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Preparation and Synthetic Applications of Sterically Hindered Secondary Amines

Hwa-Ok Kim [a], Brian Carroll [a] & Min S. Lee [a]
[a] Molecumetics, 2023 120th Ave. N.E., Suite 400, Bellevue, WA, 98005-2199
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SYNTHETIC COMMUNICATIONS, 27(14), 2505-2515 (1997)

PREPARATION AND SYNTHETIC APPLICATIONS OF STERICALLY HINDERED SECONDARY AMINES

Hwa-Ok Kim*, Brian Carroll and Min S. Lee

Molecumetics, 2023 120th Ave. N.E., Suite 400, Bellevue, WA 98005-2199

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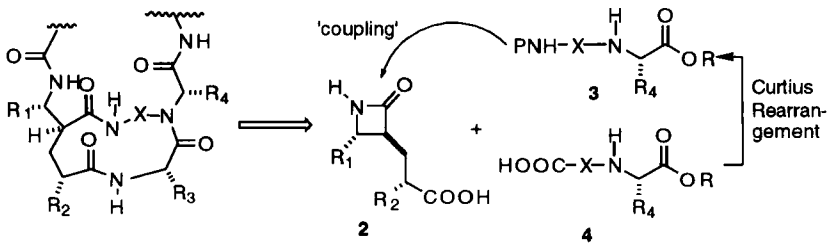
Abstract: The preparation of sterically hindered secondary amino esters from the reaction of N-protected α-amino aldehydes and 3-, or 2-oxo esters with α-amino esters by reductive amination is described. The resulting amino esters were converted to the β-lactam or acylated to form N-acyl secondary amides.

In the course of our continuing program in the area of peptide secondary structure mimetics, and in particular the generation of β-turn template **1**,[1] we required efficacious routes to β-lactams of type **2** as well as secondary amines of type **3** and **4**. We envisioned that the key intermediates in the synthesis could be accessed by reductive amination of readily available precursors.



1: **X** = $C(Me)_2CH_2$, $C(c\text{-propyl})CH_2$, CH_2

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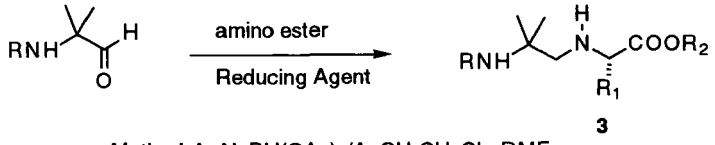
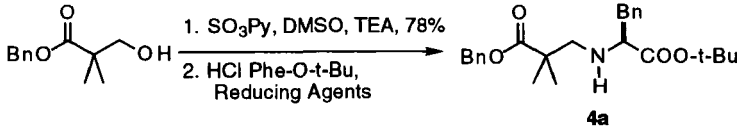
Although a variety of reductive amination methods were available,[2] we chose to investigate two methods; namely, $NaBH(OAc)_3$[3] and $ZnCl_2$ mediated $NaBH_3CN$[4] (Eq.1). The results of reductive amination of N-protected α-methylalanal[5] or alanal with representative α-amino esters are listed in Table 1. While all the cases studied showed moderate to high chemical yields, method A ($NaBH(OAc)_3$) provided slightly lower chemical yields than method B ($NaBH_3CN/ZnCl_2$). In addition, not only simple α-amino esters but dipeptide esters were also examined and afforded good yields (Entry 3 in Table 1).



(1)

Method A: $NaBH(OAc)_3/AcOH, CH_2Cl_2$, DMF.
Method B: $NaBH_3CN$, $ZnCl_2$, MeOH.

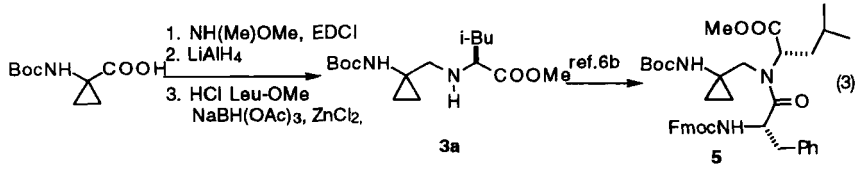
These protocols were also applicable to the synthesis of β-amino esters of type **4a** (Eq. 2 and Table 2). Ketone was also converted to the desired secondary amino ester in good yield using this procedure (Entry 3 in Table 2).



