A Novel Route to 5-Substituted 3-Isoxazolols. Cyclization of *N,O*-DiBoc *β*-Keto Hydroxamic Acids Synthesized via Acyl Meldrum's Acids

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3-Isoxazolols are most often synthesized from a *β*-keto ester and hydroxylamine. This cyclization typically gives rise to a major byproduct, the corresponding 5-isoxazolone. We have found that *N,O*-diBoc-protected *β*-keto hydroxamic acids can be synthesized and cyclized to 5-substituted 3-isoxazolols without formation of any byproduct. We present a novel and versatile three-step procedure in which carboxylic acid derivatives are converted into acyl Meldrum's acids which, upon aminolysis with *N,O*-bis(*tert*-butoxycarbonyl)hydroxylamine, lead to the *N,O*-diBoc-protected *β*-keto hydroxamic acids. These hydroxamic acid analogues were then, upon treatment with hydrochloric acid, cyclized to the corresponding 5-substituted 3-isoxazolols.

Introduction

The 3-isoxazolol moiety is a constituent of a number of biologically active compounds (Figure 1). Muscimol **(1)** and ibotenic acid **(2)** are compounds isolated from the mushroom *Amanita muscaria*.[1] Muscimol **(1)**, which is a nonselective $GABA_A$ receptor agonist,[2] has been used as a lead for the synthesis of THIP **(3)** a specific[3] and clinically active[4] $GABA_A$ agonist and THPO **(4)** a specific inhibitor of GABA uptake.[5] Whereas ibotenic acid **(2)** interacts nonselectively with all types of (*S*)-glutamate receptors,[6] the analogues (*S*)-AMPA **(5)**[7] and (*S*)-homo-AMPA **(6)**[8] are specific agonists at subtypes of ionotropic and metabotropic (*S*)-glutamate receptors, respectively. Other examples of biologically active 3-isoxazolols are 5-methyl-3-isoxazolol (Tachigaren, **7**) and the phosphorothioate Karphos **(8),** which are used as a soil fungicide and a broad-spectrum insecticide, respectively.[9]

Incorporation of the 3-isoxazolol moiety into compounds with potential biological activity normally requires multistep and low-yield reaction sequences, and there is a need for efficient and versatile synthetic methods. The most common route to 3-isoxazolols has been cyclization of *β*-keto esters with hydroxylamine (Scheme 1). This method does, however, in addition to 3-isoxazolol **9**, lead to the undesired 5-isoxazolone **10**, due to the several possible ways of attack by hydroxylamine on the *β*-keto ester.[10] The amount of this byproduct is most often substantial leading to low yields of the desired isoxazolol.

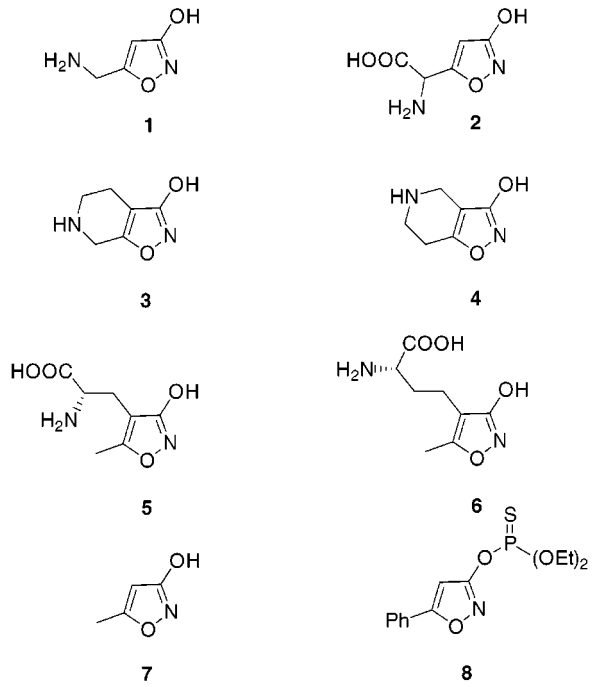

Figure 1.

