CuI-Promoted One-Pot Synthesis of *N*-Boc Protected *β*-Ketotriazole Amino Acids: Application in the Synthesis of New Class of Dipeptidomimetics

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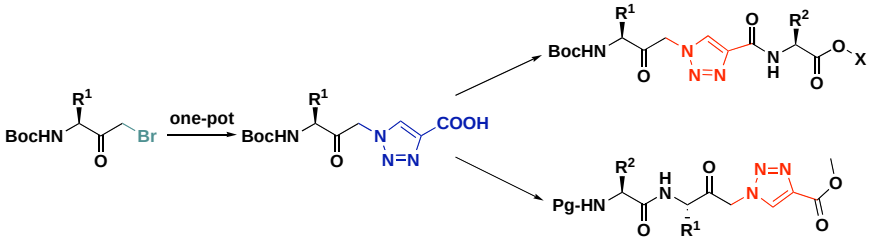
Abstract: One-pot click chemistry of N^{α}-Boc-bromomethylketones, NaN_3 and propiolic acid affords *N*-Boc protected 1,4-disubstituted 1,2,3-*β*-ketotriazole acids in good to excellent yield. The use of CuI as catalyst and DMSO as solvent leads the click reaction to efficient, practical and column-free preparation of the title compounds. The utility of the resulting unnatural amino acids as building blocks to prepare triazole possessing peptidomimetics is also delineated.



Keywords: N^{α}-Boc-bromomethylketones, one-pot click chemistry, CuI, *N*-Boc-protected 1,4-disubstituted 1,2,3 *β*-ketotriazole amino acids, peptidomimetics.

INTRODUCTION

In recent years copper source accelerated [3+2] cycloaddition of azides and alkynes has emerged as powerful tool in synthetic chemistry [1]. A wider compatibility of this protocol has led to many applications in various areas such as medicinal chemistry, surface chemistry, polymer chemistry and ligation technology for the construction of several types of mimetics [2]. 1,4-Disubstituted 1,2,3-triazoles are regarded as cis amide bond isosteres [3]. Hence, in the realm of the rapidly growing field of peptidomimetic chemistry, insertion of triazole moiety in place of a peptide bond has been found to be attractive because of potential applications as probes in biological activity and as leads for the development of peptide based drugs [4]. Apart from the use of peptidotriazoles in medicinal chemistry, there has been a wide range of literature also found concerning the peptidotriazoles in nano-sized materials [5], secondary structures such as *β*-turn mimics [6] and in self assembling peptide nanotubes [7]. In most of their reports either amino acid derived azide or acetylene has been used as unnatural linkage and their ligation under click conditions leads to construction of triazole tethered peptides.

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In spite of the great progress made towards the synthesis and application of peptide triazoles there are still unmet challenges to develop new motifs. In this regard, *β*-ketotriazoles is one such attractive functionality. *β*-Ketotriazoles have important applications in biology and medicine [8]. Vederas and Jain have prepared two examples of *N*-Boc-protected *β*-ketotriazoles which were found to be potent hepatitis A virus proteinase inhibitors [9]. The synthesis was followed through catalyst-free cycloaddition of Boc protected azidomethylketones with dimethylacetylenedicarboxylate. Franke *et al*., has discovered that *β*-ketotriazoles can be inserted into peptides by ligating protected azido-peptides to resin bound alkynes [10]. We had recently reported the step wise preparation of *N*-protected *β*-ketotriazole acids under click conditions [11].

Soon after the development of click chemistry, a one-pot procedure has also been tailored successfully to synthesize triazoles from alkyl halides. Thus, the first one pot synthesis of 1,4 disubstituted 1,2,3-triazoles had been reported by Folkin *et al*., starting from aryl and activated halides [12]. Karol Kacprzak reported the *in situ* azidation of various halides with slight excess of NaN_3 in anhydrous DMSO and then triazoles were made thereof without isolation of azides [13]. Recently, Kumar *et al*., reported an one pot synthesis of *β*-ketotriazoles under click chemistry by using polyethylene glycol as solvent [14]. In this paper we describe the one pot synthesis of *N*-Boc protected *β*-ketotriazole acids from corresponding bromomethylketones. Further, the utility of *N*-Boc-

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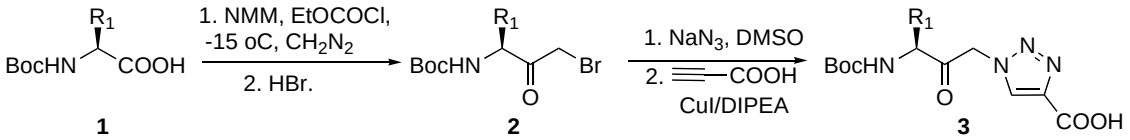


Scheme 1. One-pot synthesis of *N*-Boc-*β*-ketotriazole acids.