(2)

Method A: $NaBH(OAc)_3/AcOH, CH_2Cl_2$, DMF.
Method B: $NaBH_3CN$, $ZnCl_2$, MeOH.

To explore the scope of these methods,[6] we synthesized the cyclopropane substituted secondary amine **3a** from 1-N-Boc-aminocyclopropane-1-carboxylic acid and acylated it to prepare **5** (Eq.3). In this case, however, a combination of $NaBH(OAc)_3/ZnCl_2$ was employed for the reductive amination.



(3)

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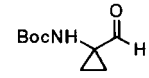
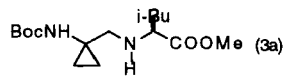
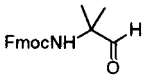
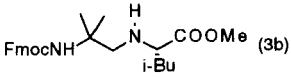
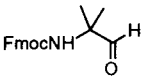
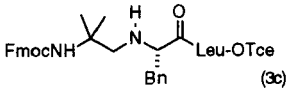
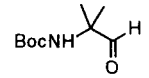
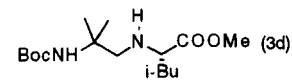
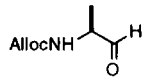
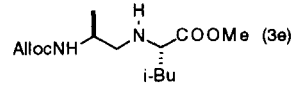
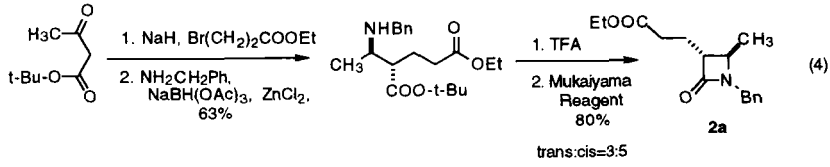
Table 1. Reductive Amination of N-Protected Amino Aldehyde with α-Amino Ester

	Aldehyde	α-Amino Ester	Method[a]	Product	Yield(%)[b]
1.		HCl Leu-OMe	B	 (3a)	69
2.		HCl Leu-OMe	B	 (3b)	80
3.		TFA Phe-Leu-OTce	A	 (3c)	53
4.		HCl Leu-OMe	B	 (3d)	73
5.		TsOH Leu-OTce	B	 (3e)	59[c]

a) Method A: $NaBH(OAc)_3$, AcOH, DMF, 1,2-dichloroethane, RT. Method B: $NaBH_3CN$, 0.5 eq. $ZnCl_2$, MeOH, RT. b) Yields are purified by flash chromatography. c) Stereochemical ratio was 5:1 and transesterification by MeOH had occurred.

We also prepared β-lactam **2a** in good overall yield by a sequence of reactions that includes alkylation of *tert*-butyl acetoacetate with ethyl bromoacetate, reductive amination with benzyl amine and Mukaiyama cyclization (Eq.4).[7]



(4)

In summary, we have described a series of efficient reductive amination reactions to synthesize sterically hindered secondary amines **3** and related compounds **4** in good yields. The reductive aminations employed in the present study were effective and useful for the synthesis of key intermediates for constrained peptide secondary structure mimetics. Further study toward the utility of these linkers are in progress and will be reported in due course.

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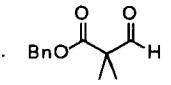
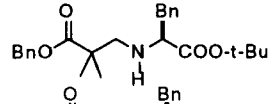
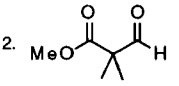
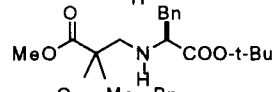
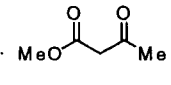
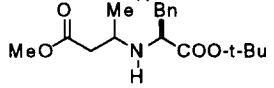
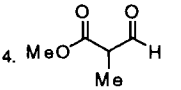
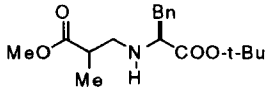
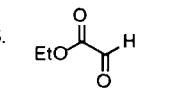
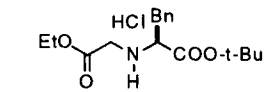
Table 2. Reductive Amination of 3-Oxo Esters with α-Amino Ester

