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Regioselective addition of 1,3-dicarbonyl dianion to *N*-sulfonyl aldimines: an expedient route to *N*-sulfonyl piperidines and *N*-sulfonyl azetidines

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Abstract—A simple route for the synthesis of δ-amino-β-keto esters and δ-amino-β-diketones is reported. This involves regioselective addition of 1,3-dianions derived from ethyl acetoacetate and acetyl acetone to *N*-sulfonyl aldimines. The δ-amino-β-keto ester derivatives were further converted into the corresponding *N*-sulfonyl piperidines and *N*-sulfonyl azetidines.

1. Introduction

1,3-Dicarbonyl dianions have been used extensively in organic synthesis for building ring systems. The anion on the terminal carbon of the dianion can be regioselectively reacted with 1 equiv of an electrophile resulting in an enolate ion, which can be trapped by the addition of a second electrophile or quenched by a proton source.[1] Comprehensive studies of 1,3-dicarbonyl dianions employing a variety of electrophiles to produce useful and synthetically important cyclic compounds, especially heterocycles, are well documented in the literature.[2] These electrophiles include *N*,*N*^{1}-dimethoxy-*N*,*N*^{1}-dimethylethanediamide,[3] 1,2-diketones,[4] 1,2-dibromo or 1,2-diiodoethane,[5] 1-bromo-2-chloroethane,[6] 1,4-dibromo-2-butene,[7] oxalic acid-bis(imidoyl)chlorides,[8] α-chloroacetic esters,[9] esters and amides,[9] aldehydes,[10] α-azidoketones,[11] cyclic sulfate esters,[12] epoxides,[13] *N*-tosyl aziridines,[14] and nitro-olefins.[15] Six-membered nitrogen heterocycles are one of the widely found structural units in various natural products and are very important intermediates in organic synthesis. In particular, the piperidine alkaloids and their synthetic analogues are the focus of great interest in the pharmaceutical industry because of their wide range of biological activities.[16] Azetidines are another important class of heterocyclic compounds found in many naturally occurring or important organic molecules, which exhibit interesting biological and pharmacological properties.[17]

In continuation of our research on enolate chemistry and also supported by the related literature on the reactivity of 1,3-dicarbonyl dianions, it was envisaged that dianions derived from suitable precursors could be regioselectively added to aldimines to give an easy access to δ-amino-β-keto esters[18] and their diketone analogues. These compounds could easily be converted into various piperidine and azetidine derivatives.

Substituted δ-amino-β-keto esters are important polyfunctionalized building blocks for the synthesis of important alkaloids, e.g., (*R*)-(+)-2-phenylpiperidine, (−)-SS20846A, (+)-241D, and its C-4 epimer, 4-hydroxypipecolic acid.[19] Similarly, δ-amino-β-diketone derivatives could be utilized as important intermediates for direct synthesis of some of these alkaloids. Davis et al. reported the synthesis of δ-amino-β-keto ester derivatives by a sequential addition of 2 equiv of methyl acetate enolate to *N*-sulfinyl aldimine.[19b,20] They utilized those δ-amino-β-keto esters as the key intermediates for elegant syntheses of the aforesaid alkaloids.[19] We report herein, a new strategy for the regioselective addition of 1,3-dicarbonyl dianions to *N*-sulfonyl aldimines as a convenient and new route to substituted δ-amino-β-keto esters and δ-amino-β-diketones in good to excellent yields. These δ-amino-β-keto esters were further transformed to *N*-sulfonyl piperidines and *N*-sulfonyl azetidines using simple chemistry.

2. Results and discussion

To test our methodology, we selected ethyl acetoacetate **1** as a precursor of 1,3-dicarbonyl dianion **2**. We anticipated that addition of the terminal carbanion of **2** to *N*-sulfonyl

Keywords: 1,3-Dianion; β-Keto ester; β-Dicarbonyl; δ-Amino-β-keto ester; δ-Amino-β-diketone; Piperidine; Azetidine.
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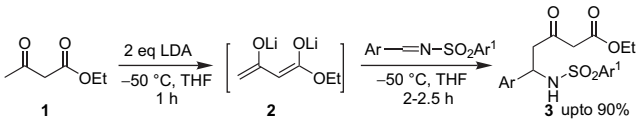
aldimines would provide the corresponding δ-amino-β-keto esters **3** in a single step (Scheme 1). Dianion **2** was generated from **1** by the treatment of LDA at −50 °C. When 1.0 equiv of *N*-sulfonyl aldimine was added to 1.0 equiv of **2** (entry 1, Table 1), a complex mixture was obtained from which only 35% of the addition product **3a** was isolated. To optimize the yield of this reaction we studied the concentration dependence of the dianion **2** and observed that 2.5 equiv of **2** increased the yield of **3a** to 77%. In order to generalize this approach, reaction of **2** with a number of *N*-sulfonyl aldimines (entries 2–8) was studied. In all cases, the reaction went smoothly to produce δ-amino-β-keto esters **3a–h** in excellent yields (Table 1). Similarly, 1,3-dianion **5** was generated from acetyl acetone **4** by the treatment of LDA at −50 °C. When 2.5 equiv of **5** was allowed to react with 1.0 equiv of *N*-sulfonyl aldimines, the corresponding δ-amino-β-diketones **6a–e** were obtained in very good yield (Scheme 2).

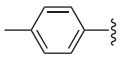
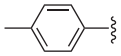
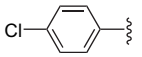
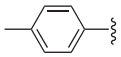
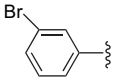
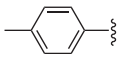
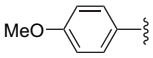
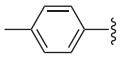
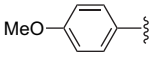
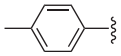


a: Ar = Ph, Ar^1 = 4-Me-C_6H_4
b: Ar = 2-Cl-C_6H_4, Ar^1 = 4-Me-C_6H_4
c: Ar = 4-Cl-C_6H_4, Ar^1 = 4-Me-C_6H_4
d: Ar = 3-Br-C_6H_4, Ar^1 = 4-Me-C_6H_4
e: Ar = 4-MeO-C_6H_4, Ar^1 = 4-Me-C_6H_4
f: Ar = 4-MeO-C_6H_4, Ar^1 = Ph
g: Ar = Ph, Ar^1 = Ph
h: Ar = furfuryl, Ar^1 = 4-Me-C_6H_4

Scheme 1. Regioselective addition of 1,3-dianion of ethyl acetoacetate to *N*-sulfonyl aldimines.

To explore the synthetic potential of this strategy, we further converted **3a–d** into the corresponding substituted piperidines **9a–d** using simple and known chemistry (Scheme 3). The keto group of **3a** was first protected as a cyclic ketal **7a** using 1,2-ethane diol in the presence of *p*-toluenesulfonic acid. The ester functionality of **7a** was further reduced to the corresponding primary alcohol **8a** by treatment with $LiAlH_4$. Treatment of **8a** with TsCl and excess KOH in refluxing THF

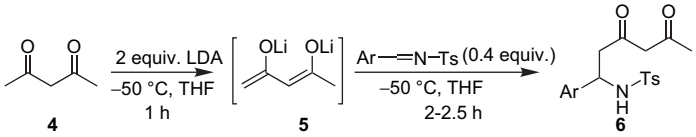
Table 1. Regioselective addition of 1,3-dianion of ethyl acetoacetate to *N*-sulfonyl aldimines

Entry	Ar	Ar^1	Yield[a] of **3** (%)
1			**3a**, 77 (35)
2			**3b**, 87
3			**3c**, 83
4			**3d**, 88
5			**3e**, 90
6			**3f**, 72
7			**3g**, 75 (30)
8			**3h**, 85

[a] Yields of isolated products after column chromatographic purification. Yield mentioned in the parenthesis is obtained by using 1:1 ratio of dianion and the aldimine.

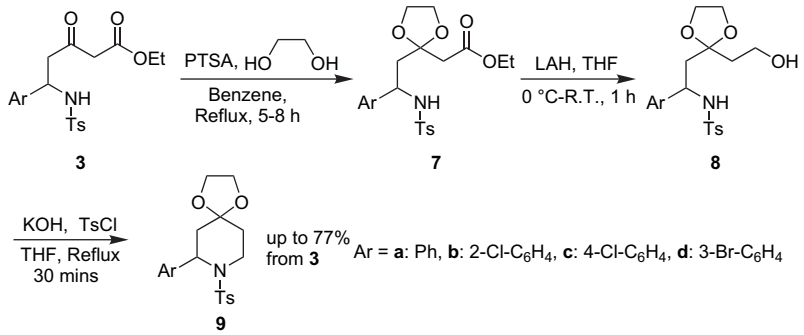
afforded *N*-sulfonyl piperidine **9a** in excellent overall yield starting from **3a**. Generalization of this approach is shown in Table 2.