The effects of temperature and pH on the relative amounts of cyclization products have been studied,[9−11] but attempts to optimize these parameters in order to maximize the yield of the 3-isoxazolol and, thus, eliminate the formation of 5-isoxazolone **10** have not been successful. Another solution could be a temporary protection of the *β*-carbonyl as an acetal. This has in fact been

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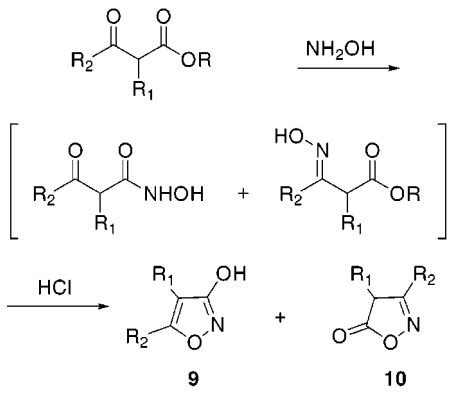
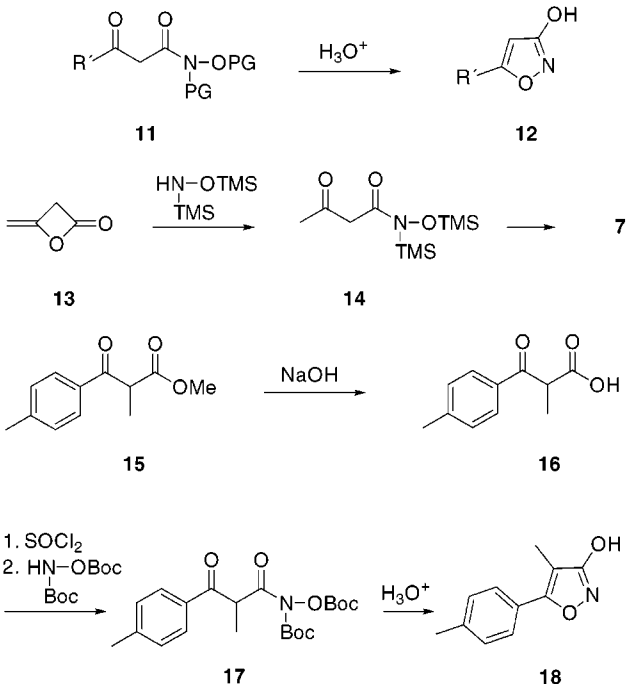
Scheme 1



Scheme 2



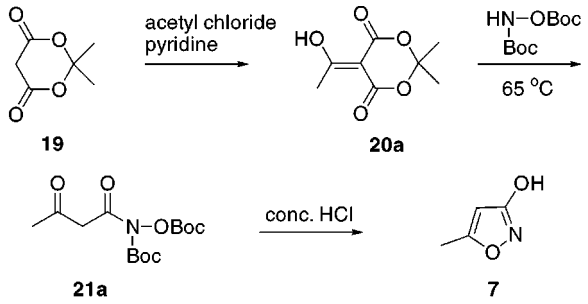
used in the synthesis of 5-methyl-3-isoxazolol **(7)**,[12] but the method is unfortunately not generally feasible since it seems to be highly dependent on the nature of the α- and *β*-substituents of the *β*-keto ester.[13]

These synthetic problems prompted us to search for an efficient synthetic route to 5-substituted 3-isoxazolols. This paper presents a novel and generally applicable method for introducing the 3-isoxazolol moiety starting from a carboxylic acid derivative without formation of any detectable 5-isoxazolone byproduct.

Results and Discussion

The basis for the approach presented here was our prediction that a *β*-keto hydroxamic acid of the general type **11**, with acid-labile protecting groups (PG's), upon treatment with acid would lead exclusively to the formation of the desired 5-substituted 3-isoxazolol **12** (Scheme 2). To our knowledge, only one related example has been described, in which diketene **(13)** was reacted with *N*,*O*-bis(trimethylsilyl)hydroxylamine to give compound **14**, which was cyclized to 5-methyl-3-isoxazolol **(7)** upon treatment with methanolic HCl.[14] This method is, however, not generally useful since the lack of analogues of diketene **(13)** limits the method to the synthesis of 3-isoxazolol **7**.