	Aldehyde/ketone	α-Amino Ester	Method[a]	Product	Yield(%)[b]
1.		HCl Phe-O-t-Bu	A	 (4a)	33[c]
			B		71[c]
2.		HCl Phe-O-t-Bu	A	 (4b)	48
3.		HCl Phe-O-t-Bu	B	 (4c)	75
4.		HCl Phe-O-t-Bu	B	 (4d)	39[c]
5.		HCl Phe-O-t-Bu	B	 (4e)	62
			C		40

a) Method A: $NaBH(OAc)_3$, AcOH, DMF, 1,2-dichloroethane, RT. Method B: $NaBH_3CN$, 0.5 eq. $ZnCl_2$, MeOH, RT. Method C: $NaBH(OAc)_3$, $ZnCl_2$, MeOH, RT. b) Yields reported are for purified compounds by flash chromatography. c) Two steps yield from alcohols.

EXPERIMENTAL SECTION

THF was distilled from sodium benzophenone ketyl prior to use. Dichloromethane was distilled from CaH_2. ^1H and ^{13}C NMR were recorded with Varian Unity 500 MHz spectrometer. TLC was performed on silica gel 60 F_{254} plates and visualiazed by UV irradiation, iodine vaper and/or PMA solution. Flash column chormatography was performed using silica gel (230-400 mesh).

General Procedure for Reductive Amination:

Method A: To a stirred solution of aldehyde or ketone (1 eq.) with amino ester (1.1 eq.) and acetic acid (20 eq.) in dichloromethane (0.1M) was added $NaBH(OAc)_3$ (3 eq.) at room temperature. Reaction was stirred at the same temperature overnight. After concentration, the residue was taken up into sat. $NaHCO_3$ and neutralized by solid NaOH (pH 7). The resulting aqueous phase was extracted with ethyl acetate. Combined extracts were washed with brine, dried, passed through a short pad of silica gel to provide an oil. DMF was used as a co-solvent depending on the solubility.

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Method B: To a stirred slurry of aldehyde or ketone (1 eq.) with amino ester (1.1 eq.) in MeOH was added dropwise a solution of $ZnCl_2$ (0.6eq.) and $NaBH_3CN$ (1.2 eq.) in MeOH (Total concentration 0.2M) over 5 min at rt. The resulting solution was stirred at rt overnight. After concentration, the residue was taken up in EtOAc, washed with sat. $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic phase and extract were washed with brine, dried, passed through a short pad of SiO_2, and concentrated to provide an oil.

Method C: To a stirred solution of aldehyde (1 eq.) with amino ester (1.1 eq.) in CH_2Cl_2 (0.1M) was added $ZnCl_2$ (1.5 eq.), followed by $NaBH(OAc)_3$ (3 eq.) at rt. The white suspension was stirred at rt overnight. After concentration, the residue was taken up in sat. $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were washed with brine, dried, and passed through a short pad of SiO_2 to provide an oil.

Spectral and Analytical Data. All crude products were purified by chromatogrpahy using indicated solvents system and resulting products were analytically pure enough. Some of compound **4** were analyzed after hydrolysis to form carboxylic acids.

3a: Method B. 2.9 mmol of aldehyde was used and crude product was purified by flash chromatography (hexane:EtOAc = 90:10 to 80:20 to 70:30) to provide an oil (69%): R_f 0.46 (hexane:EtOAc = 60:40); ^{1}H NMR ($CDCl_3$) δ 0.6-0.9 (set of m, 4H, -C*H*$_2$C*H*$_2$-), 0.92 (two d, 6H, *J*=6.5Hz, $CH_2CH(CH_3)_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.46 (m, 2H, C*H*$_2$CH(CH$_3$)$_2$), 1.76 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 2.45 (d, 1H, *J*=12.5Hz, NHC*H*$_2$-), 2.82 (m, 1H, NHC*H*$_2$-), 3.26 (t, 1H, *J*=7Hz, α of Leu), 3.70 (s, 3H, OCH_3), 5.10 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 12.2, 22.1, 22.7, 24.8, 28.3, 33.1, 42.8, 51.5, 54.0, 59.8, 79.1, 155.7, 176.7; MS CI(NH_3) m/z 315.2 ($M+H^+$).