After successful utilization of **3** for the syntheses of six-membered *N*-heterocycles **9**, we were interested in the synthesis of four-membered *N*-heterocycles (azetidines). Our initial attempt toward the synthesis of azetidine **10** is shown in Scheme 4. At first the keto group of **3a** was reduced to the corresponding alcohol by treatment with $NaBH_4$ in



6a: Ar = Ph, 78%; **6b**: Ar = 2-Cl-C_6H_4, 71%; **6c**: Ar = 4-MeO-C_6H_4, 55%; **6d**: Ar = 4-Cl-C_6H_4, 78%; **6e** Ar = 3-Br-C_6H_4, 81%.

Scheme 2. Regioselective addition of 1,3-dianion of acetyl acetone to *N*-sulfonyl aldimines.

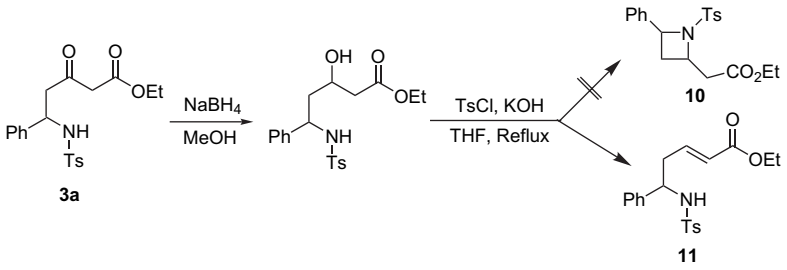


Scheme 3. Synthesis of substituted *N*-sulfonyl piperidines **9** from δ-amino-β-keto esters **3**.

Table 2. Synthesis of substituted *N*-sulfonyl piperidines **9** from δ-amino-β-keto esters **3**

Entry	**3**	Yield[a] of **7** (%)	Yield[a] of **8** (%)	Yield[a] of **9** (%)	Overall yield of **9** (%)
1	**a**: Ar=Ph	78	95	98	72
2	**b**: Ar=2-Cl–C_6H_4	88	90	90	71
3	**c**: Ar=4-Cl–C_6H_4	85	93	98	77
4	**d**: Ar=3-Br–C_6H_4	80	96	92	70

[a] Yields of isolated products after column chromatography.



Scheme 4. Attempt toward the synthesis of substituted azetidine from δ-amino-β-keto ester **3a**.

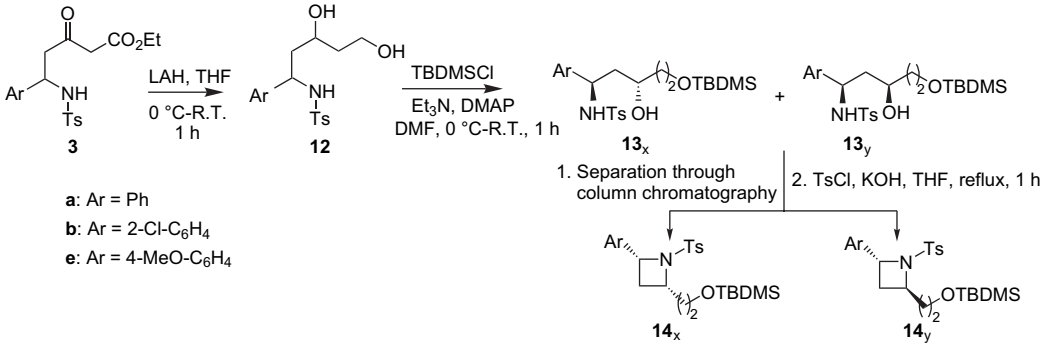
methanol. When the alcohol was treated with TsCl and excess KOH in refluxing THF, homoallyl amine **11** was formed instead of **10**.

However, **3** was converted into the corresponding *N*-sulfonyl azetidine **14** by a different strategy as shown in Scheme 5. Both the keto and ester groups of δ-amino-β-keto ester **3a** were reduced by treating with $LiAlH_4$ to give the corresponding amino diol **12a** as a mixture of diastereomers (dr 1.2:1) (Table 3). Primary alcohol group of **12a** was selectively protected as TBDMS ether **13** as a mixture of diastereomers (dr 1.2:1) by using TBDMSCl and Et_3N in the presence of catalytic DMAP in DMF.[21] Both the diastereomers $\mathbf{13_x a}$ and $\mathbf{13_y a}$ were isolated in pure forms by silica gel column chromatography. Subsequently, each of the pure diastereomers $\mathbf{13_x a}$ and $\mathbf{13_y a}$ was treated separately with TsCl and excess KOH in refluxing THF to afford the corresponding *N*-sulfonyl azetidines $\mathbf{14_x a}$ and $\mathbf{14_y a}$, respectively, in almost quantitative yields. Similar $LiAlH_4$ reduction of **3b**,**e** furnished **12b**,**e** as a mixture of diastereomers (dr 2:1). After protection of the primary alcohol group of **12b**,**e** as TBDMS ethers, both the diastereomers $\mathbf{13_x b}$,**e** and $\mathbf{13_y b}$,**e** were separated by column chromatography to afford diastereomerically pure products. In a similar fashion,

Table 3. Synthesis of *N*-sulfonyl azetidines **14** from δ-amino-β-keto esters **3**

3	Yield[b] (%) of **12** (*syn*/*anti*)[a,d]	Yield[b] (%) of **13x+13y** (*syn*/*anti*)[a,c,d,e]	Yield[b,c] (%) of **14**
3a	**12a**, 65 (1:1.2)	$\mathbf{13_x a}$+$\mathbf{13_y a}$, 98 (1:1.2)	$\mathbf{14_x a}$, 98 $\mathbf{14_y a}$, 95
3b	**12b**, 65 (1:2)	$\mathbf{13_x b}$+$\mathbf{13_y b}$, 98 (1:2)	$\mathbf{14_x b}$, 97 $\mathbf{14_y b}$, 92
3e	**12e**, 55 (1:2)	$\mathbf{13_x e}$+$\mathbf{13_y e}$, 95 (1:2)	$\mathbf{14_x e}$, 85 $\mathbf{14_y e}$, 70

[a] Ratio determined by ^1H NMR of crude reaction mixture.
[b] Yield of isolated product after column chromatography.
[c] The relative stereochemistry is shown.
[d] *syn*/*anti* Stereochemistry was decided considering the S_N2 cyclization of **13** leading to **14** (stereochemistry of **14** was determined by NOE experiment).
[e] Compounds $\mathbf{13_x}$ and $\mathbf{13_y}$ were separated by column chromatography before cyclization to **14**.



Scheme 5. Synthesis of substituted azetidines **14** from δ-amino-β-keto esters **3**.

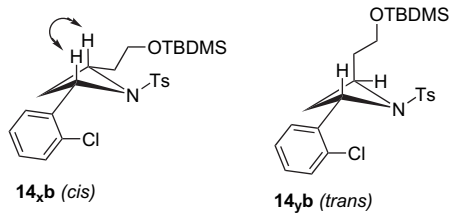


Figure 1. Determination of stereochemistry of **14b** by NOE experiment.

13$_x$b,**e** and **13$_y$b**,**e** when treated with TsCl and excess KOH in refluxing THF, the corresponding *N*-tosyl-azetidines **14$_x$b**,**e** and **14$_y$b**,**e** were obtained in diastereomerically pure forms in excellent yields. Interestingly, in all the above cases the major diastereomer **14$_x$** was obtained with 2,4-cis stereochemistry. The cis-geometry was determined by NOE measurements between the protons at C-2 and C-4 positions (Fig. 1).

When the free amino diol **12b** was treated with TsCl and excess KOH in refluxing THF, the reaction was found to be complicated as indicated by the ^{1}H NMR of the crude reaction mixture.

3. Conclusion

In conclusion, we have developed a new strategy for the regioselective addition of 1,3-dicarbonyl dianions derived from ethyl acetoacetate or acetyl acetone to *N*-sulfonyl aldimines to produce δ-amino-β-keto esters or δ-amino-β-diketones, respectively. The synthetic potential of this methodology is further demonstrated by the syntheses of various *N*-sulfonyl piperidines and azetidines. Further research in this area is under progress.

4. Experimental

4.1. General

All commercial reagents were used as received. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-LA400 instrument at 20–25 °C in $CDCl_3$ as the solvent and using TMS as the internal standard. IR spectra were recorded on BRUKER VERTEX 70 instrument. Elemental analysis data were obtained from THERMO QUEST CE Instrument (EA 1110, CHNS-O). TLC was carried out with 0.2 mm thick pre-coated silica gel plates (Merck, silica gel 60 F_{254}) using ethyl acetate/petroleum ether as the mobile phase. Visualization of spots was accomplished by UV light and iodine. Column chromatography was performed using Acme's (India) silica gel (100–200 mesh size) and Spectrochem (India) silica gel (230–400 mesh size). All solvents used in reactions were anhydrous and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon atmosphere. Glassware was oven-dried (130 °C) and purged with argon.

