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The synthesis of N^{α}-protected amino hydroxamic acids from N^{α}-protected amino acids employing versatile chlorinating agent CPI-Cl

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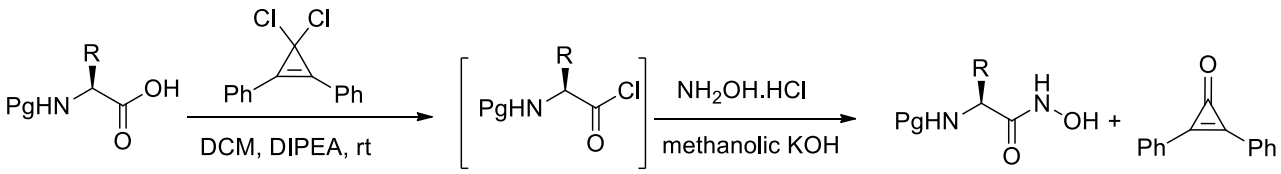
Abstract

Racemization free synthesis of N^{α}-protected amino hydroxamic acids from N^{α}-protected amino acids employing the versatile chlorinating reagent CPI-Cl has been described in one-pot. The present protocol has shown compability towards urethane protecting groups like Boc, Cbz and Fmoc, and side chain protections of amino acids showed complete tolerance.



Pg = Boc, Cbz, Fmoc
R = amino acid side chain

Keywords: N^{α}-Protected amino hydroxamic acid, 3,3-dichloro-1,2-diphenylcyclopropene, hydroxyl amine hydrochloride, racemization-free

Introduction

Hydroxamic acids are an important class of compounds, which display a broad spectrum of biological activities. Owing to their strong chelating ability towards Zn (II) ions, hydroxamic acids are excellent inhibitors of matrix metalloproteinases.[1] Compounds containing this functional moiety serve as anti-fungal (Figure 1a),[2] anti-cancer (Figure 1b),[3] anti-inflammatory (Figure 1c),[4] anti-bacterial (Figure 1d),[5] and other therapeutics. They are also known as plant growth regulators.[6] Furthermore, hydroxamic acids are important precursors to obtain ureas,[7] carbamates[8] and thiocarbamates[9] *via* Lossen rearrangement.

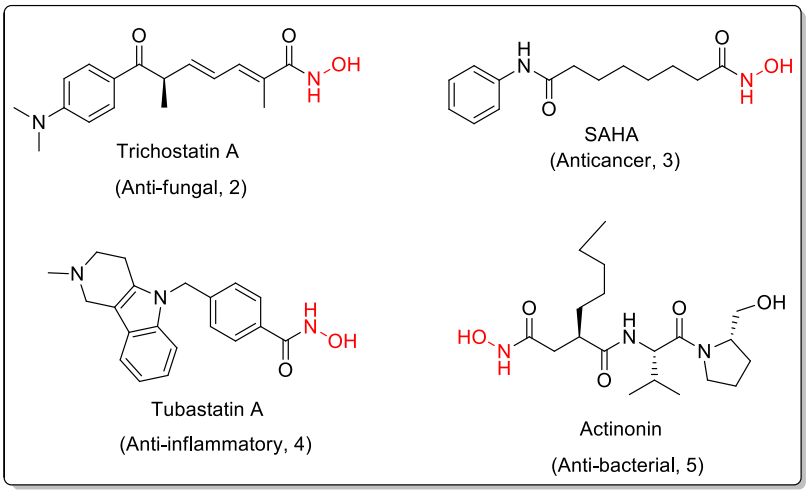


Figure 1. Selective display of biologically active hydroxamic acids.