β-ketotriazole acids as monomeric building blocks for the construction of *β*-ketotriazole tethered peptidomimetics is also described.

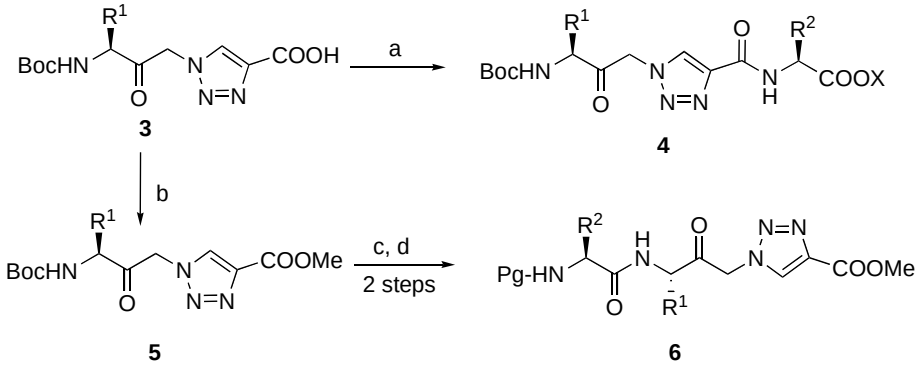
RESULTS AND DISCUSSION

The intermediates for the present study are Boc-protected bromomethylketones **2** which were prepared by following reported protocols [15]. Briefly, N^{α}-Boc-amino acids **1** were activated through mixed anhydride method, an ethereal solution of diazomethane was added and the reaction mixture was stirred for 3- 4 h. The resulting diazomethylketones were isolated after simple workup, they were further converted to bromomethylketones by a reaction with 48% HBr in THF. The *N*-Boc-bromomethylketones were isolated as stable compounds in good yields. Another important component for click chemistry was terminal acetylene, herein commercially available propiolic acid was chosen such that resulting triazole acids can be directly used as building block for the assembly of oligopeptidomimetics.

In the next step, we focused our attention on the synthesis of the title triazoles **3** (Scheme **1**). Initially we had chosen CH_3CN as solvent for one pot click chemistry. *N*-Boc-Ala-*ψ*[CH_2Br] **2b** was dissolved with CH_3CN, NaN_3 was then added. After stirring the reaction mixture for several hours, $CuSO_4.5H_2O$/NaAsc and propiolic acid were added and was further continued for another 4 hr. Interestingly, LC-MS analysis of the crude reaction revealed that NH-triazole was formed as a major product (mass obtained was 113.02 corresponds to 1H-1,2,3-triazole 4-carboxylic acid, 68%), which is a commonly expected byproduct in one-pot click chemistry and the desired product **3b** was obtained only in about 20% (mass of 397.2, was dected; Table **1**, Entry 1, 2). Thus, it has been confirmed that CH_3CN is not an appropriate solvent for one pot click chemistry.

We then sought to examine one-pot synthesis using different solvents and catalyst. It has been found that $CuSO_4.5H_2O$ and $Cu(OAc)_2$ in NaAsc yielded 67 and 73% of **3b** when *tert*-butanol was used as a solvent. The use of THF gave an improved yield of **3b** (Table **1**, Entries 3-6). Thus, variation of both solvent and catalyst significantly improved the yield. More recently, CuI was found to be effective catalyst for click chemistry. Accordingly, we then tested its efficacy in our present study. To our delight, among several solvents used (Table **1**, Entry 7-10), DMSO exhibited superior efficiency along with CuI. In a typical reaction, **2b** was dissolved in DMSO and NaN_3 was added. The completion of azidation took about one hour (as evidenced by TLC analysis), latter, propiolic acid and CuI/ DIPEA were added and stirring was continued for another one hour. Later, acidification of the crude mixture yielded **3b** in 96 %. After establishing the suitable one-pot reaction conditions, its scope and limitations were tested with *N*-Boc-bromomethylketones derived from a variety of side-chain-containing amino acids Table **2**. As shown in the Table **2**, all the products were obtained in good to excellent yield in less duration of time. Further, the IR spectrum of all the products had a strong absorption band at around 1690- 1710 cm^{-1} confirming the presence of ketone group. The ^{1}H-NMR spectrum of the product showed a distinct singlet at δ = 7.96 - 8.22 ppm for the trizolyl C_5-H proton, which confirmed the single regioisomer.

