

As demonstrated by the experimental data shown above, the Cu(I)-catalyzed cyclization protocol can be applied to a variety of alkynoic acid substrates providing enol lactones in good yields. However, the use of aqueous reaction conditions was found to be limited to the synthesis of five-membered ring enol lactones. When propargyl glycine substrates are employed, the choice of an appropriate amine protective group is key. While *N*(α)-carbamate-functionalized propargyl glycines reliably afforded cyclization products in high yields, employment of

(12) No reaction was observed when aqueous solutions of HPraOMe **1d** or BocPraOMe **1e** were treated with up to 1 equiv of CuBr for 2 days. Thus, a direct metal-catalyzed hydration of alkyne substrates can be ruled out as the origin of the acyclic products obtained.

(13) Purification of enol lactones by flash chromatography on silica gel using MeOH as eluent also resulted in rapid methanolysis of the cyclic products.

(14) The Cu(I)-catalyzed cyclization of alkynoic acids also proceeds in high yields in organic solvents (see Table 1, entry 2).

(15) Pd-catalyzed reaction of propargyl glycines can yield cyclic amines (ref 1a), and employment of Ru catalysts can lead to the formation of endocyclic enol lactones as the result of anti-Markovnikov addition of the carboxylic acid to the terminal alkyne (Jiménez-Tenorio, M.; Puerta, M. C.; Valegra, P.; Moreno-Dorado, F. J.; Guerra, F. M.; Massanet, G. M. *Chem. Commun.* **2001**, 2324−2325) or products derived from intermolecular condensation reactions (Melis, K.; Verpoort, F. *J. Mol. Catal. A: Chem.* **2003**, *194*, 39−47). None of these products have been observed using Cu(I) catalysis.

(16) The optical rotation of enol lactone (*S*)-**4a** did not correlate well with the value reported for the enantiomer (*R*)-**4a** (ref 1a). However, the one obtained for methanolysis product methyl ester **6** corresponded well to literature values (Estiarte, M. A.; Diez, A.; Rubiralta, M.; Jackson, R. F. W. *Tetrahedron* **2001**, *57*, 157−161). The optical rotation of (*S*)-**4l** was in good agreement with reported values of the enantiomer (*R*)-**4l** (ref 1a). For details, see Experimental Section and Supporting Information.

(17) For example, the *R*-enantiomers of enol lactone **4a** and **4l** have been prepared by Pd-catalyzed cyclization in 63−66% yield (ref 1a).

(18) Adoc = 1-adamantyloxy carbamate. Compound (*S*)-**1i** was prepared according to literature procedure (Mueller, M. M.; Sperl, S.; Stürzebecher, J.; Bode, W.; Moroder, L. *Biol. Chem.* **2002**, *383*, 1185−1191).

(19) The synthesis of ethyl ester of compound **1j** is described in: Kotha, S.; Brahmachary, E. *Bioorg. Med. Chem.* **2002**, *10*, 2291−2295.

(20) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 560−564.

(21) Structural assignment of the two inseparable compounds (*E*/*Z*)-**4k** was confirmed by 2D NMR spectroscopy (NOESY).

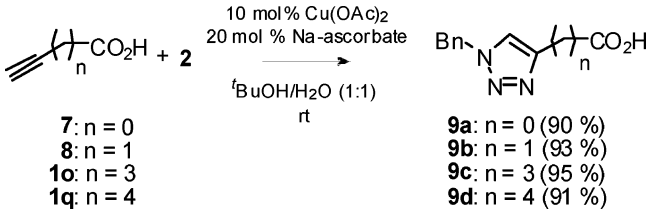
(22) Prepared according to the procedure described for synthesis of enantiomer *R*-**1l** (ref 1a).

(23) These conditions have been described for the AuCl-catalyzed cyclization of alkynoic acids (Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273−6276). Alkynoic acids **1b** and **1m** are not soluble in CH_3CN.

(24) van Hest, J. C. M.; Kiick, K. L.; Tirrell, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1282−1288.

(25) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459−5466.

