# Downloaded by: UC Santa Barbara. Copyrighted material.

# Simple Synthetic Equivalents for the $\beta$ -(*N*,*N*-Disubstituted)ethylamino Acyl Cation Synthon and their Applications

V. Selvamurugan, Indrapal Singh Aidhen\*

Department of Chemistry, Indian Institute of Technology, Madras, Chennai 600 036, India Fax 91(44)2350509; E-mail: isingh@pallava.iitm.ernet.in *Received 26 June 2001; revised 28 August 2001* 

This paper is dedicated to Professor S. Swaminathan.

**Abstract:** Various *N*,*N*-disubstituted- $\beta$ -amino-*N*-methoxy-*N*-methylpropanamides **3a**–**i** were prepared which served as an excellent  $\beta$ -aminoacyl cation equivalents. These were used to prepare  $\beta$ -amino ketones **1**, pharmacologically active tertiary 1-(3,3-diarylpropyl)amines **7a–c**, and the interesting C-glycoside **8**.

**Keywords:** Weinreb amide,  $\beta$ -amino ketones, Grignard reactions, alkylations, glycoside

 $\beta$ -Amino ketones 1 are highly attractive substances because of their value as general synthetic building blocks in the preparation of pharmaceuticals, plant protection materials or natural products.<sup>1a</sup> Of the various disconnections (Figure 1) possible to arrive at 1, it is disconnection A which provides one of the most fundamental methods for the synthesis of 1. It is based on the classical Mannich and related reactions. Although limited to aminomethylation,<sup>1</sup> many variants<sup>2</sup> of the Mannich reaction have been extremely promising. In this context, iminium salts<sup>2</sup> and imines<sup>3</sup> have served as valuable substrates for their reaction with enamines and silvl enol ethers, respectively, to obtain  $\beta$ -amino ketones. However, both substrates have some limitations. Iminium salts are extremely hygroscopic and are prone to hydrolysis. They therefore demand in situ generation. In addition, the basic nature of imines deactivates the Lewis acid, and expensive  $Zr(OTf)_4$  or  $Hf(OTf)_4$  are required for successful reactions.

Disconnection **B** is apparently simple but it demands relatively unstable and reactive aryl vinyl ketones (when  $R^3 = Aryl$ ) as starting material for the Michael reaction and hence has not been used much. The approach, however, has been very useful in preparing  $\beta$ -amino esters,<sup>4</sup> nitriles<sup>5</sup> and amides.<sup>6</sup>



Figure 1 Possible disconnections A and B of the  $\beta$ -amino ketone 1 leading to its synthesis

Synthesis 2001, No. 15, 12 11 2001. Article Identifier: 1437-210X,E;2001,0,15,2239,2246,ftx,en;T05101SS.pdf. © Georg Thieme Verlag Stuttgart · New York ISSN 0039-7881 Represented in Figure 2 are the two possible routes ensuing disconnection C. Katritzky, based on benzotriazole chemistry developed<sup>7</sup> 2 as a novel synthetic equivalent of  $\beta$ -aminoacyl anion X towards the synthesis of  $\beta$ -aminoethyl ketones. In their work the nature of the electrophile is restricted to alkyl halide and benzaldehyde. It therefore cannot be used for the synthesis of 1 where R<sup>3</sup> is an aryl residue.



Figure 2

With regard to synthon **Y**, there are few reports<sup>8</sup> wherein the  $\beta$ -(*N*,*N*-disubstituted)ethylaminoacyl unit in the form of the corresponding Weinreb amide has served as an equivalent to synthon Y. However, in these cases the unit was a fragment of a larger molecule for specific synthetic needs. With this precedence we aimed at simple and straightforward synthesis of the reagents equivalent to the N-protected  $\beta$ -aminoacyl cation Y which would be of immense interest and use as valuable reagents. Herein we disclose our systematic study towards the preparation of various  $\beta$ -(*N*,*N*-disubstituted)ethylaminoacyl cation equivalents<sup>9</sup> **3a**–i and their utility to arrive at  $\beta$ -aminoethyl ketones. The motivation to this proposal lay in the success, in which *N*-methoxy-*N*-methylamide functionality, now popularly called as Weinreb amide, has received towards clean acylation with organometallics.<sup>10</sup> Multigram quantities of the reagent 3a-i are easily and routinely prepared in high yields (75–91%) (Scheme 1, Table 1) by alkylating various amines 4a-i with N-methoxy-N-methyl-3-bromopropanamide (5) using  $K_2CO_3$  in acetonitrile as solvent. The amide 5 is prepared in two high yielding steps starting from 3-bromopropanoic acid.<sup>11</sup> Conversion