4.2. General procedure for the preparation of δ-amino-β-keto esters (3a–h)

To a solution of diisopropylamine (0.41 mL, 2.9 mmol) in 5 mL dry THF was added 2.3 M *n*-BuLi (1.26 mL, 2.9 mmol) at −50 °C and stirred for 30 min. The color of the solution changed to yellow, to which ethyl acetoacetate (0.18 mL, 1.45 mmol) was added slowly. Then stirring was continued for 1 h to allow the formation of 1,3-dianion. *N*-Sulfonyl imine (0.58 mmol) dissolved in 3 mL dry THF was added to the reaction mixture and allowed to stir for additional 2–2.5 h at the same temperature. After the completion of the reaction (monitored by TLC), it was quenched with saturated aqueous ammonium chloride solution, and extracted with 20 mL ethyl acetate in two portions. The combined organic extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. Silica gel column chromatographic purification of the crude mixture, using 20% ethyl acetate in petroleum ether as the eluant, afforded the pure products **3a**–**h**.

4.2.1. 3-Oxo-5-phenyl-5-(toluene-4-sulfonylamino)-pentanoic acid ethyl ester (3a). The general procedure described in Section 4.2 was followed to afford **3a** (173.9 mg, 77%) as a yellow liquid. [Found: C, 61.78; H, 5.90; N, 3.65. $C_{20}H_{23}NO_5S$ requires: C, 61.68; H, 5.95; N, 3.60%.] R_f (40% ethyl acetate/petroleum ether) 0.39; ν_{max} (neat) 3278, 2981, 2925, 1737, 1713, 1649, 1411, 1386, 1323, 1157, 1091, 1025, 965, 813, 754, 701, 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.31 (3H, s, $ArCH_3$), 2.92–3.13 (2H, m, CH_2CO), 3.20–3.39 (2H, m, $COCH_2CO_2Et$), 4.1 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.62–4.75 (1H, m, NC*H*Ph), 5.38 (1H, d, *J* 7.0 Hz, N*H*), 6.93–7.13 (6H, m, Ar*H*), 7.51 (2H, d, *J* 8.3 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 21.5, 49.0, 49.6, 53.8, 61.6, 126.5, 127.1, 127.7, 128.5, 129.4, 137.0, 139.5, 143.1, 166.8, 200.5; FAB Mass: *m*/*z* 390 (M^++1).

4.2.2. 5-(2-Chloro-phenyl)-3-oxo-5-(toluene-4-sulfonyl-amino)-pentanoic acid ethyl ester (3b). The general procedure described in Section 4.2 was followed to afford **3b** (213.9 mg, 87%) as a yellow liquid. [Found: C, 56.79; H, 5.25; N, 3.36. $C_{20}H_{22}ClNO_5S$ requires: C, 56.67; H, 5.23; N, 3.30%.] R_f (40% ethyl acetate/petroleum ether) 0.37; ν_{max} (neat) 3280, 3064, 2982, 2925, 1739, 1717, 1653, 1598, 1473, 1443, 1414, 1367, 1323, 1237, 1187, 1159, 1091, 1030, 813, 757, 729, 704, 666, 589 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.27 (3H, s, $ArCH_3$), 2.93–3.13 (2H, m, CH_2CO), 3.21–3.30 (2H, m, $COCH_2CO_2Et$), 4.12 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.02–5.07 (1H, m, NC*H*Ph), 5.86 (1H, d, *J* 8.0 Hz, NH), 6.93–7.25 (6H, m, Ar*H*), 7.50 (2H, d, *J* 8.3 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 21.5, 42.4, 48.9, 53.2, 61.6, 122.4, 125.3, 126.9, 129.4, 129.7, 129.9, 130.6, 136.8, 141.5, 143.5, 166.7, 200.2; FAB Mass: *m*/*z* 424 (M^++1), 426 (M^++3).

4.2.3. 5-(4-Chloro-phenyl)-3-oxo-5-(toluene-4-sulfonyl-amino)-pentanoic acid ethyl ester (3c). The general procedure described in Section 4.2 was followed to afford **3c** (204.1 mg, 83%) as a yellow liquid. [Found: C, 56.77; H, 5.30; N, 3.42. $C_{20}H_{22}ClNO_5S$ requires: C, 56.67; H, 5.23; N, 3.30%.] R_f (40% ethyl acetate/petroleum ether) 0.39; ν_{max} (neat) 3278, 2980, 1737, 1713, 1649, 1411, 1386, 1323, 1157, 1091, 1029, 965 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.33 (3H, s, $ArCH_3$), 2.89–3.12 (2H, m, CH_2CO), 3.22–3.30 (2H, m, $COCH_2CO_2Et$), 4.08 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.62–4.64 (1H,

m, NC*H*Ph), 5.62 (1H, d, *J* 6.3 Hz, N*H*), 6.95–7.12 (6H, m, Ar*H*), 7.48 (2H, d, *J* 8.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 21.5, 49.0, 49.6, 53.8, 61.6, 126.5, 127.1, 127.7, 128.5, 129.4, 137.0, 139.5, 143.1, 166.8, 200.5; FAB Mass: *m*/*z* 424 (M^++1), 426 (M^++3).

4.2.4. 5-(3-Bromo-phenyl)-3-oxo-5-(toluene-4-sulfonyl-amino)-pentanoic acid ethyl ester (3d). The general procedure described in Section 4.2 was followed to afford **3d** (238.7 mg, 88%) as a yellow liquid. [Found: C, 51.35; H, 4.82; N, 3.12. $C_{20}H_{22}BrNO_5S$ requires: C, 51.29; H, 4.73; N, 2.99%.] R_f (40% ethyl acetate/petroleum ether) 0.38; ν_{max} (neat): 3272, 3061, 2981, 2928, 1738, 1714, 1649, 1596, 1569, 1439, 1409, 1367, 1327, 1189, 1159, 1092, 1026, 963, 895, 813, 787, 736, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.32 (3H, s, $ArCH_3$), 2.90–3.11 (2H, m, CH_2CO), 3.28–3.30 (2H, m, $COCH_2CO_2Et$), 4.07 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.64–4.70 (1H, m, NC*H*Ph), 5.73 (1H, d, *J* 6.6 Hz, N*H*), 6.98–7.26 (6H, m, Ar*H*), 7.47 (2H, d, *J* 8.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 21.4, 47.2, 49.3, 51.2, 53.2, 61.6, 126.8, 127.1, 128.7, 129.0, 129.3, 129.6, 131.8, 136.4, 136.7, 143.3, 166.6, 200.5; FAB Mass: *m*/*z* 468 (M^++1), 470 (M^++3).

4.2.5. 5-(4-Methoxy-phenyl)-3-oxo-5-(toluene-4-sulfonyl-amino)-pentanoic acid ethyl ester (3e). The general procedure described in Section 4.2 was followed to afford **3e** (219 mg, 90%) as a yellow liquid. [Found: C, 60.35; H, 6.12; N, 3.29. $C_{21}H_{25}NO_6S$ requires: C, 60.13; H, 6.01; N, 3.34%] R_f (40% ethyl acetate/petroleum ether) 0.30; ν_{max} (neat) 3280, 2980, 2929, 1739, 1714, 1647, 1612, 1514, 1444, 1410, 1367, 1323, 1249, 1158, 1092, 1030, 814, 736, 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.34 (3H, s, $ArCH_3$), 2.92–3.16 (2H, m, CH_2CO), 3.20–3.29 (2H, m, $COCH_2CO_2Et$), 3.67 (3H, s, OCH_3), 4.04 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.57–4.75 (1H, m, NC*H*Ph), 5.26 (1H, s, N*H*), 6.63–7.29 (6H, m, Ar*H*), 7.52 (2H, d, *J* 8.3 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 21.5, 44.7, 49.2, 53.8, 55.2, 61.6, 113.8, 127.1, 127.8, 129.4, 131.4, 136.9, 143.2, 159.0, 166.8, 200.7; FAB Mass: *m*/*z* 420 (M^++1).