SCHEME 2. Click Reaction of Alkynoic Acids with Benzyl Azide in Water



protective groups of more pronounced electron-withdrawing character yielded enol lactones which were too labile for isolation from aqueous media. On the other hand, the presence of unprotected or alkylated amines suppressed the cyclization reaction of alkynoic acid substrates. This effect may be due to unproductive complexation of the copper via the amino group instead of the alkyne or carboxylate, a proposed mechanism for the metal-catalyzed cyclizations of alkynoic acids to enol lactones.[1a] Indeed, addition of amines (5−20 mol % of ethylenediamine or morpholine) to the reaction mixture completely inhibited the intramolecular cyclization of alkynoic acids (e.g., BocPraOH **1a** and 4-pentynoic acid **1c**).[26] These findings provided an explanation to the observation that HPraOH **1f** is a good substrate for click chemistry despite the presence of an unprotected carboxylic acid functionality (Scheme 1).[27]

To demonstrate the general utility of alkynoic acids for click chemistry applications, we investigated the reaction of benzyl azide (**2**) with alkynoic acids of different chain length (Scheme 2). Unlike 4-pentynoic acid and its derivatives ($n = 2$, **1a**−**c**; Scheme 1), alkyne substrates **7**−**8**, **1o**, and **1q** yielded the corresponding 1,2,3-triazole products **9a**−**d** in high yields by Cu(I) catalysis in water.[28]

In conclusion, the presented work reveals structural limitations of acetylenic substrates for click chemistry applications. Some alkynoic acids, in particular, 4-pentynoic acids, are unsuitable click substrates because of competing intramolecular cyclizations to enol lactones that occur under reaction conditions typically applied for the Cu(I)-catalyzed Huisgen reaction. In general, these limitations can be circumvented by using the corresponding esters of alkynoic acid substrates; however, this requires additional protection/deprotection steps. Of the 4-pentynoic acids examined, only HPraOH **1f** was an efficient click substrate presumably because the amine present prevents the intramolecular cyclization leading to enol lactones. In addition, our investigations of the Cu(I)-promoted cyclization of alkynoic acids have provided a simple protocol for the synthesis of five-membered ring enol lactones under mild aqueous reaction conditions employing inexpensive, off-the-shelf Cu(I) salts as catalysts.

(26) Click reaction of BocPraOH **1a** with azide **2** in the presence of amines (e.g., 20 mol% of morpholine) yielded again mixtures of triazole **3a** and enol lactone **4a**, presumably because the triazole formed acts as a chelator yielding a Cu(I) species capable of catalyzing the intramolecular enolization. In fact, addition of the Cu(I)-stabilizing chelator trisbenzyltriazole amine TBTA (1 equiv with respect to Cu(I) catalyst; ref 27a) accelerated the cyclization of BocPraOH **1a**, and enol lactone **4a** was formed in 6 h at rt as the sole product despite the presence of azide **2**. Similar observations were made with 4-pentynoic acid (**1c**).

(27) Click reaction of azides and terminal alkynes proceeds efficiently with Cu(I) catalysts that are complexed by nitrogen ligands. See for example: (a) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. *Org. Lett.* **2004**, *6*, 2853−2855. (b) Girard, C.; Önen, E.; Aufort, M.; Beauvière, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689−1692.

(28) Click reactions of propiolic acid **7** (Xie; J.; Seto, C. T. *Bioorg Med. Chem.* **2007**, *15*, 458−473) and 5-hexynoic acid **1o** (White, M., A.; Johnson, J. J.; Koberstein, J. T.; Turro, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 11356−11357) have been reported.

Experimental Section

General Procedure for the Cu(I)-Catalyzed Cyclization of Alkynoic Acids in Aqueous Media. Alkynoic acid substrates (0.2 mmol) were dissolved in ^{t}BuOH/H_2O (1:1, 4 mL), and CuBr (5−10 mol %) was added. The resulting mixture was stirred at rt for 12 h, diluted with water, and extracted with ethyl acetate. The organic layers were washed twice with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude products were purified by filtration through a short path of silica gel with dichloromethane or ethyl acetate/acetic acid (0−1%)[13] to yield enol lactones or their hydrolysis products, respectively. The same procedure was applied for the cyclizations of alkynoic acids in CH_3-CN but in the presence of 10 mol % of K_2CO_3.