We then extended our study for the preparation of peptidomimetics **4** and **6** through *N* as well as *C*-terminal extension of **3**. Initially, the chain elongation from C-terminal was undertaken. In a typical reaction, to a solution of **3c** in dry



Reaction conditions: a = EDC/HOBt, amino acid ester, CH_2Cl_2, 0 °C, 3-4 h; b = CH_2N_2, THF, 0 °C, 2-3 h; c = TFA, CH_2Cl_2, rt, 5-6 h; d = *N*-protected *α*-amino acid, TEA, EDC/HOBt, THF, 0 °C, 3-4 h.

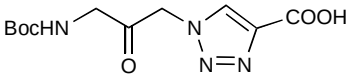
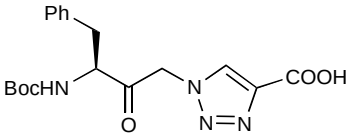
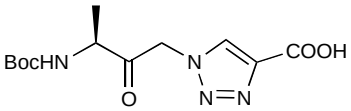
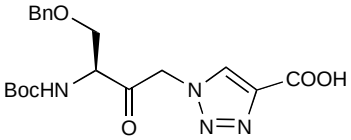
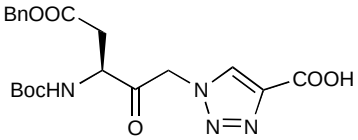
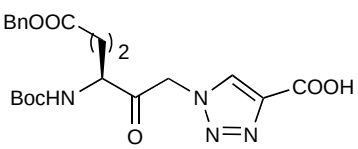
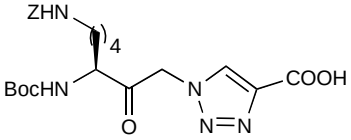
Scheme 2. Synthesis of peptidyl *β*-ketotriazole esters **5** and **6**.

Table 1. Optimization of the Click Conditions for the Synthesis of 3b **at Room Temperature**

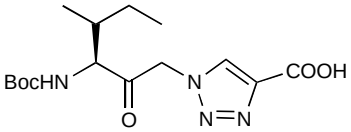
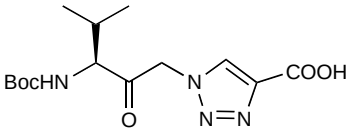
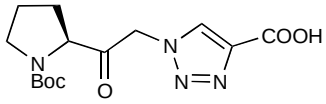
Entry	Catalyst (Equiv)[d]	Solvent[d]	Yield(%)[a,b]	Time (Hour)[c]
1	$CuSO_4.5H_2O$:NaAsc(0.2:0.4)	CH_3CN:H_2O	20	18
2	$Cu(OAc)_2$: NaAsc (0.4:0.4)	CH_3CN:H_2O	28	18
3	$CuSO_4.5H_2O$: NaAsc(0.2:0.4)	^{t}BuOH:H_2O	67	14
4	$CuSO_4.5H_2O$: NaAsc(0.2:0.5)	THF:H_2O	82	12
5	$Cu(OAc)_2$: NaAsc(0.4:0.5)	^{t}BuOH:H_2O	73	8
6	$Cu(OAc)_2$: NaAsc(0.3:0.5)	THF:H_2O	85	5
7	CuI:DIPEA(0.8:1.1)	MeOH:H_2O	49	12
8	CuI:DIPEA(1:1.5)	CH_3CN:H_2O	58	15
9	CuI:DIPEA(1.5:1.5)	THF:H_2O	88	6
10	CuI:DIPEA(2:2)	DMSO:H_2O	97	2

[a] In all the investigations only 1.0 equiv. of NaN_3 was added; [b] Yields are based on the consumption of the bromomethylketones **2**; [c] Time given for *in situ* azide formation followed by triazole synthesis; [d] equivalence of the catalyst, additive ratios.

Table 2. List of N^{α}-Boc Protected β-ketotriazoles Synthesized

Entry	Product	Yield (%)	Mp °C	HRMS $[M+Na]^+$
3a		89	113-115	307.1002
3b		91	107-108	397.1452
3c		94	133-135	321.1164
3d		86	97-99	427.1578
3e		90	104-106	455.1531
3f		79	141-143	469.1648
3g		81	139-141	512.2100

(Table 2) Contd….

Entry	Product	Yield (%)	Mp °C	HRMS $[M+Na]^+$
3h		85	119-121	363.1619
3i		90	128-130	349.1477
3j		90	122-124	347.1310

THF, EDC/HOBt were added at 0 °C. After stirring for 5 min, amino acid ester (amino acid ester hydrochloride salt was deprotonated using activated Zn dust) was added and the reaction mixture was stirred for 3 hr. Upon evaporation of the solvent, the crude product **4c** obtained was purified by column chromatography (Scheme **2**, Table **3**).