4.2.6. 5-Benzenesulfonylamino-5-(4-methoxy-phenyl)-3-oxo-pentanoic acid ethyl ester (3f). The general procedure described in Section 4.2 was followed to afford **3f** (169.3 mg, 72%) as a yellow liquid. [Found: C, 59.54; H, 5.82; N, 3.41. $C_{20}H_{23}NO_6S$ requires: C, 59.24; H, 5.72; N, 3.45%.] R_f (40% ethyl acetate/petroleum ether) 0.25; ν_{max} (neat) 3278, 3064, 2980, 2934, 1739, 1716, 1612, 1513, 1446, 1411, 1369, 1321, 1250, 1160, 1093, 1029, 833, 756, 721, 690, 597 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, t, *J* 7.3 Hz, OCH_2CH_3), 2.90–3.12 (2H, m, CH_2CO), 3.21–3.30 (2H, m, $COCH_2CO_2Et$), 3.65 (3H, s, OCH_3), 4.05 (2H, q, *J* 7.3 Hz, OCH_2CH_3), 4.63–4.77 (1H, m, NC*H*Ph), 5.68 (1H, d, *J* 3.3 Hz, N*H*), 6.58–7.42 (7H, m, Ar*H*), 7.60 (2H, d, *J* 7.1 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 42.8, 49.2, 49.5, 55.3, 61.6, 113.8, 126.9, 127.4, 127.7, 128.7, 131.3, 132.3, 140.1, 158.9, 166.7, 200.5; FAB Mass: *m*/*z* 405 (M^+).

4.2.7. 5-Benzenesulfonylamino-3-oxo-5-phenyl-pentanoic acid ethyl ester (3g). The general procedure described in Section 4.2 was followed to afford **3g** (163.3 mg, 75%) as a yellow liquid. [Found: C, 60.98; H, 5.72; N, 3.69. $C_{19}H_{21}NO_5S$ requires: C, 60.78; H, 5.64; N, 3.73%.] R_f (40% ethyl acetate/petroleum ether) 0.28; ν_{max} (neat) 3281, 3064, 2982, 2933, 1738, 1716, 1625, 1447, 1410, 1370, 1323, 1262, 1161, 1094, 1068, 1029, 941, 859, 807, 756, 721, 691, 644 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.93–3.16 (2H, m, CH_2CO), 3.21–3.43 (2H, m, $COCH_2CO_2Et$), 4.01 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.66–4.77 (1H, m, NC*H*Ph), 5.60 (1H, d, *J* 3.3 Hz, N*H*), 6.99–7.45 (8H, m, Ar*H*), 7.62 (2H, d, *J* 7.8 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 49.0, 49.6, 53.8, 61.6, 126.5, 127.1, 127.7, 128.5, 129.4, 137.0, 139.5, 143.1, 166.8, 200.5; FAB Mass: *m*/*z* 376 (M^++1).

4.2.8. 5-Furan-2-yl-3-oxo-5-(toluene-4-sulfonylamino)-pentanoic acid ethyl ester (3h). The general procedure described in Section 4.2 was followed to afford **3h** (187.1 mg, 85%) as a yellow solid, mp 50 °C. [Found: C, 56.76; H, 5.43; N, 3.35. $C_{18}H_{21}NO_6S$ requires: C, 56.98; H, 5.58; N, 3.69%.] R_f (40% ethyl acetate/petroleum ether) 0.37; ν_{max} (neat) 3277, 3122, 2984, 1746, 1719, 1599, 1501, 1443, 1410, 1327, 1156, 1090, 968, 918, 812, 752, 709, 678, 598 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.33 (3H, s, $ArCH_3$), 2.96–3.19 (2H, m, CH_2CO), 3.32–3.40 (2H, m, $COCH_2CO_2Et$), 4.12 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.73–4.83 (1H, m, NC*H*Ph), 5.47 (1H, d, *J* 8.2 Hz, N*H*), 5.91–6.10 (2H, m, Ar–*H*), 7.07–7.25 (3H, m, Ar–*H*), 7.59 (2H, d, *J* 8.3 Hz, Ar–*H*); δ_C (100 MHz, $CDCl_3$) 14.0, 21.5, 46.4, 47.7, 49.5, 61.6, 107.4, 110.4, 127.0, 129.7, 139.1, 141.9, 143.5, 151.6, 166.7, 200.2.

4.3. General procedure for the preparation of δ-amino-β-diketones (6a–e)

To a solution of diisopropylamine (0.24 mL, 1.7 mmol) in 5 mL dry THF was added 2.3 M *n*-BuLi (0.74 mL, 1.7 mmol) at −50 °C and stirred for 30 min. The color of the solution changed to yellow, to which acetyl acetone (0.087 mL, 0.85 mmol) was added slowly. Then stirring was continued for 1 h to allow the formation of 1,3-dianion. *N*-Sulfonyl imine (0.34 mmol), dissolved in 2 mL dry THF was added to the reaction mixture and allowed to stir for additional 2–2.5 h at the same temperature. After the completion of the reaction (monitored by TLC), it was quenched with saturated aqueous ammonium chloride solution and extracted with 20 mL ethyl acetate in two portions. The combined organic extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. Silica gel column chromatographic purification of the crude mixture using 20% ethyl acetate in petroleum ether as the eluant afforded the pure products **6a–e**. All these compounds exist mostly in enol form in $CDCl_3$ as indicated by the ^1H NMR spectra.

4.3.1. *N*-(3,5-Dioxo-1-phenyl-hexyl)-4-methyl-benzenesulfonamide (6a). The general procedure described in Section 4.3 was followed to afford **6a** (95.3 mg, 78%) as a yellow solid, mp 82 °C. [Found: C, 63.47; H, 5.79; N, 3.95. $C_{19}H_{21}NO_4S$ requires: C, 63.49; H, 5.89; N, 3.90%.] R_f (40% ethyl acetate/petroleum ether) 0.39; ν_{max} (neat) 3173, 3065, 2960, 2883, 2746, 1744, 1697, 1601, 1571, 1497, 1460, 1423, 1322, 1294, 1254, 1232, 1203, 1152, 1092, 1066, 1030, 1009, 965, 911, 845, 804, 751, 699,

668, 629, 582, 553, 510, 493 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.87 (3H, s, $COCH_3$), 2.29 (3H, s, $ArCH_3$), 2.55–2.66 (2H, m, CH_2), 4.59–4.64 (1H, m, ArCHN), 5.25 (1H, s, =CH of enol), 5.74 (1H, d, *J* 7.1 Hz, NH), 7.03–7.11 (7H, m, ArH), 7.50 (2H, d, *J* 8.3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.4, 24.3, 45.2, 55.1, 101.0, 126.4, 127.0, 127.5, 128.4, 129.3, 137.1, 139.7, 143.1, 190.4, 190.8; FAB Mass: *m*/*z* 360 (M^++1).

4.3.2. *N*-[1-(2-Chloro-phenyl)-3,5-dioxo-hexyl]-4-methyl-benzenesulfonamide (6b). The general procedure described in Section 4.3 was followed to afford **6b** (95.1 mg, 71%) as a yellow solid, mp 75 °C. [Found: C, 57.60; H, 5.14; N, 3.50. $C_{19}H_{20}ClNO_4S$ requires: C, 57.94; H, 5.12; N, 3.56%.] R_f (40% ethyl acetate/petroleum ether) 0.35; ν_{max} (neat) 3235, 3062, 2916, 1711, 1606, 1319, 1159, 1090, 1012, 947 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.87 (3H, s, $COCH_3$), 2.28 (3H, s, $ArCH_3$), 2.49–2.67 (2H, m, CH_2), 4.92–4.97 (1H, m, ArCHN), 5.22 (1H, m, =CH of enol), 5.84 (1H, d, *J* 7.1 Hz, NH), 7.02–7.26 (6H, m ArH), 7.52 (2H, d, *J* 7.3 Hz ArH); δ_C (100 MHz, $CDCl_3$) 21.4, 24.3, 43.4, 57.7, 100.8, 126.9, 127.1, 128.6, 128.7, 129.3, 129.5, 131.7, 136.7, 137.1, 143.2, 190.5, 191.0; FAB Mass: *m*/*z* 394 (M^++1), 396 (M^++3).

4.3.3. *N*-[1-(4-Methoxy-phenyl)-3,5-dioxo-hexyl]-4-methyl-benzenesulfonamide (6c). The general procedure described in Section 4.3 was followed to afford **6c** (72.8 mg, 55%) as a yellow solid, mp 77–80 °C. [Found: C, 61.88; H, 5.90; N, 3.50. $C_{20}H_{23}NO_5S$ requires: C, 61.68; H, 5.95; N, 3.60%.] R_f (40% ethyl acetate/petroleum ether) 0.28; ν_{max} (neat) 3276, 2923, 2844, 1705, 1611, 1513, 1445, 1323, 1250, 1157, 1092, 1030, 958, 815, 737, 667, 453 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.87 (3H, s, $COCH_3$), 2.30 (3H, s, $ArCH_3$), 2.53–2.67 (2H, m, CH_2), 3.67 (3H, s, OCH_3), 4.54–4.59 (1H, m, ArCHN), 5.26 (1H, s, =CH of enol), 5.72 (1H, d, *J* 6.5 Hz, NH), 6.62 (2H, d, *J* 8.5 Hz, ArH), 6.95 (2H, d, *J* 8.5, ArH), 7.08 (2H, d, *J* 8.0 Hz, ArH), 7.49 (2H, d, *J* 8.3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.4, 24.4, 45.2, 54.6, 55.2, 100.9, 113.7, 127.0, 127.6, 129.3, 131.8, 137.2, 143.1, 158.9, 190.4, 191.2; FAB Mass: *m*/*z* 390 (M^++1).