Scheme 3



Our first attempt to synthesize a compound of the general structure **11** was based on the conversion of *β*-keto ester **15** into the corresponding *β*-keto carboxylic acid **16**. Formation of the acid chloride under standard conditions and in situ reaction with *N*,*O*-bis(*tert*-butoxycarbonyl)hydroxylamine[15] (*N*,*O*-diBoc hydroxylamine) yielded *β*-keto hydroxamic acid **17**. Treatment of **17** with concentrated hydrochloric acid gave the expected 3-isoxazolol derivative **18** in 82% yield and as the only product.

Our experiments aiming at generalizing this method starting from ethyl acetoacetate or ethyl benzoyl acetate were, unfortunately, not successful due to rapid decarboxylation of the formed *β*-keto carboxylic acid. In comparison, *β*-keto carboxylic acid **16** underwent decarboxylation slower and could, therefore, when used without delay, be converted into hydroxamic acid **17**. Thus, formation of 3-isoxazolol **18** from **17** had been successful, but with the marked instability of the *β*-keto carboxylic acids we had to search for other ways to synthesize the protected *β*-keto hydroxamic acid **11**.

It is well-known that 2,2-dimethyl-1,3-dioxane-4,6-dione **(19)**[16,17] (Meldrum's acid) (Scheme 3) can be acylated and that such acyl Meldrum's acids can be converted into *β*-keto esters by reaction with alcohols.[16−20]

In contrast, only few examples describe the formation of *β*-keto amides from the reaction between acyl Meldrum's acids and nitrogen-containing nucleophiles.[21−23] Our approach was to perform an aminolysis of acyl derivative **20a** with *N*,*O*-diBoc-hydroxylamine, and we found that this reaction gave the corresponding *β*-keto hydroxamic acid **21a** in good yield. The subsequent treatment of **21a** with concentrated hydrochloric acid cleaved the Boc protecting groups and cleanly cyclized the hydroxamic acid to give **7** in 92% yield. We were able to reproduce these findings using a number of different

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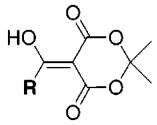
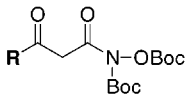
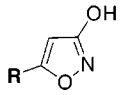
Table 1

Entry	R			
1	Me	**20a** (83 %)	**21a** (74 %)	**7** (92 %)
2	Et	**20b** (92 %)	**21b** (71 %)	**22b** (88 %)[c]
3	Isopropyl	**20c** (82 %)	**21c** (82 %)	**22c** (76 %)[c]
4	Cyclopropyl	**20d** (100 %)	**21d** (53 %)	**22d** (96 %)
5	Cyclohexyl	**20e** (99 %)[a]	**21e** (91 %)	**22e** (89 %)
6	Phenyl	**20f** (74 %)[b]	**21f** (82 %)	**22f** (99 %)
7	Neopentyl	**20g** (87 %)	**21g** (70 %)	**22g** (90 %)
8	Benzyl	**20h** (100 %)	**21h** (75 %)	**22h** (99 %)

[a] Via diethyl cyanophosphonate coupling. [b] From benzoic acid anhydride. [c] 4 M aqueous HCl in MeOH 16 h at rt.

acyl Meldrum's acids (Table 1), showing that this is a generally useful route to 5-substituted 3-isoxazolols.