3b: Method B. 3 mmol of aldehyde was used and crude product was purified by flash chromatography (hexane:EtOAc = 90:10 to 80:20 to 70:30) to provide an oil (80%): R_f 0.50 (hexane:EtOAc = 70:30); ^{1}H NMR ($CDCl_3$) δ 0.90 (two d, 6H, *J* =7 Hz, CH(C*H*$_3$)$_2$), 1.2-2.0 (set of m, 9H, C(C*H*$_3$)$_2$, C*H*$_2$C*H*(CH$_3$)$_2$), 2.40 (br, 1H, NHCH$_2$), 2.70 (br, 1H, NHCH$_2$), 3.15 (br, 1H, CHCOOC*H*$_3$), 3.77(s, 3H, OCH_3), 4.20 (m, 1H, C*H*CH$_2$OOC-), 4.30 (br, 2H, CHC*H*$_2$OOC-), 5.60 (br, 1H, NH), 7.2-7.8 (m, 8H, aromatic H's); MS CI(NH_3) m/z 439.4 ($M+H^+$).

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3c: Method A. 10 mmol of aldehyde was used and crude product was purified by flash chromatography (hexane:EtOAc = 90:10 to 80:20) to provide a foamy solid (53%): R_f 0.39 (hexane:EtOAc = 60:40); ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 6H, *J*=6Hz, $CH_2CH(CH_3)_2$), 1.30 (m, 6H), 1.6-1.8 (set of m, 3H, $CH_2CH(CH_3)_2$), 2.80 (br m 2H, CH_2), 3.20 (br, 1H, CH_2), 3.40 (br, 1H, CH_2), 4.12 (t, 1H, *J*=7.5Hz, CH), 4.20 (br, 1H, CH), 4.30 (t, 2H, CH2), 4.63 (d, 1H, *J*=12Hz, CH_2CCl_3), 4.75 (m, 1H, CH), 4.87 (d, 1H, *J*=12Hz, CH_2CCl_3), 7.2-7.8 (set of m, 13H, aromatic H's); ^{13}C NMR ($CDCl_3$) δ 21.7, 22.8, 24.9, 25.5, 25.8, 38.9, 41.0, 47.2, 50.2, 53.0, 56.7, 64.1, 66.1, 74.3, 94.5, 119.9, 124.9, 127.0, 127.0, 127.3, 127.6, 128.4, 128.7, 129.0, 137.0, 141.2, 143.9, 171.6; MS ES$^+$ m/z 702.1, 704.1 ($M+H^+$).

3d: Method B. 6 mmol of aldehyde was used and crude product was purified by flash chromatography (hexane:EtOAc = 90:10 to 80:20 to 70:30) to provide a colorless oil (73%): R_f 0.63 (hexane:EtOAc = 70:30); ^{1}H NMR ($CDCl_3$) δ 0.92 (two d, 6H, *J*=6.5Hz, $CH(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.43 (collapsed, 3H, CH_2CH-), 1.75 (m, 1H, $CH(CH_3)_2$), 2.40 (br, 1H, NCH_2), 2.64 (d, 1H, *J*=12Hz, NCH_2), 3.23 (m, 1H, $CHCOOCH_3$), 3.71 (s, 3H, OCH_3), 5.05 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 22.0, 22.7, 24.6, 25.1, 25.6, 28.4, 42.6, 51.5, 52.1, 57.2, 60.4, 78.5, 154.8, 176.2; MS CI(NH_3) m/z 317.4 ($M+H^+$).