Generally, hydroxamic acids are prepared by coupling activated carboxylic acid with *O/N*-protected hydroxylamine or deprotonated hydroxylamine hydrochloride. For this purpose, activation of carboxylic acids *via* converting them to acid halides were achieved using thionyl chloride ($SOCl_2$),[10] and tetramethylfluoroformamidinium hexafluorophosphate (TFFH) and benzyl triphenylphosphonium dihydrogen trifluoride (PTF).[11] Hydroxamic acids have been prepared by coupling mixed anhydride, obtained by the addition of carboxylic acid and ethyl chloroformate, with hydroxylamine.[7, 12]

Other coupling reagents like cyanuric chloride,[13] *N, N'*-carbonyldiimidazole (CDI), [14] 1-[(1-(cyano-2-ethoxy-2-oxoethylidenaminooxy)-dimethylamino-morpholinomethylene)] methaneaminium hexafluoro-phosphate (COMU),[15] propanephosphonic acid anhydride (T3P),[16,17] and ethyl-2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (NBsOXY),[18] were also employed to obtain hydroxamic acids from their corresponding carboxylic acids.

Literature has recorded a plethora of reports on synthesis of hydroxamic acids from carboxylic acid esters.[19-23] Especially, esters were found to be almost indispensable precursors to obtain hydroxymic acids in solid phase strategies.[24-26]

However, use of toxic and irritative ethyl chloroformate adds inconvenience, though the synthesis of hydroxamic acid from the corresponding carboxylic acid uses minimum reaction duration. Most of the reactions employed require long reaction durations, especially with the use of ester as precursor. Particularly, solid phase synthesis of hydroxamic acids have major disadvantages like they require profuse use of reagents, longer reaction times, and an additional step to release hydroxamic acid from resins makes solid phase

strategy less preferred way to obtain hydroxamic acids. There are reports where hydroxamic acids were prepared from aldehydes;[27-29] however, use of catalysts and prolonged reaction durations makes the protocol less attractive. In addition, in amino acid chemistry, carboxylic acids are readily available to obtain hydroxamic acids compared to their aldehyde derivatives.

As aforementioned not many halogenating reagents have been reported to obtain hydroxamic acids from their corresponding carboxylic acids, especially in the synthesis of amino acid derived hydroxamic acids, as it involves acid sensitive Boc group. The halogenating reagents like $SOCl_2$, oxalyl chloride and $POCl_3$ are not suitable for halogenation for Boc-protected amino acids. Therefore, activating carboxylic acids with halogenating reagent having compatibility towards acid sensitive groups to obtain hydroxamic acids can be considered a useful strategy.

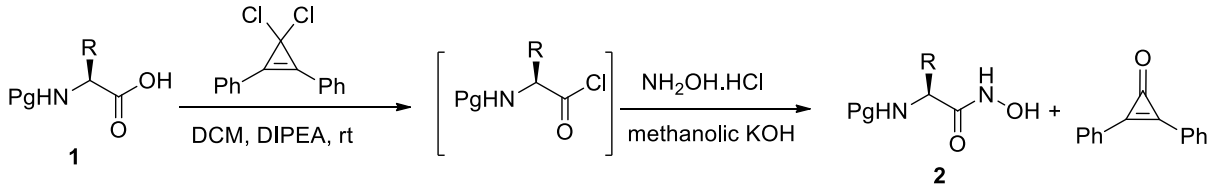
3,3-Dichloro-1,2-diphenylcyclopropene (CPI-Cl) has found its use not only as stoichiometric reagent but also as catalyst. As a result, it has been employed in many synthetic processes. CPI-Cl has been converted to cyclopropenylidene carbene complexe catalysts and employed for C-C bond formation reactions.[30,31] It was also used to chlorinate carboxylic acids [32] and alcohols. [33] It was found to catalyze Beckmann rearrangement to obtain amides/lactams from corresponding oximes.[34,35] Recently, Sureshbabu *et al*. reported N^{α}-protected amino acid azides employing stoichiometric CPI-Cl from N^{α}-protected amino acid without affecting acid sensitive groups. [36]

In this regard, we herein demonstrate a useful application of CPI-Cl in the preparation of N^{α}-protected amino hydroxamic acids from N^{α}-protected amino acids.