4.3.4. *N*-[1-(4-Chloro-phenyl)-3,5-dioxo-hexyl]-4-methyl-benzenesulfonamide (6d). The general procedure described in Section 4.3 was followed to afford **6d** (104.5 mg, 78%) as a yellow solid, mp 73 °C. [Found: C, 57.82; H, 5.24; N, 3.65. $C_{19}H_{20}ClNO_4S$ requires: C, 57.94; H, 5.12; N, 3.56%.] R_f (40% ethyl acetate/petroleum ether) 0.37; ν_{max} (neat) 3235, 1712, 1606, 1492, 1453, 1422, 1321, 1249, 1160, 1090, 1061, 1013, 948, 842, 815, 694, 660, 593, 566, 535, 450 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.94 (3H, s, $COCH_3$), 2.36 (3H, s, $ArCH_3$), 2.61–2.64 (2H, m, CH_2), 4.63–4.65 (1H, m, ArCHN), 5.28 (1H, s, =CH of enol), 5.97 (1H, d, *J* 7.0 Hz, NH), 7.02–7.29 (6H, m, ArH), 7.51 (2H, d, *J* 8.2 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.4, 24.3, 45.2, 55.1, 101.0, 126.4, 127.0, 127.5, 128.4, 129.3, 137.1, 139.7, 143.1, 190.4, 190.8.

4.3.5. *N*-[1-(3-Bromo-phenyl)-3,5-dioxo-hexyl]-4-methyl-benzenesulfonamide (6e). The general procedure described in Section 4.3 was followed to afford **6e** (120.7 mg, 81%) as a yellow solid, mp 75 °C. [Found: C, 52.16; H, 4.72; N, 3.10. $C_{19}H_{20}BrNO_4S$ requires: C, 52.06; H, 4.60; N, 3.20%]; R_f (40% ethyl acetate/petroleum ether) 0.35; ν_{max} (neat) 3358, 3266, 3061, 2921, 1702, 1598, 1528, 1493, 1473, 1414, 1336, 1305, 1253, 1207, 1156, 1091, 1055, 1018, 998, 940, 905, 842, 813, 788, 698, 672, 592, 563, 544, 505, 427 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.90 (3H, s, $COCH_3$), 2.31 (3H, s, $ArCH_3$), 2.57–2.59 (2H, m, CH_2), 4.57–4.63 (1H, m, ArCHN), 5.27 (1H, s, =CH of enol), 5.86 (1H, d, *J* 7.1 Hz, NH), 6.97–7.25 (5H, m, ArH), 7.46 (2H, d, *J* 8.3 Hz, ArH), 7.74 (1H, d, *J* 8.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.4, 24.3, 43.4, 57.7, 100.8, 126.9, 127.1, 128.6, 128.7, 129.3, 129.5, 131.7, 136.7, 137.1, 143.2, 190.5, 191.0.

4.4. General procedure for the synthesis of *N*-sulfonyl piperidines (9a–d) starting from δ-amino-β-keto ester 3

In a typical procedure, δ-amino-β-keto ester **3** (1.32 mmol) and 1,2-ethane diol (0.088 mL, 1.58 mmol) were dissolved in 10 mL dry benzene in the presence of catalytic PTSA. The mixture was refluxed for 5–8 h using Dean–Stark apparatus. After the completion of the reaction, the crude mixture was washed with aq $NaHCO_3$ solution and extracted with ethyl acetate. Silica gel column chromatographic purification of the crude mixture afforded the pure cyclic ketal **7**. To a suspension of $LiAlH_4$ (13.3 mg, 0.35 mmol) in 1.0 mL dry THF was added 0.23 mmol of **7** (dissolved in 1.0 mL dry THF) at 0 °C and the reaction was allowed to stir at room temperature for 1 h. After quenching the reaction with drop wise addition of ethyl acetate at 0 °C, the reaction mixture was filtered through a sintered funnel. The filtrate was washed with brine and concentrated under vacuum to afford **8**. The crude product was sufficiently pure as indicated by ^1H NMR to proceed for the next reaction. Finally, **8** (0.25 mmol) was treated with TsCl (57.2 mg, 0.30 mmol) and excess KOH (42 mg, 0.75 mmol) in refluxing THF for 30 min. After the completion of the reaction (monitored by TLC), it was quenched with water and extracted with 10 mL ethyl acetate in two portions. The combined organic extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. Silica gel column chromatographic purification of the crude mixture using 15% ethyl acetate in petroleum ether as the eluant afforded the pure products **9a–d**.

4.4.1. 7-Phenyl-8-(toluene-4-sulfonyl)-1,4-dioxa-8-aza-spiro[4.5]decane (9a). The general procedure described in Section 4.4 was followed to afford **9a** (354.9 mg, 72% overall starting from **3a**) as a yellow liquid. [Found: C, 64.35; H, 6.35; N, 3.80. $C_{20}H_{23}NO_4S$ requires: C, 64.32; H, 6.21; N, 3.75%.] R_f (30% ethyl acetate/petroleum ether) 0.36; ν_{max} (neat) 2929, 1601, 1493, 1451, 1345, 1226, 1158, 1095, 1035, 948, 861, 813, 728, 651, 472 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.49–1.52 (2H, m, CH_2), 1.78 (1H, dd, *J* 6.4, 14.2 Hz, CH_aH_b), 2.25 (1H, dd, *J* 3.6, 14.2 Hz, CH_aH_b), 2.30 (3H, s, $ArCH_3$), 3.37–3.44 (1H, m, CH_aH_bN), 3.63–3.83 (5H, m, CH_aH_bN, OCH_2CH_2O), 5.12 (1H, m, PhCH), 7.11–7.24 (7H, m, ArH), 7.59 (2H, d, *J* 8.3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.5, 33.8, 37.1, 41.2, 56.4, 64.0, 64.3, 106.2, 126.5, 126.7, 127.0, 128.0, 129.6, 137.7, 139.4, 143.2; FAB Mass: *m*/*z* 374 (M^++1).

4.4.2. 7-(2-Chloro-phenyl)-8-(toluene-4-sulfonyl)-1,4-dioxa-8-aza-spiro[4.5]decane (9b). The general procedure

described in Section 4.4 was followed to afford **9b** (382.3 mg, 71% overall starting from **3b**) as a white solid, mp 100 °C. [Found: C, 58.79; H, 5.35; N, 3.48. $C_{20}H_{22}ClNO_4S$ requires: C, 58.89; H, 5.44; N, 3.43%.] R_f (30% ethyl acetate/petroleum ether) 0.35; ν_{max} (neat) 2976, 2937, 2894, 1596, 1466, 1440, 1349, 1310, 1216, 1155, 1121, 1089, 1033, 943, 851, 818, 774, 749, 714, 688, 652, 618, 559, 503, 477 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.62–1.69 (1H, m, CH_aH$_b$), 1.76–1.84 (2H, m, CH$_a$$H_bCH_cH_d$), 2.2 (1H, dd, *J* 8.0, 13.9 Hz, CH$_c$$H_d$), 2.30 (3H, s, ArC$H_3$), 3.53–3.59 (1H, m, C$H_aH_b$N), 3.63–3.91 (5H, m, CH$_a$$H_bN, OCH_2CH_2$O), 5.02–5.05 (1H, m, ArC*H*), 7.02–7.12 (6H, m, Ar*H*), 7.35–7.44 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.4, 34.4, 38.8, 44.1, 55.3, 64.1, 64.3, 106.3, 126.4, 127.3, 128.3, 129.2, 129.3, 132.1, 136.2, 138.1, 143.0; FAB Mass: *m*/*z* 408 (M^++1), 410 (M^++3).