3e: Method B. 7 mmol of aldehyde and 8 mmol of TsOH·Leu-OTce were used and crude transesterifed product was purified by flash chromatography (hexane:EtOAc = 90:10 to 80:20 to 70:30 to 60:40) to provide an oil (59%): R_f 0.23 (hexane:EtOAc = 70:30); ^{1}H NMR ($CDCl_3$) δ 0.91 (two d , 6H, *J*=6.5 Hz, $CH_2CH(CH_3)_2$), 1.15 (d, 3H, *J*=6.5 Hz, $CHCH_3$), 1.45 (m, 2H, $CH_2CH(CH_3)_2$), 1.70 (br, 1H, NH), 1.73 (m, 1H, CH_2 $CH(CH_3)_2$), 2.41 (dd, 1H, A of ABX, *J*=6,12 Hz, $NHCH(CH_3)CH_2NH$-), 2.69 (dd, 1H, B of ABX, *J*=5, 12 Hz, $NHCH(CH_3)CH_2NH$-), 3.25 (t, 1H, *J*=7.5 Hz, NHC*H* in Leu), 3.71 (collapsed s, 4H, OCH_3 and X of ABX, $NHCH(CH_3)CH_2NH$-), 4.54 (d, 2H, *J*=5 Hz, CH_2=$CHCH_2$-), 4.90 (br, 1H, NH), 5.20 (dt, 1H, *J*=1.5, 10.5 Hz, CH_2=$CHCH_2$-), 5.30 (dt, 1H, *J*=1.5, 17 Hz, CH_2=$CHCH_2$-), 5.91 (m, 1H, CH_2=$CHCH_2$-); ^{13}C NMR ($CDCl_3$) δ 18.8, 22.1, 22.7, 24.8, 42.4, 47.0, 41.6, 52.6, 60.0, 62.2, 117.4, 132.9, 155.8, 176.1; MS EI m/z 287.3 ($M+H^+$).

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4a: Method A. Amino alcohol was oxidized (SO_3/pyridine, DMSO) and the crude aldehyde (6.5 mmol) was used for reductive amination. The crude product was purified by flash chromatography (hexane:EtOAc = 95:5 to 90:10 to 80:20) to provide a colorless oil (33%): ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 6H, CMe_2), 1.34 (s, 9H, $OCMe_3$), 1.58 (brs, 1H, NH), 2.52 (d, 1H), 2.7-2.9 (set of m, 3H), 3.28 (m, 1H), 5.04 (ABq, 2H, CH_2Ph), 7.1-7.4 (m, 10H, phenyls): MS EI m/z 412.0 ($M+H^+$).

Further identification was performed by hydrogenolysis of benzyl ester to carboxylic acid as following: To a stirred solution of above benzyl *t*-butyl ester (860 mg, 2.1 mmol) with 10% Pd/C (900 mg) in absolute EtOH (20 mL) was added 1,4-cyclohexadiene (0.94 mL, 10 mmol) at rt. Within less than an hour, the reaction was completed (TLC monitoring). After filtration through a short pad of SiO_2 by aid of EtOAc (50 mL), the filtrate was concentrated to provide a white solid in almost quantitative yield (690 mg). ^{1}H NMR ($CDCl_3$) δ 1.11 and 1.19 (two s, 6H, CMe_2) 1.42 (s, 9H, $OCMe_3$), 2.45 (d, 1H, *J*=12.0 Hz), 2.76 (d, 1H, *J*=12.5 Hz), 3.00 (m, 2H), 3.46 (m, 1H), 7.1-7.6 (m, 5H, phenyl): MS CI(isobutene) m/z 322.4 ($M+H^+$). Above solid (480 mg) was then taken up in 6N HCl (10 mL) in H_2O (50 mL) and extracted with EtOAc (2x10 mL). The combined extracts were dried (Na_2SO_4), concentrated to give a foamy solid (280 mg). HCl salt: ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H, $OCMe_3$), 1.36 and 1.58 (two s, 6H, CMe_2), 3.03 (ABq, 2H), 3.27 (dd, 1H, *J*=13.5, 11 Hz), 4.05 (m, 2H), 7.30 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 24.3, 24.4, 27.7, 36.3, 40.7, 54.0, 63.0, 84.4, 127.4, 128.6, 129.7, 134.7, 167.3, 179.9; MS EI m/z 322.3 ($M+H^+$).