Results and Discussion

In the initial trial reaction, Cbz-Gly (**1a**, 1.0 mmol) was taken as model substrate in CH_2Cl_2, and DIPEA (1.1 mmol) and CPI-Cl (generated by the treatment of 2, 3-diphenylcyclopropenone with oxalyl chloride in CH_2Cl_2, 1.0 mmol) were added at room temperature and stirred at the same temperature for ten minutes.

The reaction mixture was then cooled to -10 ^{o}C and treated with deprotonated hydroxylamine hydrochloride (obtained by treating hydroxylamine hydrochloride with methanolic potassium hydroxide) and stirred till the completion of the reaction. After simple aqueous workup and column chromatography, the compound **2a** was isolated in good yield. In the next reaction, Boc-Phg was taken and the protocol was found to be compatible towards acid sensitive Boc-group, too. Similarly, Fmoc-amino acid hydroxamic acids were obtained in good yields. During the present study, water miscible solvents like acetonitrile, acetone and *N*, *N'*-dimethylformamide were also tested and found to give poor yields of products.

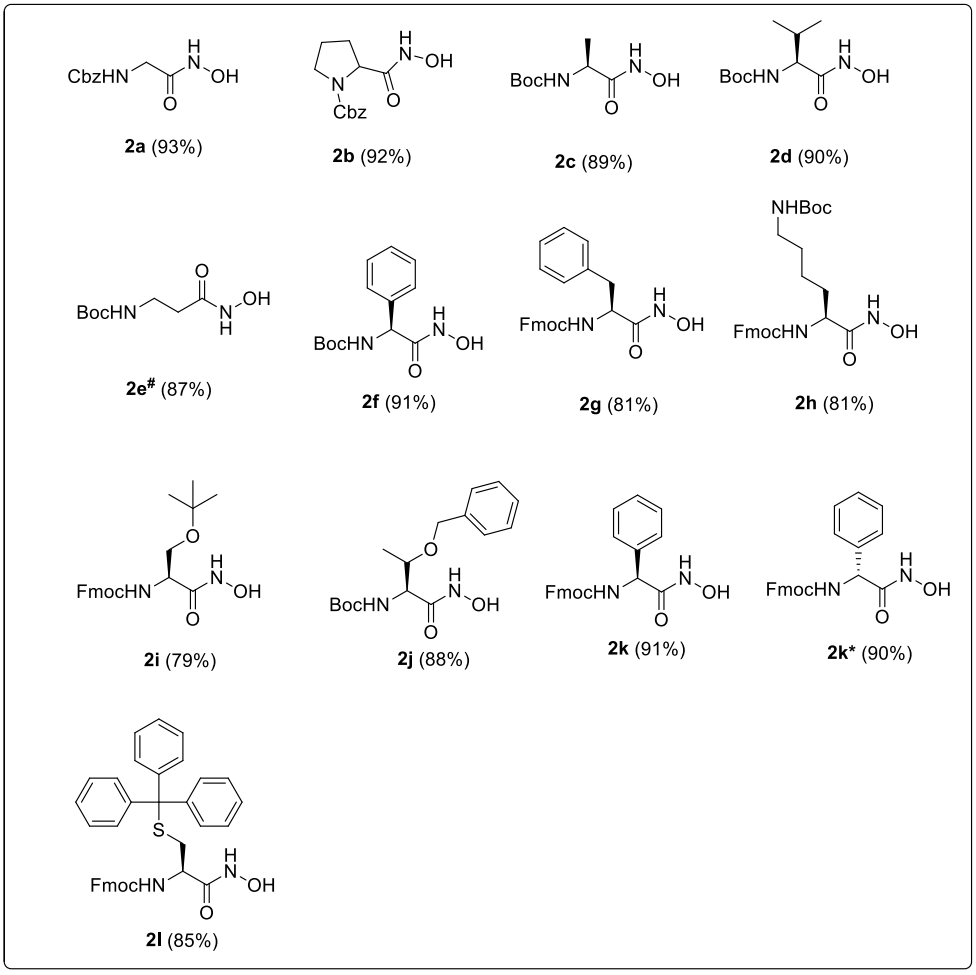


Scheme 1. Synthesis of N^{α}-protected amino hydroxamic acids using CPI-Cl

N^{α}-protected serine, threonine and cystiene when employed in the present protocol, resulted in side reactions and found not suitable to use without their side chain protections. Fortunately, on employing their