4.4.3. 7-(4-Chloro-phenyl)-8-(toluene-4-sulfonyl)-1,4-dioxa-8-aza-spiro[4.5]decane (9c). The general procedure described in Section 4.4 was followed to afford **9c** (414.6 mg, 77% overall starting from **3c**) as a yellow liquid. [Found: C, 58.95, H, 5.54, N, 3.45. $C_{20}H_{22}NO_4S$ requires: C, 58.89; H, 5.44; N, 3.43%.] R_f (30% ethyl acetate/petroleum ether) 0.28; ν_{max} (neat) 2964, 2931, 2885, 1650, 1596, 1491, 1448, 1401, 1348, 1304, 1263, 1233, 1160, 1093, 1037, 984, 948, 870, 817, 748, 714, 656, 601, 553 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.35–1.53 (2H, m, CH_2), 1.77 (1H, dd, *J* 6.1, 14.2 Hz, CH_aH$_b$), 2.18 (1H, dd, *J* 3.4, 14.1 Hz, CH$_a$$H_b$), 2.35 (3H, s, ArC$H_3$), 3.32–3.40 (1H, m, C$H_aH_b$N), 3.66–3.83 (5H, m, CH$_a$$H_bN, OCH_2CH_2$O), 5.07–5.11 (1H, m, ArC*H*), 7.16–7.21 (6H, m, Ar*H*), 7.58 (2H, d, *J* 8.3 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.3, 33.7, 37.1, 41.2, 56.0, 64.0, 64.3, 106.1, 126.9, 127.0, 127.9, 128.3, 129.8, 137.6, 138.0, 143.5; FAB Mass: *m*/*z* 408 (M^++1), 410 (M^++3).

4.4.4. 7-(3-Bromo-phenyl)-8-(toluene-4-sulfonyl)-1,4-dioxa-8-aza-spiro[4.5]decane (9d). The general procedure described in Section 4.4 was followed to afford **9d** (418 mg, 70% overall starting from **3d**) as a yellow liquid. [Found: C, 53.25; H, 5.17; N, 3.15. $C_{20}H_{22}BrNO_4S$ requires: C, 53.10; H, 4.90; N, 3.10%.] R_f (30% ethyl acetate/petroleum ether) 0.30; ν_{max} (neat) 2962, 2928, 2886, 1655, 1596, 1568, 1449, 1425, 1350, 1303, 1262, 1233, 1160, 1092, 1037, 987, 950, 900, 858, 812, 741, 696, 660, 624, 549, 472, 432 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.50–1.55 (2H, m, CH_2), 1.78 (1H, dd, *J* 6.4 Hz, *J* 14.2 Hz, CH_aH$_b$), 2.18 (1H, dd, *J* 3.6, 14.2 Hz, CH$_a$$H_b$), 2.35 (3H, s, ArC$H_3$), 3.33–3.40 (1H, m, C$H_aH_b$N), 3.66–3.83 (5 H m, CH$_a$$H_bN, OCH_2CH_2$O), 5.08–5.11 (1H, m, ArC*H*), 7.01–7.28 (6H, m, Ar*H*), 7.57 (2H, d, *J* 8.32 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.6, 33.8, 37.1, 41.3, 53.3, 56.4, 64.0, 74.1, 106.1, 126.5, 126.9, 127.3, 128.0, 129.8, 137.5, 139.4, 143.0; Mass: *m*/*z* 452 (M^++1), 454 (M^++3).

4.5. General procedure for the synthesis of *N*-sulfonyl azetidines starting from δ-amino-β-keto ester 3

To a suspension of $LiAlH_4$ (190 mg, 5.0 mmol) in 15 mL dry THF was added **3** (1.0 mmol dissolved in 5 mL dry THF) at 0 °C and the reaction was stirred at room temperature for 1 h. After quenching the reaction with drop wise addition of ethyl acetate at 0 °C, the reaction mixture was filtered through a sintered funnel. The filtrate was concentrated by evaporation to afford crude **12**, which was purified through a flash column chromatography (230–400 mesh size) using 30% acetone in petroleum ether as the eluant. To a solution of DMAP (6.1 mg, 0.05 mmol), **12** (0.5 mmol), and triethyl amine (0.1 mL, 0.75 mmol) in 2.0 mL dry DMF was added drop wise a solution of TBDMSCl (90.4 mg, 0.6 mmol) in 1.0 mL dry DMF at 0 °C over a period of 1 h. The reaction mixture was stirred for additional 1 h at room temperature and monitored by TLC. The reaction was quenched with cold water and crude product was extracted with ethyl acetate. Silica gel column chromatographic purification of the crude mixture furnished the pure diastereomers $\mathbf{13_x}$ and $\mathbf{13_y}$. To a solution of $\mathbf{13_x}$ or $\mathbf{13_y}$ (0.25 mmol) and KOH (42 mg, 0.75 mmol) in 1.0 mL dry THF was added TsCl (57.2 mg, 0.30 mmol) in portions at room temperature, then the reaction was refluxed for 1 h. After the completion of the reaction (monitored by TLC), it was quenched with water and extracted with ethyl acetate. The organic extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give the crude product. Both diastereomers were purified through silica gel column chromatography to provide the pure products $\mathbf{14_x}$ and $\mathbf{14_y}$.

4.5.1. *N*-(5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-1-phenylpentyl)-4-methyl benzenesulfonamide ($\mathbf{13_x}$a). The general procedure described in Section 4.5 was followed to afford $\mathbf{13_x}$**a** (103.2 mg, 44.5% from **12a**) as colorless liquid. R_f (35% ethyl acetate/petroleum ether) 0.50; ν_{max} (neat) 3504, 3278, 3063, 3030, 2952, 2928, 2883, 2856, 1717, 1599, 1495, 1471, 1458, 1421, 1360, 1323, 1305, 1288, 1255, 1214, 1184, 1159, 1092, 1020, 1005, 938, 837, 812, 778, 701, 667, 564, 547 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, CH_3Si), 0.07 (3H, s, CH_3Si), 0.89 (9H, s, *t-Bu*Si), 1.41–1.44 (1H, m, CH_aH$_b$), 1.57–1.83 (3H, m, CH$_a$$H_b$, C$H_c$$H_d$), 2.36 (3H, s, ArC$H_3$), 3.67–3.89 (4H, m, OC$H_2$, C*H*OH, O*H*), 4.61–4.66 (1H, m, ArC*H*N), 6.44 (1H, d, *J* 7.32 Hz, N*H*), 7.09–7.20 (7H, m, Ar*H*), 7.58 (2H, d, *J* 8.0 Hz, Ar*H*).

4.5.2. *N*-(5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-1-phenylpentyl)-4-methyl benzenesulfonamide ($\mathbf{13_y}$a). The general procedure described in Section 4.5 was followed to afford $\mathbf{13_y}$**a** (124 mg, 53.5% from **12a**) as a white solid, mp 98–100 °C. R_f (35% ethyl acetate/petroleum ether) 0.43; ν_{max} (neat) 3487, 3273, 2952, 2929, 2857, 1599, 1494, 1461, 1430, 1325, 1254, 1158, 1089, 937, 835, 812, 779, 701, 667, 549, 427 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, CH_3Si), 0.90 (9H, s, *t-Bu*Si), 1.41–1.68 (3H, m, CH_aCH$_b$, CH_cH$_d$), 1.87–1.96 (1H, m, CH$_c$$H_d$), 2.37 (3H, s, ArC$H_3$), 3.70–3.76 (2H, m, OC$H_2$), 3.81–3.86 (1H, m, C*H*OH), 4.00 (1H, s, O*H*), 4.32–4.36 (m, 1H, ArC*H*N), 6.44 (1H, d, *J* 2.4 Hz, N*H*), 7.13–7.20 (7H, m, Ar*H*), 7.55 (2H, d, *J* 8.3 Hz, Ar*H*).

4.5.3. *N*-(5-(*tert*-Butyldimethylsilyloxy)-1-(2-chlorophenyl)-3-hydroxypentyl)-4-methyl benzenesulfonamide ($\mathbf{13_x}$b). The general procedure described in Section 4.5 was followed to afford $\mathbf{13_x}$**b** (81.4 mg, 32.7% from **12b**) as a white solid, mp 101–103 °C. R_f (35% ethyl acetate/petroleum ether) 0.51; ν_{max} (neat) 3491, 3283, 2952, 2930, 2885, 2857, 1598, 1469, 1444, 1329, 1255, 1214, 1160, 1091, 1040, 939, 836, 813, 780, 755, 731, 704, 666, 549, 461, 418 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s,

CH_3Si), 0.02 (3H, s, CH_3Si), 0.85 (9H, s, *t-Bu*Si), 1.32–1.77 (4H, m, (CH_2)$_a$, (CH_2)$_b$), 2.31 (3H, s, ArCH_3), 3.60–3.76 (3H, m, OCH_2, C*H*OH), 4.94–4.95 (1H, m, ArC*H*N), 6.78–6.79 (1H, m, Ar*H*), 7.05–7.40 (7H, m, Ar*H*), 7.59 (2H, d, *J* 8.3 Hz, Ar*H*).