Acylation of Meldrum's acid **(19)** has been performed by several different methods. Carboxylic acid chlorides[18,19,23] and anhydrides,[24] acyl imidazolides,[25] and peptide coupling reagents such as DCC[26] or diethyl cyanophosphonate[27,28] have all proved to be equally useful, but in the literature we found remarkably few examples of acylations using benzoic acid derivatives[23,24,29] and none with other aromatic or heteroaromatic acid derivatives. Our own experiments demonstrated the difficulties in synthesizing such acylated Meldrum's acids. Thus, we were unable to acylate Meldrum's acid **(19)** with either furoyl chloride or nicotinoyl chloride. Using the peptide-coupling reagent diethyl cyanophosphonate, we obtained the desired product **20e** from cyclohexylcarboxylic acid in 99% yield, whereas no acylation product could be detected under the same conditions using benzoic acid and **19**. Only benzoic anhydride was successfully reacted with the sodium salt of **19** yielding compound **20f** in 74% yield. Reactions under the same conditions using nicotinic anhydride[30] or *tert*-butanoic anhydride were, however, without result, and the desired compound could not be detected among several reaction products of unknown structure. Also, lowering the temperature or changing the base to triethylamine or 4-(dimethylamino)pyridine had no improving effect.

The aminolyses of acyl Meldrum's acids with *N*,*O*-diBoc-protected hydroxylamine in toluene at 65 °C proceeded smoothly, and the bulk of the two Boc groups did not seem to hinder attack by the nitrogen atom on the carbonyl group to any significant extent. Furthermore, we did not observe that varying the structure of the acyl Meldrum's acid had any large effect on reactivity, since all products **21a**−**h** were isolated in good yields after a reaction time of typically 4−16 h.

The cyclizations of the β-keto hydroxamic acids were carried out in hot concentrated hydrochloric acid, since this is the typical condition used for the cyclization step when β-keto esters are reacted with hydroxylamine.[11,12] We later found that a mixture of methanol and 4 M aqueous hydrochloric acid at room temperature worked equally well, although with prolonged reaction time. To compare the two methods, **22b** was first prepared using concentrated hydrochloric acid at 50 °C for 2 h, and next the reaction was performed in a (3:2) mixture of 4 M aqueous hydrochloric acid and methanol at room temperature overnight. Both methods turned out to give **22b** in 85−88% yield. Thus, the latter milder cyclization conditions give a further advantage compared to the much harsher method commonly used.

In conclusion, we have in this paper presented a novel and efficient three-step procedure for the synthesis of 5-substituted 3-isoxazolols without formation of the undesired 5-isoxazolone byproduct. The method uses the easily accessible starting materials Meldrum's acid, *N*,*O*-diBoc-hydroxylamine,[15] and an activated carboxylic acid derivative. Furthermore, the method gives easy access to N,O-protected β-keto hydroxamic acids from the reaction of an acyl Meldrum's acid and N,O-protected hydroxylamine.

Experimental Section

General Methods. Solvents and reagents were purchased from commercial sources and used without further purification

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unless otherwise stated. Meldrum's acid was recrystallized from acetone/hexane before use as previously described.[31] Melting points were determined in open capillaries and are uncorrected. Elemental analyses were performed by Analytical Research Department, H. Lundbeck A/S, Denmark, or by J. Theiner, Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna, Austria. Column chromatography (CC) was performed using silica gel 60 (0.063−0.200 mm) from Merck. Compounds were visualized on TLC (silica gel 60 F_{254} plates; Merck) using UV light and an $FeCl_3$ spraying reagent.

General Procedure for the Preparation of 5-Substituted 3-Isoxazolols. Method A: Synthesis of 5-Methyl-3-isoxazolol (7). Compound **21a** (450 mg, 1.42 mmol) dissolved in MeOH (3 mL) was added to concentrated HCl (10 mL) at 50 °C. The mixture was stirred for 1 h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in water (10 mL) and pH adjusted to 3−4 with 2 M aqueous NaOH followed by extraction with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. CC (EtOAc/hexane 1:9, 1% AcOH) yielded **7** as a crystalline solid (130 mg, 92%): mp 83−84 °C (lit.[14] mp 84−85 °C); ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 5.69 (s, 1H), 11.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 93.9, 170.6, 171.3; MS(FAB$^+$) *m*/*z* 100 ([M + 1]$^+$, 100). Anal. Calcd for $C_4H_5NO_2$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.62; H, 5.05; N, 14.03.