side chain protected analogues resulted in hydroxamic acids without affecting their side chain protections. Side chains of amino acids protected by benzyl, tertiary butyl and trityl groups were found to be stable towards present approach.

Table 1. Library of N^{α}-protected amino hydroxamic acids



#β-amino acid

Interestingly, 2, 3-diphenylcyclopropenone generated at the end of the reaction can be isolated by column chromatography and reused to prepare CPI-Cl.

Fmoc-D-Phe-NHOH was prepared and compared with Fmoc-L-Phe-NHOH by RP-HPLC studies using chiral column. Retention time (t_R) of Fmoc-L-Phe-NHOH was found to be 8.14 min and of Fmoc-D-Phe-NHOH was 5.51 min (Figures 2 and 3). Further, Fmoc-L-Phg-NHOH and Fmoc-D-Phg-NHOH showed retention times 9.16 min and 7.08 min, respectively, and thier equimolar mixture gave two distinct peaks at 9.77 and 7.56 min. These studies confirmed the present method is racemization free.

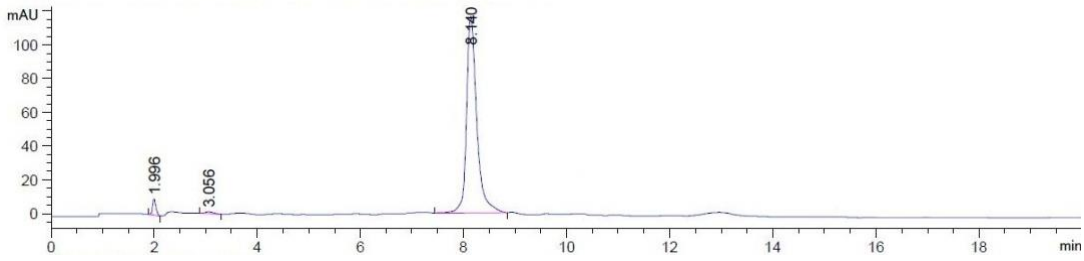


Figure 2. RP-HPLC profile of Fmoc-L-Phe-NHOH

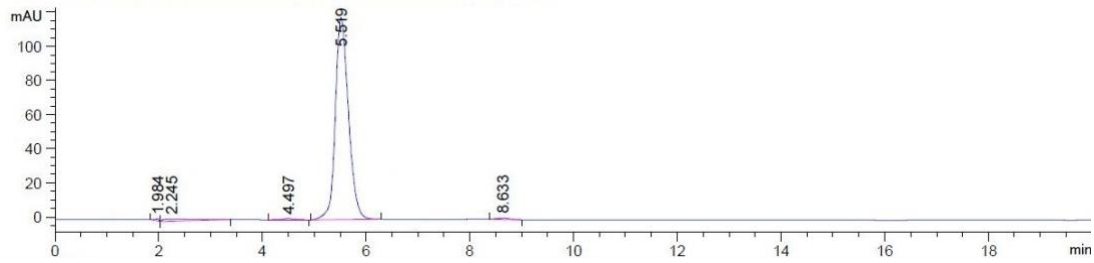


Figure 3. RP-HPLC profile of Fmoc-D-Phe-NHOH

Conclusions

We have developed a mild protocol to synthesize N^{α}-protected amino hydroxamic acids from N^{α}-protected amino acids employing CPI-Cl. The reaction found to tolerate commonly employed N-protecting groups such as Boc, Cbz and Fmoc and retain optical purity of amino acids.