Method B: 6.7 mmol of amino alcohol was oxidized (SO_3/pyridine, DMSO) and the crude aldehyde was used for reductive amination. The crude product was purified by flash chromatography (hexane:EtOAc = 95:5 to 90:10 to 80:20) to provide a colorless oil (71% for two steps): R_f 0.65 (hexane:EtOAc = 80:20).All spectral data were in good agreement with an authentic sample.

4b: Method A. Amino alcohol was oxidized (SO_3/pyridine, DMSO) and the crude aldehyde (5 mmol) was used for reductive amination (48%, oil). The crude product was pure enough for the next reaction: R_f 0.40 (hexane:EtOAc = 80:20); ^{1}H NMR (CD_3OD) δ 1.14 (s, 6H, $C(CH_3)_2$), 1.37 (s, 9H, $OC(CH_3)_3$), 1.58 (br, 1H, NH), 2.46 (br d, 1H, *J*=10 Hz), 2.74 (d, 1H, *J*=11.5 Hz), 2.84 (m, 2H), 3.29 (m, 1H), 3.59 (s, 3H, OCH_3), 7.1-7.3 (m, 5H, phenyl).

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Further identification was performed by hydrolysis of methyl ester to carboxylic acid as following: To a stirred solution of above methyl t-butyl diester (750 mg, 2.23 mmol) in MeOH/ THF/H_2O (20/20/20 mL) was added $LiOH{\cdot}H_2O$ (200 mg) at room temperature. The resulting solution was stirred for 30 min. After removal of most of organic solvent, the aqueous phase was washed with ethyl ether (50 mL), acidified with 6N HCl (pH @ 2), extracted with ethyl acetate (2 x 100 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), concentrated to give a foamy solid (310 mg). Low yield was likely due to incompletion of the reaction. Thus, above etheral washing was concentrated to give an oil, which was then dissolved in THF/H_2O(20/20 mL). To this stirred solution was added $LiOH{\cdot}H_2O$ (300 mg) and stirred at room temperature overnight. After washing with ethylether (30 mL), aqueous phase was acidified by 6N HCl (pH 1), extracted with ethyl acetate (2x50 mL). Combined extracts were dried (Na_2SO_4), and concentrated to provide a foamy solid (250 mg). Overall yield was then 78%. All spectral data were in good agreement with an authentic sample as above.

4c: Method B. 3.0 mmol of ketone was used and the crude product was analyzed by NMR to show 1.5:1 ratio of diastereomeric mixtue and purified by flash chromatography (hexane:EtOAc = 95:5 to 90:10 to 80:20 to 70:30) to provide an oil (75%); R_f 0.45 (hexane:EtOAc = 60:40); ^{1}H NMR ($CDCl_3$) δ 1.07 and 1.10 (two d, 3H, *J*= 6Hz, $CHCH_3$, ratio 1:1), 1.33 (s, 9H, $OC(CH_3)_3$), 2.2-2.4 (set of m, 2H, $(O{=})CCH_2$), 2.8-2.9 (set of m, 2H, CH_2Ph), 3.05 (m, 1H, $CH_2CH(CH_3)$-), 3.48 (two t, 1H, *J*= 8.5 Hz, CH_2Ph), 3.61 and 3.66 (two s, 3H, OCH_3), 7.2-7.4 (m, 5H, phenyl); MS EI m/z 322.3 ($M+H^+$).

Further identification was performed by hydrolysis of methyl ester to carboxylic acid as following: To a stirred solution of above methyl t-butyl diester (710 mg, 2.2 mmol) in THF/H_2O (20/20 mL) was added $LiOH{\cdot}H_2O$ (210 mg, 5 mmol) at rt. The resulting solution was stirred at rt overnight. After washing with Et_2O (50 mL), the remained aqueous phase was acidified by 6N HCl (@ pH 6), extracted with EtOAc (3x 100mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), concentrated to provide a foamy solid (630 mg, 93 %). ^{1}H NMR ($CDCl_3$) δ 1.21 and 1.28 (two s, 3H, *J*=6.5 Hz, $CHCH_3$), 1.35 and 1.39 (two s, 9H, $OC(CH_3)_3$), 2.26 (dd, 0.5H, *J*=5, 20 Hz), 2.57 (dt, 1H, *J*=3, 17.5 Hz), 2.80 (m, 0.5 H), 3.03 (m, 1H), 3.25 (dd and m, 2H), 3.56 (t, 1H, *J*=8.5 Hz), 3.85 (t, 1H, *J*=8.5 Hz), 7.2-7.4 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 16.72(18.92),