General Procedure for the Click Reaction of Alkynoic Acids with Azides. Alkynoic acid derivatives (0.2 mmol) were dissolved in ^{t}BuOH/H_2O (1:1, 4.0 mL), and benzyl azide (**2**, 0.2 mmol), Cu(OAc)$_2$ (10 mol %), and sodium ascorbate (20 mol %) were added. The resulting mixture was stirred at rt over night, saturated with NaCl, and extracted with ethyl acetate. The organic layers were washed once with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude products were purified by flash chromatography on silica gel with CH_2Cl_2/MeOH to yield the corresponding 1,2,3-triazole products.

Triazole 3b: Colorless oil (yield 32%); IR (neat) ν 3148, 2944, 1743, 1228, 1074, 723 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.83 (s, 1H), 7.39−7.27 (m, 5H), 5.58 (s, 2H), 5.25 (dd, 1H, J = 7.5 and 4.6 Hz), 3.27 (dd, 1H, J = 15.4 and 4.8 Hz), 3.23 (dd, 1H, J = 15.4 and 8.0 Hz), 2.03 (s, 3H) ppm; ^{13}C NMR (MeOH-d_4) δ 172.5, 172.0, 144.2, 137.0, 130.1, 129.7, 129.1, 124.9, 72.7, 55.0, 28.7, 20.6 ppm; HR-MS $[M - H + 2Na]^+$ = 334.0769 (calcd for $C_{14}H_{14}N_3O_4Na_2$, 334.0780).

Triazole 3c: White solid (35%); mp 129−131 °C; IR (neat) ν 3371, 2927, 1715, 1339, 1207, 1067, 726 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.16 (br s, 1H), 7.93 (s, 1H), 7.40−7.27 (m, 5H), 5.55 (s, 2H), 2.88−2.79 (m, 2H), 2.65−2.56 (m, 2H) ppm; ^{13}C NMR (DMSO-d_6) δ 173.7, 136.2, 128.7, 128.0, 127.8, 122.5, 52.6, 33.1, 20.8 ppm; HR-MS $[M + Na]^+$ = 254.0899 (calcd for $C_{12}H_{13}N_3O_2$-Na, 254.0905).

Triazole 3d: White solid (96%); mp 79−81 °C; IR (neat) ν 3377, 2948, 1731, 1438, 1219, 1201, 1173, 1051, 721 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.76 (s, 1H), 7.39−7.28 (m, 5H), 5.56 (s, 2H), 3.76 (t, 1H, J = 6.2 Hz), 3.63 (s, 3H), 3.09 (dd, 1H, J = 14.5 and 5.7 Hz), 3.02 (dd, 1H, J = 14.5 and 7.0 Hz) ppm; ^{13}C NMR (MeOH-d_4) δ 176.0, 145.1, 137.1, 130.1, 129.7, 129.2, 124.7, 55.3, 55.0, 52.6, 50.0, 31.6 ppm; HR-MS $[M + Na]^+$ = 261.1347 (calcd for $C_{13}H_{17}N_4O_2$, 261.1352).

Triazole 3e: White solid (94%); mp 89−92 °C; IR (neat) ν 2912, 1706, 1413, 1355, 1294, 1227, 1058, 725 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.87 (s, 1H), 7.41−7.22 (m, 5H), 5.57 (s, 2H), 4.28−4.22 (m, 1H), 3.58 (s, 3H), 3.05 (dd, 1H, J = 14.8 and 6.6 Hz), 2.95 (dd, 1H, J = 14.8 and 9.8 Hz), 2.51 (br s, 1H), 1.33 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 172.2, 155.3, 143.1, 136.2, 128.7, 128.0, 127.7, 123.1, 78.3, 53.5, 52.6, 51.8, 28.1, 27.2 ppm; HR-MS $[M + Na]^+$ = 363.1686 (calcd for $C_{18}H_{24}N_4O_4Na$, 383.1695).