4.5.4. *N*-(5-(*tert*-Butyldimethylsilyloxy)-1-(2-chlorophenyl)-3-hydroxypentyl)-4-methyl benzenesulfonamide (13$_y$b). The general procedure described in Section 4.5 was followed to afford **13$_y$b** (162.7 mg, 65.3% from **12b**) as a white solid, mp 103–108 °C. R_f (35% ethyl acetate/petroleum ether) 0.44; ν_{max} (neat): 3450, 3269, 2952, 2929, 2557, 1596, 1468, 1442, 1332, 1255, 1160, 1088, 941, 836, 814, 779, 756, 729, 666, 559, 460, 425 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (6H, s, CH_3Si), 0.84 (9H, s, *t-Bu*Si), 1.41–1.62 (4H, m, (CH_2)$_a$, (CH_2)$_b$), 2.33 (3H, s, ArCH_3), 3.59–3.79 (3H, m, OCH_2, C*H*OH), 4.62–4.65 (1H, m, ArC*H*N), 7.03–7.22 (5H, m, Ar*H*), 7.45 (1H, d, *J* 7.3 Hz, Ar*H*), 7.61 (2H, d, *J* 8.3 Hz, ArH).

4.5.5. *N*-(5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-1-(4-methoxyphenyl)pentyl)-4-methyl benzenesulfonamide (13$_x$e). The general procedure described in Section 4.5 was followed to afford **13$_x$e** (78.2 mg, 31.7% from **12e**) as colorless liquid. R_f (35% ethyl acetate/petroleum ether) 0.38; ν_{max} (neat) 3482, 3278, 3054, 2953, 2929, 2856, 1733, 1653, 1612, 1558, 1540, 1513, 1463, 1440, 1361, 1321, 1304, 1265, 1250, 1177, 1158, 1091, 1036, 938, 836, 812, 779, 738, 704, 666, 565, 454, 417 cm^{-1}; δ_H (400 MHz, $CDCl_3$): δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.89 (9H, s, *t-Bu*Si), 1.41–1.80 (4H, m, (CH_2)$_a$, (CH_2)$_b$), 2.36 (3H, s, ArCH_3), 3.68–3.92 (6H, m, OCH_2, OCH_3), 4.56–4.57 (1H, m, ArC*H*N), 6.35 (1H, d, *J* 6.8 Hz, N*H*), 6.69 (2H, d, *J* 8.0 Hz, Ar*H*), 7.03 (2H, d, *J* 8.2 Hz, Ar*H*), 7.13 (2H, d, *J* 8.0 Hz, Ar*H*), 7.57 (2H, d, *J* 8.0 Hz, Ar*H*).

4.5.6. *N*-(5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-1-(4-methoxyphenyl)pentyl)-4-methyl benzenesulfonamide (13$_y$e). The general procedure described in Section 4.5 was followed to afford **13$_y$e** (156.3 mg, 63.3% from **12e**) as a white solid, mp 105–107 °C. R_f (35% ethyl acetate/petroleum ether) 0.31; ν_{max} (neat) 3490, 3273, 2952, 2929, 2856, 1612, 1513, 1463, 1441, 1360, 1323, 1305, 1249, 1177, 1158, 1091, 1036, 939, 835, 812, 778, 735, 806, 666, 548, 464, 419 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, CH_3Si), 0.90 (9H, s, *t-Bu*Si), 1.47–1.95 (4H, m, (CH$_2$)$_a$, (CH$_2$)$_b$), 2.38 (3H, s, ArCH_3), 3.71–3.86 (6H, m, OCH_2, OCH_3), 4.29 (1H, dd, *J* 4.8, 9.7 Hz, ArC*H*N), 6.70 (2H, d, *J* 8.5 Hz, Ar*H*), 7.05 (2H, d, *J* 8.5 Hz, Ar*H*), 7.14 (2H, d, *J* 8.0 Hz, Ar*H*), 7.55 (2H, d, *J* 8.0 Hz, Ar*H*).

4.5.7. 2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-phenyl-1-tosylazetidine (14$_x$a). The general procedure described in Section 4.5 was followed to afford **14$_x$a** (109.2 mg, 98% from **13$_x$a**) as a white solid, mp 125–130 °C. [Found: C, 64.61; H, 7.85; N, 3.20. $C_{24}H_{35}NO_3SSi$ requires: C, 64.68; H, 7.92; N, 3.14%.] R_f (10% ethyl acetate/petroleum ether) 0.41; ν_{max} (neat) 3030, 2953, 2927, 2884, 2855, 1598, 1494, 1471, 1386, 1346, 1304, 1289, 1256, 1161, 1092, 1018, 939, 885, 834, 812, 775, 742, 698, 665, 614, 599, 550, 527 cm^{-1}; δ_H (400 MHz, $CDCl_3$) −0.02 (3H, s, CH_3Si), −0.01 (3H, s, CH_3Si), 0.83 (9H, s, *t-Bu*Si), 1.83–1.93 (2H, m, CH_2), 2.10–2.19 (1H, m, CH_aH$_b$), 2.35–2.43 (4H, m, ArCH_3, CH$_a$$H_b$), 3.61–3.71 (2H, m, OC$H_2$), 3.92–4.00 (1H, m, NC*H*), 4.58 (1H, t, *J* 8.3 Hz, ArC*H*N), 7.17–7.35 (7H, m, Ar*H*), 7.62 (2H, d, *J* 8.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) −5.5, −5.4, 18.1, 21.6, 25.8, 33.2, 39.1, 58.5, 59.3, 62.9, 126.3, 127.8, 128.4, 128.5, 129.6, 132.2, 140.8, 143.8.

4.5.8. 2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-phenyl-1-tosylazetidine (14$_y$a). The general procedure described in Section 4.5 was followed to afford **14$_y$a** (105.8 mg, 95% from **13$_y$a**) as colorless liquid. [Found: C, 64.79; H, 7.75; N, 3.27. $C_{24}H_{35}NO_3SSi$ requires: C, 64.68; H, 7.92; N, 3.14%.] R_f (10% ethyl acetate/petroleum ether) 0.34; ν_{max} (neat) 3063, 3031, 2954, 2927, 2884, 2856, 1598, 1494, 1471, 1460, 1388, 1343, 1304, 1287, 1255, 1158, 1094, 1028, 1006, 972, 939, 911, 882, 835, 813, 777, 735, 698, 673, 609, 547, 520 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, CH_3Si), 0.87 (9H, s, *t-Bu*Si), 1.98–2.06 (1H, m, CH_aH$_b$), 2.32–2.40 (4H, m, ArCH_3CH$_a$$H_b$), 2.47–2.55 (2H, m, C$H_2$), 3.76 (2H, t, *J* 5.9 Hz, OCH_2), 4.53–4.59 (1H, m, NC*H*), 5.21 (1H, dd, *J* 5.6, 8.8 Hz, ArC*H*N), 7.02–7.41 (9H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) −5.5, −5.4, 18.1, 21.4, 25.8, 31.9, 36.9, 59.7, 62.2, 65.2, 127.1, 127.6, 127.9, 128.2, 128.9, 136.8, 138.5, 142.5.

4.5.9. 2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-(2-chlorophenyl)-1-tosylazetidine (14$_x$b). The general procedure described in Section 4.5 was followed to afford **14$_x$b** (116.4 mg, 97% from **13$_x$b**) as a white solid, mp 92–94 °C. [Found: C, 60.21; H, 7.18; N, 3.10. $C_{24}H_{34}ClNO_3SSi$ requires: C, 60.04; H, 7.14; N, 2.92%.] R_f (10% ethyl acetate/petroleum ether) 0.46; ν_{max} (neat) 2953, 2928, 2857, 1596, 1467, 1439, 1379, 1349, 1255, 1163, 1085, 1026, 942, 885, 832, 754, 662, 603, 553, 465 cm^{-1}; δ_H (400 MHz, $CDCl_3$) −0.03 (3H, s, CH_3Si), 0.00 (3H, s, CH_3Si), 0.83 (9H, s, *t-Bu*Si), 1.68–1.75 (1H, m, CH_aH$_b$), 1.84–1.90 (1H, m, CH$_a$$H_b$), 2.15–2.22 (1H, m, C$H_aH_b$), 2.44 (3H, s, ArC$H_3$), 2.52–2.59 (1H, m, CH$_a$$H_b$), 3.60–3.66 (1H, m, OC$H_aH_b$), 3.69–3.74 (1H, m, OCH$_a$$H_b$), 3.93–4.00 (1H, m, NC*H*), 4.93 (1H, t, *J* 8.3 Hz, ArC*H*N), 7.16–7.35 (5H, m, Ar*H*), 7.69 (2H, d, *J* 8.3 Hz, Ar*H*), 7.87 (1H, d, *J* 7.6 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) −5.5, −5.4, 18.1, 21.6, 25.8, 32.1, 39.3, 58.7, 59.0, 60.0, 127.0, 128.0, 128.6, 128.7, 128.9, 129.7, 131.0, 131.3, 138.7, 144.1.