Finally, the *N*-terminal extension of **3** was carried out. *N*-Boc-*β*-ketotriazole acids were treated with diazomethane at 0 °C to afford the corresponding methyl ester in good yield. In the next step, deprotection of Boc-group of **5** was achieved using TFA at rt which was found to be complete within 4-5 h. The amino free *β*-ketotriazole esters thus obtained were directly coupled with another *N*-protected *α*-amino acid (Scheme **2**, Fig. (**1**)). The resulted peptidomimetics **6** were obtained in good yield after purification. All the new compounds prepared in this report have been fully characterized.

CONCLUSION

In conclusion we have demonstrated the potential of one-pot click chemistry as means of obtaining a series of N^{α}-Boc-protected *β*-ketotriazole acids starting from respective bromomethylketones. Application of these building blocks in the synthesis of new class of peptidomimetics is also described. CuI has been found to be efficient catalyst for one-pot click chemistry.

EXPERIMENTAL PROCEDURES

General

All solvents were freshly distilled prior to use. Amino acids and chemicals were used as received from Sigma-Aldrich Company, USA. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400S model spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX spectrometer. Mass spectra were recorded on MALDI-TOF (KRATOS) mass spectrometer. TLC analysis was carried out using the precoated silica gel G_{254} plates. Optical rotations were recorded on a Jasco P-2000 model polarimeter.

1. General Experimental Procedure for N^{α}*-Boc-amino alkyl-α'-bromomethylketones 2*

Step 1: A solution of N^{α}-Boc-amino acid (10.0 mmol) in dry THF was cooled to -25 ºC, TEA (1.1 equiv.) and ethyl chloroformate (1.1 equiv.) were added. After 15 min, freshly prepared CH_2N_2 solution in dry Et_2O was added until the yellow color of the solution persisted. The stirring was continued to 5-6 h. It was acidified with citric acid and extracted with equal volume of Et_2O. The organic phase was washed with water, saturated $NaHCO_3$ solution and brine. After evaporation of the solvent followed by recrystallization with pentane resulted diazoketones (used directly for next step).

Step 2: To the THF solution of N^{α}-Boc-aminoalkyl diazomethylketone (10.0 mmol), 45 % aqueous HBr solution (2.4 mL) was added under stirring at rt and the stirring was continued for 5 min within which disappearance of the reactant was recorded on TLC. The reaction mixture was then diluted with excess of water, the precipitated product was filtered and purified by recrystallization from THF-water.

2. General Experimental Procedure for One-pot Preparation of N^{α}*-Boc-aminoalkyl-α'-β-ketotriazole Acids 3*

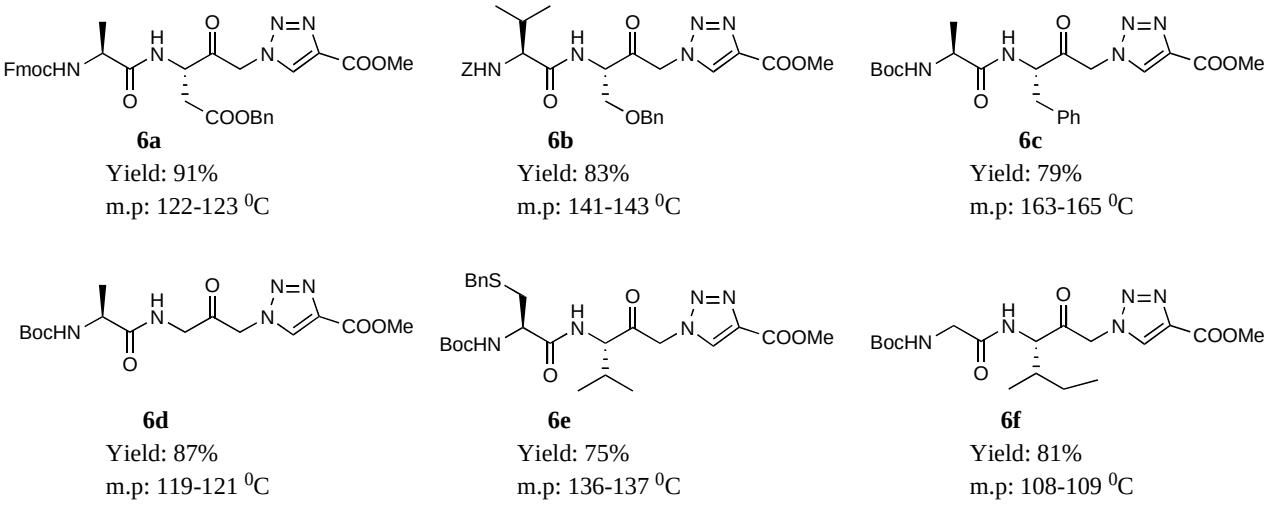
To a stirred anhydrous DMSO solution of NaN_3 (1 mL, 1 equiv.), N^{α}-Boc-aminoalkyl-*α*'-bromomethylketones (1 equiv.) was added and the stirring continued for 2-3 h. Water (2–3 mL) was added followed by DIPEA (2 equiv), alkyne (1 equiv.) and CuI (2equiv.). The resulting solution was stirred for additional 1-2 h, then acidified with citric acid solution (1N, 10 mL). The product was extracted with EtOAc (2 X 5 mL), evaporation of the solvent followed by recrystallization using THF:H_2O (0.5:0.2 mL) yielded desired triazoles as pure products.