Triazole 3g: Colorless oil (yield 91%); IR (neat) ν 2950, 1741, 1219, 1044, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33−7.25 (m, 4H), 7.20−7.15 (m, 2H), 5.46 (dd, 1H, J = 14.8 Hz), 5.42 (dd, 1H, J = 14.8 Hz), 5.24 (dd, 1H, J = 7.4 and 5.0 Hz), 3.62 (s, 3H), 3.27−3.15 (m, 2H), 1.98 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.1, 169.8, 142.7, 134.9, 129.2, 128.8, 128.0, 122.3, 77.2, 71.3, 54.1, 52.5, 28.0, 20.6 ppm; HR-MS $[M + Na]^+$ 326.1112 (calcd for $C_{15}H_{17}N_3O_4$-Na, 326.1117).

Enol Lactone (*S*)-4a: White solid (yield 91%); mp 113−114 °C; IR (neat) ν 3359, 2980, 1813, 1692, 1514, 1252, 1142, 980 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.56 (d, 1H, J = 8.0 Hz), 4.66−4.63 (m, 1H), 4.47 (q, 1H, J = 9.2 Hz), 4.36−4.32 (m, 1H), 3.09 (dd, 1H, J = 16.5 and 9.8 Hz), 2.76 (ddt, 1H, J = 16.5, 9.8, and 2.4 Hz), 1.38 (s, 9H) ppm; ^{13}C NMR (DMSO-d_6) δ 173.7, 155.0, 153.4, 88.2, 78.9, 49.2, 31.3, 28.1 ppm; HR-MS [M + Na]$^+$ = 236.0894 (calcd for $C_{10}H_{15}NO_4Na$, 236.0899); $[\alpha]_D = -80.5$ (c = 1.0 in CH_2Cl_2) (lit.[1a] for (*R*)-**4a**: $[\alpha]_D = +64.1$ (c = 1.0 in CH_2Cl_2)).

Enol Lactone (*S*)-4h: White solid (yield 82%); IR (neat) ν 3330, 3045, 1818, 1681, 1533, 1443, 1264, 1150, 1007, 734 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.05 (d, 1H, J = 7.2 Hz), 7.90 (d, 2H, J = 7.2 Hz), 7.68 (d, 2H, J = 7.2 Hz), 7.42 (t, 2H, J = 7.2 Hz), 7.33 (t, 2H, J = 7.2 Hz), 4.68−4.65 (m, 1H), 4.55 (q, 1H, J = 9.6 Hz), 4.41−4.33 (m, 3H), 4.24 (t, 1H, J = 6.7 Hz), 3.12 (dd, 1H, J = 16.0 and 9.6 Hz), 2.77 (ddt, 1H, J = 16.0, 9.4 and 2.6 Hz) ppm; ^{13}C NMR (DMSO-d_6) δ 173.4, 155.6, 153.3, 143.6, 140.7, 127.6, 127.1, 125.0, 120.1, 88.4, 65.8, 49.4, 46.5, 31.2 ppm; HR-MS [M + Na]$^+$ = 358.1049 (calcd for $C_{20}H_{17}NO_4Na$, 358.1055).

Enol Lactone (*S*)-4i: Colorless oil (yield 84%); IR (neat) ν 3353, 2908, 2855, 1813, 1685, 1247, 1133, 1058, 976 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.61 (d, 1H, J = 9.7 Hz), 4.66−4.63 (m, 1H), 4.44 (q, 1H, J = 8.9 Hz), 4.36−4.33 (m, 1H), 3.09 (dd, 1H, J = 16.1 and 9.2 Hz), 2.76 (ddt, 1H, J = 16.1, 8.9, and 2.4 Hz), 2.14−2.08 (m, 3H), 2.05−1.97 (m, 6H), 1.63−1.57 (m, 6H) ppm; ^{13}C NMR (DMSO-d_6) δ 174.1, 154.7, 153.7, 88.5, 78.8, 49.2, 41.2, 35.6, 30.2 ppm; HR-MS [M + Na]$^+$ = 314.1364 (calcd for $C_{16}H_{21}NO_4Na$, 314.1368).