Methyl 2-Methyl-3-oxo-3-(4-tolyl)propionate (15). A stirred solution of methyl 4-methylbenzoate (41.2 g, 271 mmol) and NaH (60% in mineral oil, 16.2 g, 406 mmol) in dry DMF (350 mL) was added methyl propionate (35.8 g, 406 mmol) dropwise under N_2. After being stirred at room temperature for 16 h, the reaction mixture was concentrated in vacuo, and to the residue was added saturated aqueous $NaHCO_3$ followed by extraction with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (EtOAc/hexane 1:9) yielded **15** as a colorless oil (49.3 g, 88%): ^{1}H NMR ($CDCl_3$) δ 1.48 (d, 3H, J = 7.2 Hz), 2.41 (s, 3H), 3.67 (s, 3H), 4.38 (q, 1H, J = 7.2 Hz), 7.22−7.30 (m, 2H), 7.84−7.92 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.7, 48.0, 52.6, 129.0, 129.7, 133.4, 144.8, 171.8, 195.8.

2-Methyl-3-oxo-3-(4-tolyl)propionic Acid (16). To a solution of **15** (3.90 g, 18.9 mmol) in EtOH (140 mL) was added NaOH (832 mg, 20.8 mmol) and the mixture stirred 16 h at room temperature. The reaction mixture was concentrated in vacuo, H_2O was added, and the mixture was washed with CH_2Cl_2. The pH was adjusted to 2−3 with 4 M HCl and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (EtOAc/hexane 1:9, 1% AcOH) afforded **16** in 73% yield (2.66 g): ^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3H, J = 7.2 Hz), 2.41 (s, 3H), 4.42 (q, 1H, J = 7.2 Hz), 7.23−7.30 (m, 2H), 7.82−7.93 (m, 2H), 10.4 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.6, 47.3, 128.9, 129.6, 132.9, 145.0, 176.5, 195.9.

***N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)-2-(4-methylbenzoyl)propionamide (17).** Compound **16** (0.50 g, 2.60 mmol) dissolved in $SOCl_2$ (3.0 mL) was added 1 drop of DMF, and the solution was stirred under N_2 for 14 h at room temperature. The reaction mixture was concentrated in vacuo and the residue dissolved in dry CH_2Cl_2 (1.0 mL). This solution was added dropwise to a mixture of *N*,*O*-diBoc-hydroxylamine[15] (607 mg, 2.60 mmol) and Et_3N (263 mg, 2.60 mmol) in dry CH_2Cl_2 (5.0 mL) and stirred at room temperature for 16 h (N_2 atm). To the reaction mixture was added saturated aqueous $NaHCO_3$, and this mixture was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo.The residue was purified by CC (EtOAc/hexane 1:9) affording **17** in 56% yield (590 mg): ^{1}H NMR ($CDCl_3$) δ 1.44−1.53 (m, 21H), 2.41 (s, 3H), 5.18−5.30 (m, 1H), 7.26−7.28 (m, 2H), 7.84−7.86 (m, 2H). Anal. Calcd for $C_{21}H_{29}NO_7$: C, 61.90; H, 7.17; N, 3.44. Found: C, 62.16; H, 7.21; N, 3.52.

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4-Methyl-5-(4-tolyl)-3-isoxazolol (18). Method A: 76 mg, 82%; mp >210 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.41 (s, 3H), 4.8 (br s, 1H), 7.22−7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 6.8, 21.5, 100.7, 126.6, 129.8, 130.2, 140.4, 165.0, 171.0; MS-(FAB$^+$) *m*/*z* 190 ([M + 1]$^+$, 22). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.79; H, 6.01; N, 7.46.

General Procedure for the Preparation of Acyl Meldrum's Acids. Method B: Synthesis of 5-(1-Hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (20a). A solution of Meldrum's acid (3.00 g, 20.8 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C, and pyridine (3.29 g, 41.6 mmol) was added. After stirring 15 min, acetyl chloride (1.63 g, 20.8 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1.5 h followed by 1.5 h at room temperature. To this solution was added 2 M aqueous HCl, and the reaction mixture was then extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (EtOAc/hexane 1:9, 1% AcOH) yielded **20a** as a crystalline solid (3.20 g, 83%): mp 83−84 °C (lit.[20] mp 83.5−84.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 6H), 2.69 (s, 3H), 15.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 26.9, 92.0, 105.1, 160.8, 170.5, 195.0. Anal. Calcd for $C_8H_{10}O_5$: C, 51.61; H, 5.41. Found: C, 51.83; H, 5.43.