3. General Experimental Procedure for the Synthesis of N^{α}*-Boc-β-ketotriazole Tethered Dipeptide Esters 4*

N-Boc-ketotriazole amino acid **3** (1.0 mmol) was dissolved in dry THF (5 mL), and cooled to 0 ºC, EDC (0.1 ml, 1.0 mmol), HOBt (1.1 mmol) were added to the above solution and stirred for 10 min. While maintaining the temperature, the resulting reaction mixture was treated with amino acid methyl ester (1.0 mmol) in THF solution and the reac-

Table 3. List of Dipeptidomimetics 4 Prepared

Entry	R^1	R^2	X	Yield (%)	HRMS $[M+Na]^+$	Mp °C
4a	CH_3	$CH_2CH(CH_3)_2$	Me	88	448.2151	159-160
4b	$CH_2C_6H_5$	$CH_2COOCH_2C_6H_5$	Me	79	616.2340	181-183
4c	$CH_2OCH_2C_6H_5$	$CH(CH_3)_2$	Bn	82	616.2711	138-140
4d	$CH_2CH(CH_3)_2$	C_6H_5	Bn	80	586.2623	115-117
4e	$-(CH_2)_3-$	CH_3	Et	71	446.2000	108-110



6a Yield: 91% m.p: 122-123 ^{0}C

6b Yield: 83% m.p: 141-143 ^{0}C

6c Yield: 79% m.p: 163-165 ^{0}C

6d Yield: 87% m.p: 119-121 ^{0}C

6e Yield: 75% m.p: 136-137 ^{0}C

6f Yield: 81% m.p: 108-109 ^{0}C

Fig. (1). Dipeptidomimetics **6** prepared from *N*-terminal extension of **3**.

tion mixture was allowed to stir for 6 h (monitored by TLC). The THF was evaporated under reduced pressure and the residue was taken in EtOAc (15 ml) and was washed with 5% Na_2CO_3 (2 X 10 ml), 10% citric acid (2 X 10 ml), water (2 X 10 ml) and brine (1 X 10 ml), and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure. The crude product was purified through column chromatography [eluent, $CHCl_3$:MeOH, 9:1].

4. General Experimental Procedure for the Synthesis of N^{α}-Boc-aminoalkyl-α'-β-ketotriazole Methyl Esters 5

To a solution of N^{α}-Boc-aminoalkyl-α'-*β*-ketotriazole acid **3** (1.0 mmol) in anhydrous THF (5 mL), an ethereal solution of CH_2N_2 (3.0 mmol) was added with cooling until a permanent yellow color was obtained. The mixture was stored in an ice-bath for 30 min and the excess solvent and CH_2N_2 were evoprated under reduced pressure. Crystallization of the product was completed during overnight storage at 0 °C. The mixture was filtered and the precipitate was washed with Et_2O and dried (conformation was made through only TLC and IR analysis)

5. General Experimental Procedure for the Preparation of N^{α}-Boc-aminoalkyl-α'-β-ketotriazole Methyl Esters 6:

Step 1: A solution of **5** (1.0 mmol) in anhydrous DCM (5.0 mL) and TFA (10 mL) were stirred for 3-4 hr at rt. After complete deprotection (TLC analysis), the solvent and excess TFA were removed completely by repeated co-evaporation with DCM. The resulting residue was recrystallized using EtOH/water. The resulting products were directly used in the subsequent study.