4.5.10. 2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-(2-chlorophenyl)-1-tosylazetidine (14$_y$b). The general procedure described in Section 4.5 was followed to afford **14$_y$b** (110.4 mg, 92% from **13$_y$b**) as colorless liquid. [Found: C, 60.18; H, 7.21; N, 2.95. $C_{24}H_{34}ClNO_3SSi$ requires: C, 60.04; H, 7.14; N, 2.92%.] R_f (10% ethyl acetate/petroleum ether) 0.38; ν_{max} (neat) 2955, 2929, 2856, 1597, 1470, 1441, 1346, 1257, 1158, 1092, 1035, 834, 778, 755, 668, 607, 546, 462, 416 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, CH_3Si), 0.89 (9H, s, *t-Bu*Si), 1.83–1.91 (1H, m, CH_aH$_b$), 2.19–2.26 (1H, m, CH$_a$$H_b$), 2.37–2.63 (5H, m, ArC$H_3$ CH_2), 3.65–3.71 (2H, m, OCH_2), 4.58–4.64 (1H, m, NC*H*), 5.66 (1H, dd, *J* 6.8, 9.2 Hz, ArC*H*N), 7.19–7.42 (5H, m, Ar*H*), 7.63–7.69 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) −5.6, 18.1, 21.5, 25.8, 32.0, 35.2, 59.7, 61.2, 62.4, 126.9, 127.6, 128.0, 128.7, 129.1, 129.4, 131.8, 136.8, 137.8, 143.3.

4.5.11. 2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-(4-methoxyphenyl)-1-tosylazetidine (14$_x$e). The general

procedure described in Section 4.5 was followed to afford **14_xe** (101.1 mg, 85% from **13_xe**) as a white solid, mp 93–96 °C. [Found: C, 63.23; H, 7.89; N, 2.96. $C_{25}H_{37}NO_4SSi$ requires: C, 63.12; H, 7.84; N, 2.94%.] R_f (10% ethyl acetate/petroleum ether) 0.26; ν_{max} (neat) 2953, 2928, 2894, 2856, 1613, 1558, 1514, 1463, 1386, 1347, 1303, 1250, 1162, 1091, 1034, 940, 887, 833, 776, 712, 680, 661, 604, 550, 470 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (6H, s, CH_3Si), 0.85 (9H, s, *t-Bu*Si), 1.87–1.95 (2H, m, CH_2), 2.16–2.19 (1H, m, CH_aH_b), 2.36–2.42 (4H, m, ArCH_3, CH_aH_b), 3.68–3.79 (5H, m, OCH_3, OCH_2), 3.93–3.97 (1H, m, NC*H*), 4.55 (1H, t, *J* 8.3 Hz, ArC*H*N), 6.82–6.85 (2H, m, Ar*H*), 7.28–7.33 (4H, m, Ar*H*), 7.64 (2H, d, *J* 8.1 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) −5.4, 18.1, 21.5, 25.8, 33.3, 39.1, 55.2, 58.2, 59.3, 62.6, 113.8, 127.8, 128.4, 129.5, 132.4, 133.0, 143.7, 159.2.

4.5.12. 2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-(4-methoxyphenyl)-1-tosylazetidine (14_ye). The general procedure described in Section 4.5 was followed to afford **14_ye** (83.2 mg, 70% from **13_ye**) as colorless liquid. [Found: C, 63.15; H, 7.74; N, 2.86. $C_{25}H_{37}NO_4SSi$ requires: C, 63.12; H, 7.84; N, 2.94%.] R_f (10% ethyl acetate/petroleum ether) 0.22; ν_{max} (neat) 2954, 2928, 2856, 1699, 1684, 1653, 1611, 1559, 1541, 1514, 1496, 1463, 1388, 1342, 1304, 1291, 1251, 1177, 1157, 1095, 1034, 971, 883, 833, 812, 777, 709, 674, 609, 548, 440 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.06 (6H, s, CH_3Si), 0.89 (9H, s, *t-Bu*Si), 1.96–2.04 (1H, m, CH_aH_b), 2.30–2.52 (6H, m, CH_aH_b, CH_2, ArCH_3), 3.74–3.81 (5H, m, OCH_3, OCH_2), 4.49–4.57 (1H, m, NC*H*), 5.17 (1H, dd, *J* 5.4, 8.5 Hz, ArC*H*N), 6.66–6.69 (2H, m, Ar*H*), 6.99–7.26 (7H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) −5.4, 18.1, 21.4, 25.8, 31.8, 37.2, 55.2, 59.7, 61.9, 64.9, 113.5, 127.1, 128.9, 129.0, 130.5, 136.9, 142.3, 159.4.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.081.

References and notes

1. Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702.
2. (a) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125; (b) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
3. (a) Langer, P.; Stoll, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1803; (b) Sibi, M. P.; Marvin, M.; Sharma, R. *J. Org. Chem.* **1995**, *60*, 5016.
4. Gawish, A.; Mitschka, R.; Cook, J. M. *Tetrahedron Lett.* **1981**, *22*, 211.
5. Hampton, K. G.; Christie, J. J. *J. Org. Chem.* **1976**, *41*, 2772.
6. (a) Langer, P.; Bellur, E. *J. Org. Chem.* **2003**, *68*, 9742; (b) Langer, P.; Holtz, E.; Karime, I.; Saleh, N. N. R. *J. Org. Chem.* **2001**, *66*, 6057.
7. (a) Langer, P.; Holtz, E. *Angew. Chem.* **2000**, *112*, 3208; (b) Langer, P.; Holtz, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 3086.
8. Langer, P.; Döring, M. *Synlett* **2001**, 1437.
9. Shibato, K.; Yamaguchi, M.; Nakashima, H.; Minami, T. *Tetrahedron* **1988**, *44*, 4767.
10. Kraus, G. A.; Gottschalk, P. *J. Org. Chem.* **1983**, *48*, 2111.
11. Langer, P.; Freifeld, I. *Chem. Commun.* **2002**, 2668.
12. Pound, M. K.; Davies, D. L.; Pilkington, M.; Pina Vaz Sousa, M. M.; Wallis, J. D. *Tetrahedron Lett.* **2002**, *43*, 1915.
13. (a) Hoffman, R. V.; Patonay, T.; Nayyar, N. K.; Tao, J. *Tetrahedron Lett.* **1996**, *37*, 2381; (b) Bryson, T. A. *J. Org. Chem.* **1973**, *38*, 3428; (c) Langer, P.; Freifeld, I.; Holtz, E. *Synlett* **2000**, 501.
14. Lygo, B. *Synlett* **1993**, 764.
15. (a) Seebach, D.; Ehrig, V. *Angew. Chem.* **1974**, *86*, 446; (b) Seebach, D.; Ehrig, V. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 401.
16. (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991; (b) Bailey, P. D. *Chem. Commun.* **1998**, 633.
17. (a) Fowden. *Nature* **1955**, *176*, 347; (b) Bannon, A. W.; Decker, M. W.; Holladay, M. W.; Curzon, P.; Donnelly-Roberts, D.; Puttfarcken, P. S.; Bitner, R. S.; Diaz, A.; Dickenson, A. H.; Porsolt, R. D.; Williams, M.; Arneric, S. P. *Science* **1998**, *279*, 77; (c) Suzuki, K.; Shimada, K.; Nozoe, S.; Tanzawa, K.; Ogita, T. *J. Antibiot. (Tokyo)* **1996**, *49*, 1284; (d) Figueiredo, R. M. d; Fröhlich, R.; Christmann, M. *J. Org. Chem.* **2006**, *71*, 4147; (e) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393 and reference cited therein.
18. Li, B.; Franck, R. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2629.
19. (a) Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169; (b) Davis, F. A.; Chao, B.; Fang, T. *Org. Lett.* **2000**, *2*, 1041; (c) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623; (d) Davis, F. A.; Fang, T. *Synthesis* **2000**, *4*, 2106; (e) Davis, F. A.; Zhang, J.; Li, Y.; Xu, H.; DeBrosse, C. *J. Org. Chem.* **2005**, *70*, 5413.
20. From the experimental procedure[19b,c] provided by Davis et al. where methyl acetate was added slowly to a solution of excess NaHMDS at −78 °C, it is clear that their reaction proceeds by the following mechanism. The addition of methyl acetate enolate to aldimine produces β-amino ester, which subsequently reacts with one more equivalent of the ester enolate to give δ-amino-β-keto esters probably via a Claisen type ester condensation reaction.
21. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99.