5-(1-Hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (20b). Method B: 3.85 g, 92%; mp 48−49 °C (lit.[18] mp 55 °C); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.5 Hz), 1.70 (s, 6H), 3.08 (q, 2H, J = 7.5 Hz), 15.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.4, 26.6, 29.3, 90.8, 104.7, 160.2, 170.6, 199.0; IR (KBr) 2990, 1740, 1660, 1550 cm^{-1}. Anal. Calcd for $C_9H_{12}O_5$: C, 54.04; H, 6.04. Found: C, 54.44; H, 5.96.

5-(1-Hydroxy-2-methyl-propylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (20c). Method B: 3.65 g, 82%; yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 1H, J = 6.9 Hz), 1.74 (s, 6H), 4.10 (septet, 6H, J = 6.9 Hz), 15.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.9, 26.6, 32.8, 90.0, 104.6, 160.1, 171.0, 202.5.

5-(Cyclopropylhydroxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (20d). Method B: 4.54 g, quantitative yield; yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.15−1.49 (m, 4H), 1.76 (s, 6H), 3.48−3.56 (m, 1H), 15.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.3, 26.4, 90.9, 104.5, 161.1, 170.5, 197.9.

5-(Cyclohexylhydroxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (20e). Method B: 4.45 g, 84%; mp 76−78 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−1.90 (m, 10H), 1.74 (s, 6H), 3.74−3.85 (m, 1H), 15.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3, 25.4, 26.5, 29.0, 42.7, 90.1, 104.5, 160.1, 171.0, 201.5. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13. Found: C, 61.14; H, 7.05.

Method C. Cyclohexanecarboxylic acid (615 mg, 4.80 mmol) and Meldrum's acid (692 mg, 4.80 mmol) dissolved in dry DMF (10 mL) was cooled to 0 °C, and to this mixture were dropwise added diethyl cyanophosphonate (862 mg, 5.28 mmol) and Et_3N (1.51 g, 14.9 mmol) (N_2 atm). The reaction mixture was stirred at 0 °C for 0.5 h followed by 16 h at room temperature. The mixture was then concentrated in vacuo, 2 M aqueous HCl was added, and the mixture extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (EtOAc/hexane 1:9, 1% AcOH) afforded pure **20e** in 99% yield (1.21 g).

5-(Hydroxyphenylmethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (20f).[24] A solution of the sodium salt of Meldrum's acid (1.50 g, 9.03 mmol) in dry DMF (15 mL) was cooled to 0 °C, and benzoic acid anhydride (2.04 g, 9.03 mmol) dissolved in anhyd DMF (6 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h followed by 16 h at room temperature. The mixture was concentrated in vacuo, and 2 M aqueous HCl was added. This solution was then extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (EtOAc/hexane 1:9, 1% AcOH) yielded **20f** as a crystalline solid (1.62 g, 72%); mp 107−109 °C dec (lit.[29] mp 114 °C dec); ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 6H), 7.42−7.70 (m, 5H), 15.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.6, 90.8, 104.9, 128.0, 129.4, 132.6, 133.3, 159.8, 171.0, 189.3. A sample was recrystallized (EtOAc/hexane) for elemental analysis. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.65; H, 4.99.

5-(3,3-Dimethyl-1-hydroxybutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (20g). Method B: 4.45 g, 87%; yel-

lowish oil; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 1.74 (s, 6H), 3.13 (s, 2H), 15.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.6, 29.8, 33.8, 46.2, 92.9, 104.4, 160.6, 170.7, 197.0.

5-(1-Hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (20h). Method B: 5.50 g, quantitative yield; mp 94−96 °C dec (lit.[32] mp 90−92 °C dec); ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 6H), 4.43 (s, 2H), 7.21−7.40 (m, 5H), 15.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.6, 40.6, 91.3, 104.9, 127.5, 128.6, 129.6, 134.0, 160.3, 170.5, 194.7. Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 64.20; H, 5.38.