Step 2: *N*-Protected amino acid (1.0 mmol) was dissolved in dry THF (5 mL), and cooled to 0 ºC, EDC (0.1 ml, 1.0 mmol), HOBt (1.1 mmol) were added and stirred for 10 min. The TFA salt of triazole ester prepared through step (1.0 mmol), and TEA (1.0 mmol) were added and the reaction mixture was allowed to stir for 3-4 h (monitored by TLC). The THF was evaporated under reduced pressure and the residue was taken in EtOAc (15 ml) and was washed with 5% Na_2CO_3 (2 X 10 ml), 10% citric acid (2 X 10 ml), water (2 X 10 ml) and brine (1 X 10 ml), and dried over anhydrous sodium sulfate. The crude product was purified through column chromatography[eluent, $CHCl_3$:MeOH, 8:2].

Spectroscopic Characterization Data

3a: IR (KBr): 1591, 1698, 1725, 2900 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 9H), 3.96 (d, 2H, *J* = 2.8 Hz), 4.18 (s, 2H), 6.18 (s, br, 1H), 8.01 (s, 1H), 10.23 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 27.8, 48.9, 59.5, 78.9, 124.4, 140.2, 155.2, 166.9, 205.8.

3b: IR (KBr): 1548, 1657, 1734, 2987 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 9H), 2.96-3.11 (m, 2H), 4.59

(m, 1H), 4.20 (s, 2H), 6.55 (s, br, 1H), 6.98-7.22 (m, 5H), 8.05 (s, 1H), 10.11 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 27.6, 34.8, 57.9, 62.6, 78.8, 119.8, 123.6, 124.8, 128.6, 138.4, 140.4, 155.5, 166.6, 206.2.

3c: IR (KBr): 1497, 1690, 1741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 9H), 1.34 (d, 3H, *J* = 3.8 Hz), 4.43-4.61 (m, 1H), 4.19 (s, 2H), 6.8 (s, br, 1H), 8.0 (s, 1H), 10.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8, 27.6, 55.5, 57.6, 78.5, 124.8, 140.1, 155.2, 166.3, 205.6.

3d: IR (KBr): 1498, 1687, 1731, 2901 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 9H), 3.14-3.44 (m, 2H), 3.91 (s, 2H), 4.32-4.44 (m, 1H), 4.58 (s, 1H), 6.12 (s, br, 1H), 6.89-7.12 (m, 5H), 8.04 (s, 1H), 10.11 (s, br,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9, 28.0, 57.6, 60.9, 67.0, 72.1, 78.8, 119.8, 123.4, 124.5, 127.6, 135.1, 140.1, 155.6, 166.8, 206.1

3e: IR (KBr): 1550, 1699, 1745, 2984 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 9H), 2.22-2.34 (m, 2H), 4.41 (s, 2H), 4.48 (s, 2H), 4.91-4.94 (m, 1H), 5.96 (s, br, 1H), 6.59-7.22 (m, 5H), 8.01 (s, 1H), 10.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 27.9, 34.5, 55.6, 57.8, 67.6, 78.8, 121.2, 124.5, 125.8, 128.6, 139.2, 140.0, 155.1, 165.2, 171.1, 205.2.

3f: IR (KBr): 1547, 1686, 1751, 3101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.12-2.35 (m, 4H), 4.31 (d, 1H, *J* = 5.2 Hz), 4.66 (s, 1H), 5.01 (s, 2H), 6.11 (s, br, 1H), 6.96-7.22 (m, 5H), 8.11 (s, 1H), 10.12 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 27.9, 28.0, 28.2, 55.6, 60.0, 67.6, 78.8, 119.2, 124.4, 127.6, 128.0, 139.8, 140.0, 155.6, 168.3, 172.1, 206.1.

3g: IR (KBr): 1534, 1691, 1735, 3000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 9H), 1.34-2.01 (m, 6H), 2.91 (t, 2H, *J* = 6.9 Hz), 4.32 (t, 1H, *J* = 3.6 Hz), 4.71 (s, 2H), 5.01 (s, 2H), 6.29-6.32 (s, br, 2H), 6.96-7.32 (m, 5H), 8.10 (s, 1H), 10.55 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 28.3, 28.5, 29.0, 29.5, 40.1, 57.6, 64.5, 64.2, 78.2, 124.2, 126.2, 127.8, 128.2, 139.5, 140.2, 155.5, 155.6, 166.1, 206.0.

3h: IR (KBr): 1591, 1688, 1761, 2967 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, 3H, *J* = 2.9 Hz), 1.03 (d, 3H, *J* = 5.9 Hz), 1.11-1.28 (m, 2H), 1.31 (s, 9H), 2.46-2.51 (m, 1H), 4.12 (d, 1H, *J* = 2.9 Hz), 4.85 (s, 2H), 6.11 (s, br, 1H), 7.96 (s, 1H), 10.21 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8, 14.5, 24.5, 28.5, 33.1, 55.6, 60.1, 77.9, 124.8, 139.9, 155.5, 166.1, 206.5.