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27.77, 37.65 (38.18), 39.33 (38.46), 50.22(50.62), 59.03 (60.14), 83.66(83.35), 127.37, 127.42, 128.68, 129.48, 129.64, 134.79(135.18), 168.22(170.53), 175.12(174.17); MS EI m/z 306.1 (M^+), 341.9 (M+Cl), 343.2 (M+HCl).

4d: Method B. 10 mmol of amino alcohol was oxidized (SO_3/pyridine, DMSO) and the crude aldehyde was used for reductive amination. The crude product was purified by flash chromatography (hexane:EtOAc = 95:5 to 90:10 to 80:20 to 70:30) to provide a colorless oil (39% for two steps). ^{1}H NMR ($CDCl_3$) δ 1.11 and 1,13 (two d, 3H, *J*=7.5 Hz, $CHCH_3$, ratio 1.5:1), 1.36 (s, 9H, $C(CH_3)_3$), 1.60 (br, NH), 2.55 (m, 1H), 2.70 (d, 1H, *J*=6.6 Hz), 2.88 (set of m, 3H), 3.35 (t, 1H, *J*=7 Hz), 3.62 and 3.64 (two s, 3H, OCH_3), 7.2-7.4 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 15.26, 28.16, 39.86, 39.95, 40.29, 40.64, 51.08, 51.20, 51.70, 63.71, 81.21, 126.58, 128.30, 129.54, 137.82, 173.73, 173.90, 176.03, 176.21; MS CI(NH_3) m/z 322.1 ($M+H^+$).

4f: Method B. Ethylglyoxylate (6 mmol) was used and crude product was purified by flash chromatography (hexane:EtOAc = 95:5 to 90:10 to 80:20 to 70:30) to provide a colorless oil (62 %): R_f 0.22 (hexane:EtOAc = 80:20); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.5 Hz, OCH_2CH_3), 1.39 (s, 9H, $C(CH_3)_3$), 3.00 (m, 2H, *J*=8 Hz, CH_2Ph), 3.41 (ABq, 2H, (O=)CCH_2NH), 3.51 (t, 1H, *J*=8Hz, NHCH), 4.20 (q, 2H, *J*=7.5Hz, OCH_2CH_3), 7.2-7.4 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 14.4, 28.2, 39.9, 49.3, 61.0, 62.8, 81.6, 126.9, 128.5, 129.6, 137.4, 171.8, 173.1; IR (neat) 2979, 2933, 1740, 1368, 1152 cm^{-1}; MS CI(i-butane) m/z 203.3 ($M+H^+$), 252.3, 206.2, 177.1.

Method C. Ethylglyoxylate (10 mmol) was used and crude product was purified by flash chromatography (hexane:EtOAc = 95:5 to 90:10 to 80:20 to 70:30) to provide a colorless oil (40 %). All spectral data were in good agreement with an authentic sample as above.

β-Lactam 2a: To a stirred solution of t-butyl acetoacetate (1.58g, 10 mmol) in THF (50 mL) was added portionwise NaH (480 mg of 60% in oil, 12 mmol) at 0 °C. The resulting solution was stirred at the same temperature for 10 min. To this stirred solution was added 3-bromo ethyl propionate (1.99 g, 11 mmol) was added. The resulting solution was stirred at rt for 12h. After addition of 1N HCl (60 mL), the solution was extracted with EtOAc (2x100 mL). The combined organic extracts

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were washed with brine (100 mL), dried (Na_2SO_4), and concentrated to provide an oil (2.90g). NMR ($CDCl_3$) δ 1.25 (two d, 3H, *J*=7.0Hz, CH_2CH_3), 1.45 (s, 9H, $OC(CH_3)_3$), 2.10 (m, 2H, -CH_2CH_2-), 2.23 (s, 3H, $CH_3C(=O)$), 2.33 (m, 2H, -CH_2CH_2-), 3.43 (t, 0.5H, *J*=7.5 Hz, (O=)CCHC(=O)), 4.12 (two q, 2H, *J*=7Hz, CH_2CH_3). NMR showed that product consisted of enol and keto mixture form. Without further purification, above oil was used for the next reaction.