General Procedure for the Preparation of β-Keto Hydroxamic Acids. Method D: Synthesis of *N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)acetylacetamide (21a). To **20a** (1.50 g, 8.06 mmol) dissolved in toluene (75 mL) was added *N*,*O*-diBoc hydroxylamine[15] (1.88 g, 8.06 mmol). The stirred solution was heated to 65 °C for 4 h and then cooled to room temperature. After concentration in vacuo, the residue was purified by CC (EtOAc/hexane 1:19) to afford compound **21a** as a colorless oil (1.89 g, 74%): ^{1}H NMR ($CDCl_3$) δ 1.51−1.56 (m, 18H), 2.27 (s, 3H), 3.87−4.09 (m, 2H). Anal. Calcd for $C_{14}H_{23}NO_7 \cdot 0.15\ C_6H_{14}$: C, 54.19; H, 7.66; N, 4.24. Found: C, 54.23; H, 7.81; N, 4.31.

***N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)-propionylacetamide (21b).** Method D: 4.70 g, 71%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.4 Hz), 1.50−1.56 (m, 18H), 2.57 (q, 2H, J = 7.4 Hz), 3.88−4.10 (m, 2H); IR (KBr) 3300, 2980, 2920, 1780, 1750, 1460 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_7$: C, 54.37; H, 7.60; N, 4.23. Found: C, 54.64; H, 7.42; N, 4.49.

***N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)-isopropionylacetamide (21c).** Method D: 1.33 g, 82%; colorless oil; reaction time 16 h; ^{1}H NMR ($CDCl_3$) δ 1.14 (d, 6H, J = 7.2 Hz), 1.50−1.56 (m, 18H), 2.74 (septet, 1H, J = 7.2 Hz), 3.94−4.20 (m, 2H). Anal. Calcd for $C_{16}H_{27}NO_7$: C, 55.64; H, 7.88; N, 4.06. Found: C, 55.39; H, 8.09; N, 4.29.

***N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)-4-cyclopropyl-3-oxopropionamide (21d).** Method D: 1.82 g, 53%; colorless oil; reaction time 16 h; ^{1}H NMR ($CDCl_3$) δ 1.08−1.27 (m, 4H), 1.50−1.55 (m, 18H), 1.96−2.05 (m, 1H), 4.04−4.23 (m, 2H).

***N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)-4-cyclohexyl-3-oxopropionamide (21e).** Method D: 2.08 g, 91%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.15−1.95 (m, 10H), 1.50−1.56 (m, 18H), 2.42−2.53 (m, 1H), 3.91−4.19 (m, 2H).

***N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)-benzoylacetamide (21f).** Method D: 800 mg, 82%; mp 109−111 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.56 (s, 9H), 4.44−4.74 (m, 2H), 7.45−7.95 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.3, 27.6, 48.5, 85.7, 86.1, 128.3, 128.7, 133.6, 136.0, 149.4, 150.9, 163.8, 192.2. Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 60.09; H, 6.61; N, 3.69.

***N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)-5,5-dimethyl-3-oxohexanoamide (21 g).** Method D: 2.60 g, 70%; colorless oil; reaction time 16 h; ^{1}H NMR ($CDCl_3$) δ 1.01−1.08 (m, 9H), 1.50−1.56 (m, 18H), 2.45 (s, 2H), 3.85−4.07 (m, 2H). Anal. Calcd for $C_{18}H_{31}NO_7$: C, 57.89; H, 8.37; N, 3.75. Found: C, 58.11; H, 8.61; N, 3.59.

***N*-(*tert*-Butoxycarbonyl)-*N*-(*tert*-butoxycarbonyloxy)-3-oxo-4-phenylbutyramide (21h).** Method D: 2.94 g, 75%; colorless oil; reaction time 16 h; ^{1}H NMR ($CDCl_3$) δ 1.48−1.53 (m, 18H), 3.83 (s, 2H), 3.83−4.10 (m, 2H), 7.19−7.35 (m, 5H).