Enol Lactone *rac*-4j: Colorless oil (yield 85%); IR (neat) ν 3295. 2977, 1806, 1680, 1498, 1247, 1144, 1051, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.21 (br s, 1H), 4.79−4.77 (m, 1H), 4.36−4.34 (m, 1H), 3.31 (br d, 1H, J = 16.4 Hz), 3.07 (d, 1H, J = 16.4 Hz), 2.65 (dd, 1H, J = 16.4 and 2.4 Hz), 2.59 (dd, 1H, J = 16.4 and 2.5 Hz), 2.15 (t, 1H, J = 2.5 Hz), 1.41 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 174.4, 154.6, 153.1, 87.7, 79.5, 77.2, 74.8, 58.6, 36.0, 28.0, 26.3 ppm; HR-MS [M + Na]$^+$ = 274.1048 (calcd for $C_{13}H_{17}NO_4Na$, 274.1055).

Enol Lactone *rac*-4k: Colorless oil (yield 51%; E/Z = 1.5:1); ^{1}H NMR (DMSO-d_6) δ 7.68 (d, 0.6H, J = 7.8 Hz, *E*-isomer), 7.25 (d, 0.4H, J = 8.5 Hz, *Z*-isomer), 5.11−5.07 (m, 1H), 4.53−4.44 (m, 0.6H, *E*-isomer), 4.29−4.19 (m, 0.4H, *Z*-isomer), 3.13 (ddd, 0.6H, J = 16.6, 10.8 and 1.3 Hz, *E*-isomer), 2.67−2.60 (m, 0.6H, *E*-isomer), 2.37−2.29 (m, 0.8H, *Z*-isomer), 2.23 (br s, 1.8H, *E*-isomer), 1.85−1.83 (m, 1.2H, *Z*-isomer), 1.40 (s, 3.6H, *Z*-isomer), 1.38 (s, 5.4H, *E*-isomer) ppm; HR-MS [M + Na]$^+$ = 250.1045 (calcd for $C_{11}H_{17}NO_4Na$, 250.1055).

Enol Lactone (*S*)-4l. Colorless oil (yield 80%); IR (neat) ν 3284, 2977, 2905, 1806, 1681, 1344, 1155, 1090, 1040, 814, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2H, J = 7.7 Hz), 7.33 (d, 2H, J = 7.7 Hz), 5.22 (d, 1H, J = 5.1 Hz), 4.80 (dt, 1H, J = 3.0 and 0.9 Hz), 4.44 (dt, 1H, J = 3.0 and 1 Hz), 4.08 (ddd, 1H, J = 10.3, 9.1, and 4.1 Hz), 3.25 (ddt, 1H, J = 16.0, 9.1, and 0.9 Hz), 2.90−2.83 (m, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 172.1, 151.9, 144.8, 135.8, 130.3, 127.6, 91.8, 52.3, 34.9, 21.8 ppm; HR-MS [M + Na]$^+$ = 290.0456 (calcd for $C_{12}H_{13}NO_4SNa$, 290.0463); $[\alpha]_D$= +29.5 (c = 1.0 in CH_2Cl_2) (lit.[1a] for (*R*)-**4l**: $[\alpha]_D$= −27.2 (c = 1.0 in CH_2Cl_2)).

Enol Lactone *rac*-4p: Pale yellow oil (yield 65%); IR (neat) ν 3359, 2972, 2927, 1767, 1709, 1670, 1513, 1366, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.21 (br s, 1H), 4.73−4.72 (m, 1H, J = 1.0 Hz), 4.39−4.38 (m, 1H, J = 1.4 Hz), 4.32−4.22 (m, 1H), 2.73−2.57 (m, 2H), 2.49−2.39 (m, 1H), 1.72−1.59 (m, 1H, J = 9.0 Hz), 1.43 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 185.6, 155.2, 153.7, 96.6, 78.7, 52.5, 50.7, 28.1, 25.7, 25.2 ppm; HR-MS [M + Na]$^+$ = 250.1047 (calcd for $C_{11}H_{17}NO_4Na$, 250.1055).

Acknowledgment. We thank Dr. Bernhard Pfeiffer and Tatjana Hofmann (ETH Zurich) for NMR spectroscopic measurements.

Supporting Information Available: General methods, synthesis and characterization of alkynoic acid derivatives, acyclic hydrolysis products and triazoles **9a**−**d**, and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702030E