3i: IR (KBr): 1499, 1698, 1721, 3102 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, 6H, *J* = 7.1 Hz), 1.31 (s, 9H), 2.55-2.61 (m, 1H), 4.11 (d, 1H, *J* = 5.4 Hz), 4.55 (s, 2H), 6.11 (s, br, 1H), 7.98 (s, 1H), 10.11 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 17.3, 27.3, 27.6, 28.0, 57.8, 64.2, 78.5, 124.5, 139.5, 155.1, 165.6, 205.1; ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 17.0, 27.5, 27.8, 28.0, 57.1, 65.6, 79.2, 124.8, 130.2, 155.6, 165.6, 205.1.

3j: IR (KBr): 1459, 1656, 1721, 2998 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 9H), 1.55-1.91 (m, 4H), 3.11 (dd, 2H, *J* = 3.6, 5.9 Hz), 4.00 (dd, 1H, *J* = 2.9, 7.6 Hz), 4.41 (s, 2H), 8.04 (s, 1H), 10.22 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 25.8, 27.4, 27.8, 46.6, 57.9, 64.1, 78.8, 124.5, 139.2, 155.6, 166.1, 205.6.

4a: IR (KBr): 1487, 1540, 1645, 1740, 1755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 6H, *J* = 5.6 Hz), 1.12 (d, 3H, *J* = 3.2 Hz), 1.31 (s, 9H), 1.56-1.61 (m, 1H), 1.72-1.75 (m, 2H), 3.55 (s, 3H), 4.25 (t, 1H, *J* = 7.6 Hz), 4.35-4.38 (m, 1H), 4.75 (s, 2H), 5.65 (s, br, 1H), 6.11 (s, br, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 21.5, 22.0, 27.9, 39.5, 48.7, 50.9, 56.4, 57.1, 78.0, 130.8, 142.9, 155.0, 160.1, 171.2, 207.1.

4b: IR (KBr): 1435, 1602, 1734, 1765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 9H), 2.25-2.41 (m, 2H), 2.91-3.05 (m, 2H), 3.55 (s, 3H), 4.73-4.76 (m, 1H), 4.81 (s, 2H), 4.96-5.02 (m, 1H), 5.22 (s, 2H), 6.11 (s, br, 1H), 6.41 (s, br, 1H),7.01-7.22 (m, 10H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 34.2, 35.9, 47.5, 51.1, 57.1, 63.5, 67.4, 78.1, 123.3, 124.6, 127.4, 128.8, 129.0, 130.4, 137.9, 140.5, 142.0, 155.1, 160.2, 171.0, 172.5, 205.8.

4c: IR (KBr): 1498, 1548, 1687, 1730, 1767 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 6H, *J* = 4.9 Hz), 1.31 (s, 9H), 2.91-2.98 (m, 1H), 3.55-3.67 (m, 2H), 4.11 (d, 1H, *J* = 7.2 Hz), 4.32 (s, 2H), 4.41-4.48 (m, 1H), 4.75 (s, 2H), 5.06 (s, 2H), 5.85 (s, br, 1H), 6.11 (s, br, 1H), 7.03-7.25 (m, 10H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 27.9, 29.4, 54.1, 56.7, 60.9, 65.1, 67.4, 73.5, 78.1, 125.8, 127.2, 127.8, 128.5, 130.4, 135.5, 140.5, 142.8, 155.1, 159.6, 170.1, 205.9.

4d: IR (KBr): 1411, 1547, 1682, 1711, 1778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, 6H, *J* = 5.9 Hz), 1.31 (s, 9H), 1.45-1.49 (m, 1H), 1.51-1.59 (m, 1H), 3.55 (s, 3H), 4.32 (d, 1H, *J* = 5.4 Hz), 4.58 (s, 2H), 5.13 (s, 1H), 5.98 (s, br, 1H), 6.11 (s, br, 1H), 7.01-7.28 (m, 5H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 21.5, 27.4, 37.1, 50.2, 53.7, 56.9, 58.1, 78.1, 125.4, 127.5, 128.7, 129.1, 130.0, 133.6, 142.1, 156.4, 160.9, 170.7, 206.2.

4e: IR (KBr): 1411, 1607, 1721, 1734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (t, 3H, *J* = 5.1 Hz), 1.24 (s, 9H), 1.32 (d, 3H, *J* = 7.1 Hz), 1.43-1.65 (m, 4H), 3.11-3.18 (m, 2H), 4.01-4.09 (m, 1H), 4.13-4.17 (m, 1H), 4.28-4.32 (m, 1H), 4.45 (s, 2H), 6.19 (s, br, 1H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 17.1, 21.1, 27.2, 28.1, 45.6, 47.2, 58.0, 60.4, 64.4, 78.0, 130.5, 142.2, 155.4, 160.2, 171.2, 205.2.