of 3-bromopropanoic acid to the corresponding acid chloride and its subsequent reaction with N,O-dimethylhydroxylamine hydrochloride in the presence of two equivalents of pyridine furnished N-methoxy-N-methyl-3-bromopropanamide<sup>9</sup> (5) in 76% yield. All the amides **3a–i** can be stored indefinitely on shelf without any decomposition.





It was observed that substrates **3a,c,d** and **g** underwent clean reaction with various Grignard reagents at 0 °C (Scheme 2) forming the corresponding  $\beta$ -amino ethyl ketones in good to excellent yields (Table 2). On the other hand the reaction of phenylmagnesium bromide with 3b at 0 °C was complex. This could be in part due to the cleavage<sup>12</sup> of N-SO<sub>2</sub>Ph by the attack of Grignard reagent on the electrophilic sulfur atom and subsequent fragmentation. To avoid the decomposition, the reaction temperature was systematically lowered and the addition of phenylmagnesium bromide at various temperatures was investigated. Finally it was observed that at -40 °C, decomposition was completely eliminated and a clean reaction ensued affording 1bm in 67% yield. The condition developed was general and not specific to phenylmagnesium bromide as exemplified by succesful reaction with other Grignard reagents (Table 2). In case of substrates 3e and 3f the Grignard reagent was added at -40 °C and then the temperature was allowed to reach 0 °C for successful reaction. Substrates 3b and 3c are particularly noteworthy. In the case of **3b** further functionalisation at the nitrogen center is possible after desulphonylation<sup>13</sup> whereas the two benzyl groups in 3c are orthogonal and therefore would allow greater flexibility in manipulating the nitro-







Entry	Secondary Amine	Prod- uct <sup>a,b</sup>	Yield <sup>c</sup> (%)	IR (CHCl <sub>3</sub> ) (cm <sup>-1</sup> )
1	(Bn) <sub>2</sub> NH <b>1a</b>	3a	80	2816, 1676, 1484, 1452,1369
2	MeNHSO <sub>2</sub> Ph 1b	3b	79	2944, 2368, 1673, 1462, 1340
3	3,4- (MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> NHBn <b>1c</b>	3с	75	2901, 1679, 1490, 1434, 1380
4	(Me <sub>2</sub> CH) <sub>2</sub> NH <b>1d</b>	3d	78	2960, 2840, 1669, 1450, 1375
5	Boc-NNH	3e	78	2990, 1708, 1676, 1450, 1310
6	1e	3f	75	3060, 1676, 1600, 1310, 1375
7	lf oNH	3g	91	2990, 1679, 1472, 1450, 1375
8	1g NH	3h	87	2990, 2840, 1673, 1440, 1350
9	1h Me <sub>2</sub> NH <sup>d</sup> 1i	3i	76	2900, 1679, 1472, 1450, 1375

 $^a$  Satiafactory microanalyses were obtained for all the new compounds: C  $\pm 0.30,$  H  $\pm 0.27,$  N  $\pm 0.31.$ 

<sup>b</sup> Syrupy liquid.

<sup>c</sup> Yield of isolated product.

 $^d$  Reaction conditions: To an excess of 40% aq Me<sub>2</sub>NH (50 mL) was added a solution of **5** (2.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (75 mL) and stirred for 12 h at 0 °C.

gen center.<sup>4</sup> In the case of allylmagnesium bromide (Entries 6 and 13 in Table 2) the initially formed  $\beta$ , $\gamma$ -unsaturated product isomerised to more stable  $\alpha$ , $\beta$ -unsaturated product during acidic workup and purification using silica gel chromatography.