Experimental Section

General. All the chemicals were purchased from Sigma Aldrich Company, USA. All the solvents were freshly distilled and dried whenever required. TLC analysis was carried out using Merck aluminium TLC sheets (Silica gel 60 F_{254}), the chromatograms were visualized by UV light and also by exposing in an iodine chamber. Column chromatography using mixtures of ethyl acetate and hexane as eluents through silica gel (100-200 mesh). HRMS spectra were recorded in a XEVO-G2-XS-Q-TOF mass spectrometer. ^{1}H and ^{13} C NMR were determined in Brucker AV NMR (400 MHz, 100 MHz) spectrometer. Melting points were determined in an open capillary and are uncorrected. Optical rotations were recorded at 25 ^{o}C. The RP-HPLC analysis of epimers was carried out using an Agilent instrument (method: gradient 0.1% TFA water-acetonitrile (0–100%) in 20 min; VWD at λ 254 nm; flow rate: 1.0 mL/min; column: Agilent Eclipse, XDB-C18, pore size 5 µm, diameter × length = 4.6 × 150 nm).

General procedure for the synthesis of N^{α}-protected amino hydroxamic acid. To a solution of 3,3-dichloro-1,2-diphenylcyclopropene at -10 ^{o}C [1.1 equiv. prepared by adding diphenylcyclopropenone (1.0 equiv.) in DCM and oxalyl chloride (1.0 equiv.) at rt and stirred until the gas evolution has ceased] was added a solution

of N^{α}-protected amino acid (1.0 equiv.) and diisopropylethylamine (1.2 equiv.) in dichloromethane and stirred. After 10 min hydroxylamine hydrochloride ($NH_2OH.HCl$, 1.5 equiv.) in methanolic potassium hydroxide was added to the reaction mixture and stirred of another 45 min. The solvent was removed under reduced pressure; the residue obtained was diluted with EtOAc, washed with 10% citric acid solution, water and brine solution. The organic phase was dried over anhydrous Na_2SO_4 and removed under reduced pressure. The crude residue was purified by column chromatography using *n*-hexane and ethyl acetate as eluents.

Benzyl (2-(hydroxyamino)-2-oxoethyl)carbamate (2a). White solid; Yield 93%; $[\alpha]^{25}_D$ -1.6 (c 1.0, MeOH); mp 115-117 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 8.79 (s, 1H), 7.46-7.31 (m, 5H), 5.04 (s, 2H), 3.54 (d, *J* 8 Hz, 2H);^{13}C NMR (100 MHz, DMSO-d_6): δ166, 156.3, 137, 128.3, 127.7, 127.6, 65.4, 41.4; HRMS (ESI): calcd. for $C_{10}H_{12}N_2O_4$ [M+ Na]$^+$: 247.0695, found: 247.0696.

Benzyl 2-(hydroxycarbamoyl)pyrrolidine-1-carboxylate (2b). White solid; Yield 92%; $[\alpha]^{25}_D$ - 49.6 (c 1.0, MeOH); mp 81-83 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.6 (s, 1H), 7.39-7.31 (m, 5H), 5.08 (dd, *J* 12 Hz, 12 Hz, 2H), 4.15-4.05 (m, 1H), 3.51-3.39 (m, 2H), 1.95-1.76 (m, 4H);^{13}C NMR (100 MHz, DMSO-d_6): δ 168.7, 153.9, 136.9, 128.3, 128.2, 127.7, 127.4, 126.9, 65.8, 57.9, 47, 30, 23.8; HRMS (ESI): calcd. for $C_{13}H_{16}N_2O_4$ [M+ Na]$^+$: 287.1008, found: 287.1007.