To a stirred solution of above β-keto ester (2.90 g, 10 mmol) with benzylamine (1.2 mL, 11 mmol) in EtOH (40 mL) was added dropwise a suspension of $NaBH_3CN$ (760 mg, 12 mmol) with $ZnCl_2$ (820 mg, 6 mmol) in EtOH (5 mL) at rt. The resulting white suspension was stirred at rt for 2d. After concentration, the residue was taken up in sat. $NaHCO_3$ (200 mL), extracted with EtOAc (3x100 mL). The combined extracts were washed brine (100 mL), dried ($MgSO_4$), passed through a short pad of SiO_2, and concentrated to provide an oil. The crude product was purified by flash chromatography (hexane:EtOAc=95:5 to 90:10 to 80:20 to 60:40) to provide a pure fraction (2.18g, 63%) and reasonably pure fraction (350 mg, 10 %) as an oil. NMR ($CDCl_3$) δ 1.10 and 1.13 (two d 3H, *J* = 6.5Hz, NHCHCH_3, ratio 35:65), 1.25 (two t, 3H, *J*=7Hz, CH_2CH_3), 1.45 (s, 9H, $OC(CH_3)_3$), 1.9-2.5 (set of m, 6H), 2.88 and 2.95 (two pentet, 1H, *J*=6.5Hz, CH_3CH(NHBn)CH-), 3.80 (m, 2H, CH_2Ph), 4.12 (two q, *J*=7Hz, CH_2CH_3),7.2-7.4 (m, 5H, phenyl).

To a stirred solution of above amino ester (350 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL) at rt. The resulting solution was stirred at rt overnight. After concentration, the oily residue was dissolved in CH_2Cl_2 (50 mL, 0.02 M) and treated with TEA (0.42 mL, 3 mmol) and 1-methyl-2-chloropyridine iodide (590 mg, 2 mmol) at rt. After stirring at rt for 2d, the solution was concentrated to give a brown residue, which was then taken up in EtOAc (50 mL), washed with 1N HCl (50 mL), sat. $NaHCO_3$ (2x50 mL), dried ($MgSO_4$), passed through a short pad of SiO_2 to provide a brown oil. The crude product was purified by flash chromatography (hexane:EtOAc=80:20 to 70:30 to 60:40) to provide a pale yellow oil (220 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 1.12 and 1.20 (two d, 3H, *J*=6.5Hz, NHCHCH_3, ratio 63:37), 1.25 (two t, 3H, *J*=7Hz, CH_2CH_3), 1.8-2.1 (m, 2H, -CH_2CH_2-), 2.4-2.6 (m, 2H, -CH_2CH_2-), 2.75 and 3.16 (m, 1H, CH), 3.24 (dq, 0.4H, *J*=2.5, 6.5 Hz, -NCHCH_3, trans form), 3.65 (pentet, 0.6H, *J*=5.5Hz, NCHCH_3, cis form), 4.12 (m, 3H, CH_2CH_3 and CH_2Ph), 4.60 (two d, 1H, *J*=15Hz, CH_2Ph, ratio 60:40), 7.2-7.4 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 13.7,

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14.1, 17.8, 20.1, 23.6, 31.8, 32.0, 43.7, 43.8, 50.2, 51.1, 53.6, 56.2, 60.4, 127.5, 127.7, 128.0, 128.3, 128.6, 127.7, 135.7, 135.8, 169.7, 1172.9; IR (neat) 1740 cm^{-1}; MS CI(NH_3) m/z 276 ($M+H^+$).

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