The developed route to  $\beta$ -amino ketones was applied to the synthesis of therapeutically important tertiary 1-(3,3-diarylpropyl)amines<sup>14</sup> **7a**–c (Figure 3) as depicted in Scheme 3. This approach is particularly important when the two aryl residues are not equivalent (Table 3).

The elegance of these synthetic equivalents was further confirmed by its ready use in appending the  $\beta$ -(*N*,*N*-dibenzyl)ethylamino acyl fragment at the anomeric carbon of glycosyl residue. Treatment of 3,4,6-tri-*O*-benzyl-2deoxy- $\alpha$ -D-*arabino*-hexopyranosyllithium<sup>15</sup> with **3a** re-

# Synthesis 2001, No. 15, 2239-2246 ISSN 0039-7881 © Thieme Stuttgart · New York

Entry	Starting Amide	Grignard Re- agent	Reaction Temp (°C)	Product <sup>a,b</sup>	Yield (%) <sup>c</sup>	IR (CHCl <sub>3</sub> ) (cm <sup>-1</sup> )
1	3a	6a	0	1aa	79	2816, 1689, 1491, 1443, 1347
2	3a	6b	0	1ab	73	2944, 1676, 1587, 1480, 1456
3	<b>3</b> a	6c	0	1ac	74	2861, 1671, 1491, 1443, 1371
4	<b>3</b> a	6d	0	1ad	83	2864, 1712, 1488, 1444, 1363
5	<b>3</b> a	6e	0	1ae	72	2872, 1714, 1490, 1360, 1210
6	3a	6f	0	1af	68	2912, 1696, 1422, 1491, 1356
7	<b>3</b> a	6g	0	1ag	65	2874, 1681, 1483, 1448, 1339
8	3b	6a	-40	1ba <sup>d</sup>	67	2816, 1683, 1443, 1337, 1180
9	3b	6b	-40	1bb <sup>e</sup>	68	2955, 1670, 1456, 1340, 1160
10	3b	6c	-40	1bc <sup>f</sup>	70	2816, 1671, 1450, 1370, 1150
11	3b	6d	-40	1bd	77	2865, 1714, 1440, 1375, 1176
12	3b	6e	-40	1be	74	2860, 1712, 1449, 1368, 1169
13	3b	6f	-40	1bf	65	2973, 1691, 1430, 1370, 1171
14	3b	6g	-40	1bg <sup>g</sup>	66	2911, 1690, 1447, 1368, 1169
15	3c	6a	0	1ca	71	2888, 1690, 1487, 1443, 1334
16	3c	6b	0	1cb	69	3032, 1688, 1587, 1487, 1443
17	3c	6c	0	1cc	75	2896, 1678, 1444, 1332, 1371
18	3c	6d	0	1cd	70	2998, 1710, 1488, 1465, 1355
19	3c	6e	0	1ce	70	2902, 1710, 1490, 1360, 1299
20	3d	6a	0	1da	76	2973, 1690, 1448, 1350, 1175
21	3e	6b	-40 to 0	1eb	70	2990, 1708, 1688, 1443, 1332
22	3f	6c	-40 to 0	1fc	68	3040, 1688, 1611,1313, 1340
23	3g	6g	0	1gg	78	2985, 1691, 1485, 1432, 1330

Table 2Addition of Grignard Reagent to 3a-g to form Various  $\beta$ -(*N*,*N*-Disubstituted)ethylamino Ketones 1

 $^a$  Satiafactory microanalyses were obtained for all the new compounds. C ±0.26, H ±0.29, N ±0.22.

<sup>b</sup> Syrupy liquid, unless otherwise indicated.

° Yield of isolated product.

 $^{\rm d}$  Mp 58–60 °C.

° Mp 79–81 °C.

<sup>f</sup> Mp 91–92 °C.