(*S*)-tert-Butyl (1-(hydroxyamino)-1-oxopropan-2-yl)carbamate (2c). White solid; Yield 89%; $[\alpha]^{25}_D$ -20.1 (c 1.0, MeOH); mp 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (s, 1H), 5.05 (s, 1H), 4.19-4.09 (m, 1H), 1.43 (s, 9H), 1.38 (d, *J* 4Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ170.3, 155.8, 72.4, 47.5, 28.3, 17.6; HRMS (ESI): calcd. for $C_8H_{16}N_2O_4$ [M+ Na]$^+$: 227.1008, found: 227.1008.

***tert*-Butyl (1-(hydroxyamino)-3-methyl-1-oxobutan-2-yl)carbamate (2d).** White solid; Yield 90%; $[\alpha]^{25}_D$ -10.5 (c 1.0, DMSO); mp 137-139 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 1H), 8.81 (s, 1H), 3.58 (t, *J* 8 Hz, 1H), 1.90-1.81 (m, 1H), 1.39 (s, 1H), 0.85 (d, 6H);^{13}C NMR (100 MHz, DMSO-d_6): δ168, 155.2, 77.8, 57.6, 30.1, 28.1, 19, 18.6; HRMS (ESI): calcd. for $C_{10}H_{20}N_2O_4$ [M+ Na]$^+$: 255.1321, found: 255.1321.

tert-Butyl (3-(hydroxyamino)-3-oxopropyl)carbamate (2e). White solid; Yield 87%; mp 73-75 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.39 (s, 1H), 8.73 (s, 1H), 3.12 (dd, *J* 12 Hz, 4 Hz, 2H), 2.12 (t, *J* 8 Hz, 2H), 1.38 (s, 9H);^{13}C NMR (100 MHz, DMSO-d_6): δ167.2, 155.4, 77.5, 36.6, 32.7, 28.1; HRMS (ESI): calcd. for $C_8H_{16}N_2O_4$[M+ Na]$^+$: 227.1008, found: 227.1008.

(*S*)-*tert*-butyl (2-(hydroxyamino)-2-oxo-1-phenylethyl)carbamate) (2f). The spectral data of the compound was similar to that of earlier report.[13]

(9*H*-Fluoren-9-yl)methyl (1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate (2g). White solid; Yield 81%; $[\alpha]^{25}_D$ -45.5 (c 1.0, DMSO); mp 151-153 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H), 8.88 (s, 1H), 7.90-7.18 (m, 13H), 4.22-4.02 (m, 4H), 2.96-2.82 (m, 2H);^{13}C NMR (100 MHz, DMSO-d_6): δ 168.1, 155.6, 143.7, 140.6, 137.9, 129.1, 128, 127.5, 127, 126.2, 125.2, 120, 65.6, 53.9, 46.5, 37.6; HRMS (ESI): calcd. for $C_{24}H_{22}N_2O_4$ [M+ Na]$^+$: 425.1477, found: 425.1478.

(9*H*-Fluoren-9-yl)methyltert-butyl (6-(hydroxyamino)-6-oxohexane-1,5-diyl)dicarbamate (2h). White solid; Yield 81%; $[\alpha]^{25}_D$ -12.7 (c 1.0, MeOH); mp 120-122 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.82 (s, 1H), 7.91-7.33 (m, 8H), 6.76 (s, 1H), 4.27-4.14 (m, 3H), 3.85 (dd, *J* 12 Hz, 8 Hz, 1H), 2.91-2.84 (m, 2H), 1.84-1.71 (m, 2H), 1.60-1.54 (m, 2H), 1.38 (s, 9H), 1.30-1.15 (m, 2H);^{13}C NMR (100 MHz, DMSO-d_6): δ168.6, 155.8, 155.5, 143.7, 140.6, 127.6, 127, 125.3, 120, 77.3, 65.6, 52.3, 46.6, 42.5, 31.6, 29.1, 28.2, 22.7; HRMS (ESI): calcd. for $C_{26}H_{33}N_3O_6$ [M+ Na]$^+$: 506.2267, found: 506.2266.