6a: IR (KBr): 1439, 1691, 1733, 1741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, 3H, *J* = 5.6 Hz), 2.35-2.56 (m, 2H), 3.56 (s, 3H), 4.32 (t, 1H, *J* = 3.6 Hz), 4.46 (d, 2H, *J* = 7.2 Hz), 4.51-4.55 (m, 1H), 4.67 (s, 2H), 4.91-4.96 (m, 1H), 5.26 (s, 2H), 6.12 (s, br, 1H), 6.58 (s, br, 1H), 7.03-7.58 (m, 13H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0, 34.6, 45.8, 49.4, 50.1, 55.0, 58.2, 65.9, 67.3, 119.6, 121.3, 124.5, 124.9, 127.3, 127.5, 128.0, 128.2, 129.0, 139.4, 140.0, 140.5, 140.9, 142.3, 155.8, 165.7, 170.1, 171.8, 205.6.

6b: IR (KBr): 1547, 1690, 1722, 1747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (d, 6H, *J* = 4.9 Hz), 2.59-2.61 (1H, m), 3.58 (s, 3H), 3.88 (dd, 1H, *J* = 3.6, 2.1 Hz), 3.91 (dd, 1H, *J* = 6.5, 3.1 Hz), 4.18 (d, 1H, *J* = 4.9 Hz), 4.46-4.52 (m, 1H), 4.52 (s, 2H), 4.79 (s, 1H), 5.32 (s, 2H), 6.11 (s, br, 1H), 6.23 (s, br, 1H), 6.98-7.20 (m, 10H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 30.2, 50.8, 56.4, 59.1, 60.4, 64.7, 66.1, 73.1, 120.7, 121.8, 124.5, 127.9, 128.8, 137.7, 139.3, 140.2, 155.2, 166.1, 170.0, 206.5.

6c: IR (KBr): 1415, 1678, 1704, 1767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9H), 1.41 (d, 3H, *J* = 3.2 Hz), 2.91-3.08 (m, 2H), 3.55 (s, 3H), 4.65-4.69 (m, 1H), 4.79-4.81 (m, 1H), 4.91 (s, 2H), 6.66 (s, br, 1H), 6.81 (s, br, 1H), 8.21 (s, 1H),7.11-7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 27.9, 34.1, 49.6, 50.8, 57.4, 60.3, 78.4, 124.8, 126.5, 127.8, 128.0, 138.2, 139.2, 155.2, 165.2, 170.2, 206.6.

6d: IR (KBr): 1511, 1690, 1711, 1768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (d, 3H, *J* = 3.9 Hz), 1.40 (s, 9H), 3.65 (s, 3H), 4.45 (s, 2H), 4.34-4.41 (m, 1H), 4.91 (s, 2H), 6.65 (s, br, 1H), 6.72 (s, br, 1H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 27.4, 28.1, 47.6, 50.2, 51.3, 59.4, 78.2, 124.4, 139.5, 155.2, 170.1, 166.5, 205.5.

6e: IR (KBr): 1467, 1511, 1677, 1719, 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 6H, *J* = 7.2 Hz), 1.34 (s, 9H), 2.58-2.61 (m, 1H), 2.91-3.12 (m, 2H), 3.55 (s, 2H), 3.59 (s, 3H), 4.31 (d, 1H, *J* = 2.9 Hz), 4.78 (s, 2H), 5.96 (s, br, 1H), 6.11 (s, br, 1H), 7.12-7.22 (m, 5H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 27.8, 28.1, 32.6, 37.9, 50.5, 54.2, 57.6, 62.6, 78.4, 124.5, 127.2, 128.4, 136.8, 139.1, 155.1, 166.7, 170.4, 205.8.

6f: IR (KBr): 1134, 1545, 1678, 1752, 1770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.87 (t, 3H, *J* = 5.8 Hz), 1.02 (d, 3H, *J* = 7.1 Hz), 1.12-1.16 (m, 2H), 1.34 (s, 9H), 2.45-2.51 (m, 1H), 3.45 (s, 2H), 3.51 (s, 3H), 4.13 (d, J = 6.2 Hz, 1H), 4.59 (s, 2H), 5.95 (s, br, 1H), 6.12 (s, br, 1H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5, 14.8, 25.1, 27.9, 33.9, 44.6, 51.0, 55.9, 60.1, 78.6, 124.8, 139.7, 155.4, 166.4, 170.8, 208.1.

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