5-Ethyl-3-isoxazolol (22b). Method A: 290 mg, 85%; mp 42−43 °C (lit.[33] mp 45−46 °C); reaction time 2 h; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.7 Hz), 2.66 (q, 2H, J = 7.7 Hz), 5.67 (s, 1H), 11.9 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.1, 20.5, 92.4, 171.2, 175.8. IR (KBr): 3000, 2650, 1620, 1530, 1320 cm^{-1}; MS(FAB$^+$) m/z 114 ([M + 1]$^+$, 100). Anal. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.36; H, 6.14; N, 12.46.

Method E. Compound **21b** (750 mg, 2.26 mmol) dissolved in MeOH (20 mL) and 4 M aqueous HCl (30 mL) was stirred at room temperature overnight. The mixture was concentrated in vacuo, H_2O was added, and the mixture was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (EtOAc/hexane 1:9, 1% AcOH) yielded pure **22b** in 88% yield (225 mg).

5-Isopropyl-3-isoxazolol (22c). Method E: 265 mg, 76%; mp 42−43 °C (lit.[9] mp 41−42 °C); ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 6H, J = 6.9 Hz), 2.94 (d septet, 1H, J = 6.9 and 0.9 Hz), 5.64 (d, 1H, J = 0.9 Hz), 11.2 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3, 27.4, 91.2, 171.1, 179.6; MS(FAB$^+$) m/z 128 ([M + 1]$^+$, 100). Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.39; H, 6.91; N, 10.80.

5-Cyclopropyl-3-isoxazolol (22d). Method A: 280 mg, 96%; mp 103−104 °C (lit.[34] mp 103−105 °C); reaction time 2 h; ^{1}H NMR ($CDCl_3$) δ 0.92−0.99 (m, 4H), 1.89−1.99 (m, 1H), 5.59 (s, 1H), 11.5 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.0, 8.3, 90.8, 171.3, 175.6; MS(FAB$^+$) m/z 126 ([M + 1]$^+$, 100). Anal. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.32; H, 5.60; N, 10.95.

5-Cyclohexyl-3-isoxazolol (22e). Method A: 385 mg, 89%; mp 120−121 °C (lit.[13] mp 123 °C); reaction time 5 h; ^{1}H NMR ($CDCl_3$) δ 1.20−2.05 (m, 10H), 2.59−2.68 (m, 1H), 5.62 (s, 1H), 11.5 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.4, 25.5, 30.5, 36.5, 91.3, 171.1, 178.7; MS(FAB$^+$) m/z 168 ([M + 1]$^+$, 100). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.43; H, 7.74; N, 8.28.

5-Phenyl-3-isoxazolol (22f). Method A: 190 mg, 99%; mp 159−161 °C (lit.[35] mp 162−163 °C); ^{1}H NMR ($CDCl_3$) δ 6.24 (s, 1H), 7.45−7.50 (m, 3H), 7.72−7.78 (m, 2H), 10.8 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 91.3, 125.7, 127.2, 129.0, 130.7, 170.2, 171.5; MS(FAB$^+$) m/z 162 ([M + 1]$^+$, 18). Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.96; H, 4.37; N, 8.64.

5-Neopentyl-3-isoxazolol (22g). Method A: 375 mg, 90%; mp 105−106 °C (lit.[36] mp 102−103 °C); reaction time 8 h; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 9H), 2.52 (s, 2H), 5.67 (s, 1H), 11.2 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.2, 31.4, 41.2, 94.7, 171.1, 172.8; MS(FAB$^+$) m/z 156 ([M + 1]$^+$, 65). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.93; H, 8.57; N, 9.08.

5-Benzyl-3-isoxazolol (22h). Method A: 410 mg, 99%; mp 93−94 °C (lit.[37] mp 94−95 °C); ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 2H), 5.62 (s, 1H), 7.22−7.46 (m, 5H), 11.5 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.5, 94.2, 127.3, 128.8, 128.8, 135.3, 171.2, 172.9; MS(FAB$^+$) m/z 176 ([M + 1]$^+$, 100). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.33; H, 5.34; N, 7.96.

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