(*S*)-(9*H*-Fluoren-9-yl)methyl(3-(tert-butoxy)-1-(hydroxyamino)-1-oxopropan-2yl)carbamate (2i). White solid; Yield 79%; $[\alpha]^{25}_D$+2.1 (c 1.0, MeOH); mp 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 7.75-7.26 (m, 8Hz), 5.80 (d, *J* 4 Hz, 1H), 4.40-4.17 (m, 4H), 3.72 (m, 1H), 3.43 (t, *J* 8 Hz, 1H), 1.17 (s, 9H);^{13}C NMR (100 MHz,

$CDCl_3$): δ 168.5, 156.2, 143.6, 141.3, 127.7, 127.1, 125.1, 120, 79.81, 67.3, 61.3, 53.1, 47.1, 27.3; HRMS (ESI): calcd. for $C_{22}H_{26}N_2O_5$ [M+ Na]$^+$: 421.1739, found: 421.1737.

***tert*-Butyl ((2*S*, 3*S*)-3-(benzyloxy)-1-(hydroxyamino)-1-oxobutan-2-yl)carbamate (2j).** White solid; Yield 88%; $[\alpha]^{25}_D$+7.8 (c 1.0, MeOH); mp 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.34-7.26 (m, 5H), 5.48 (d, *J* 8Hz, 1H), 4.53 (dd, *J* 24Hz, 8Hz, 2H), 4.32-4.24 (m, 1H), 4.19-4.13 (m, 1H), 1.43 (s, 9H), 1.16 (d, *J* 8Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 159.4, 137.7, 128.5, 127.9, 127.8, 80.6, 74.2, 71.6, 56.4, 28.2, 15.7; HRMS (ESI): calcd. for $C_{16}H_{24}N_2O_5$ [M+ Na]$^+$: 347.1583, found: 347.1582.

(*S*)-(9*H*-fluoren-9-yl)methyl (2-(hydroxyamino)-2-oxo-1-phenylethyl)carbamate (2k). White solid; Yield 91%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.96 (s, 1H), 7.87 (d, *J* 8 Hz, 2H), 7.76 (d, *J* 8 Hz, 2H), 7.45-7.27 (m, 9H), 5.12 (d, *J* 12 Hz, 1H), 4.24-4.17 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.6, 155.6, 143.6, 140.6, 138.5, 128.1, 127.5 (4C), 127, 125.4 (3C), 120, 65.9, 55.8, 46.5.

(*R*)-(9*H*-fluoren-9-yl)methyl (2-(hydroxyamino)-2-oxo-1-phenylethyl)carbamate (2k*). White solid; Yield 90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.96 (s, 1H), 7.87 (d, *J* 8 Hz, 2H), 7.76 (d, *J* 8 Hz, 2H), 7.45-7.27 (m, 9H), 5.13 (d, *J* 8 Hz, 1H), 4.24-4.17 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.6, 155.6, 143.6, 140.6, 138.5, 128.1, 127.5, 127 (4C), 125.4, 125.3, 120, 65.9, 55.8, 46.5.

(*R*)-(9*H*-fluoren-9-yl)methyl (1-(hydroxyamino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate (2l). White solid; Yield 85%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.69 (s, 1H), 8.88 (s, 1H), 7.87 (d, *J* 8 Hz, 2H), 7.74 (d, *J* 8 Hz, 2H), 7.41-7.19 (m, 19H), 4.26-4.16 (m, 3H), 4.02 (d, *J* 16Hz, 1H), 2.39-2.28 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.4, 155.4, 144.2, 143.6, 140.6, 129, 128, 127.5, 126.9, 126.7, 125.3, 120, 65.8, 59.6, 51.6, 46.5, 33.9.

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Supplementary Material

^{1}H NMR, ^{13}C NMR, Mass and RP-HPLC data for the title compounds.

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