<sup>g</sup> Mp 95–97 °C.

mp *75 77* 0.



# Scheme 3

sulted in the formation of **8**, an interesting C-glycoside (Scheme 4). The axial addition of the  $\beta$ -aminoacyl unit was shown by <sup>1</sup>H NMR spectroscopy;  $\delta = 4.98$  (d, 1 H,

 $J_{1,2ax} = 3.4$  Hz, H-1).<sup>15</sup> The efficiency of the developed approach to the  $\beta$ -amino ketones tempted us to explore the synthesis of  $\gamma$ -amino ketones by replacing **5** with its high-



Figure 3 Chemical Structures of compounds 7a-c

Table 3 Application of 3g-i Towards the Preparation of 7a-c

Entry	Starting Amide	β-Amino Ketone (yield %)	Grignard Reagent (ArMgBr)	γ,γ-Dia- rylpropy- lamine	Overall Yield (%) <sup>a</sup>
1	3g	<b>1ga</b> (75)	$Ar = 4-MeOC_6H_4$	7c	68
2	3h	<b>1ha</b> (81)	Ar = Ph	7b	70
3	3i	<b>1ia</b> (80)	$Ar = 4-MeC_6H_4$	7c	69

<sup>a</sup> Yield of isolated product based on 3g-i.

er homologue **9a**. Substrate **9a** was, however, found to be unstable, as substantial amounts of it readily decomposed to  $\gamma$ -butyrolactone and amine hydrobromide by reaction with water during the workup procedure. On the contrary the chloro analogue **9b** was found to be very stable. Alkylation of morpholine with **9b** afforded **10** which upon treatment with 2-naphthylmagnesium bromide resulted in the formation of 4-morpholino-1-(2-naphthyl)butan-1one (**11**), a valuable  $\gamma$ -amino ketone found to be a potent inhibitor of Jak3 kinase (Scheme 4).<sup>16</sup> This further illustrates the usefulness and the generality associated with the proposed synthetic equivalents for  $\beta$  or  $\gamma$ -(*N*,*N*-disubstituted)aminoacyl cations.

In summary, various *N*-protected- $\beta$ -aminoacyl cation equivalents have been prepared which undergo a clean reaction with various Grignard reagents leading to the convenient synthesis of  $\beta$ -aminoethyl ketones. Given the fact that there are many reagents available for enantioselective reduction<sup>17</sup> of the aromatic ketone functionality, the developed approach to *N*-protected  $\beta$ -amino ketone should also be a valuable starting point for rapid and potential entry into  $\gamma$ -amino alcohol functionality, which is present in many of the important antidepressents.<sup>18</sup> The synthetic equivalents proposed herein, become even more interesting and versatile due to the flexibility that exists in changing the nature of the substitution at nitrogen centre as per requirement of the synthetic objective.

All the solvents and reagents were distilled before use. Anhyd solvents were prepared according to the standard procedures. Reactions requiring inert atmosphere were carried out under dry N<sub>2</sub>. Melting points were determined in capillary using a Toshniwal melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker (300 MHz <sup>1</sup>H, 75 MHz <sup>13</sup>C) or a Jeol (400 MHz <sup>1</sup>H, 100 MHz <sup>13</sup>C) NMR spectrometers using TMS as an internal standard. IR spectra were recorded on a Heraeus CHN analyzer. Optical rotation was measured by a Jasco DIP 370 polarimeter. The TLC tests for monitoring the course of the reaction were performed on silica gel (Merck, TLC grade) coated on a glass plate (7 cm  $\times$  2.5 cm) followed by staining in iodine vapors. For column chromatography, silica gel (100–200 mesh) was used, unless otherwise indicated.

3-Bromo-*N*-methoxy-*N*-methylpropanamide (**5**) was prepared according to the procedure described in the literature.<sup>9</sup> *N*-Methyl-*N*-phenylsulphonyl amine<sup>19a</sup> and *N*-benzyl-*N*-(3,4-dimethoxybenzyl) amine<sup>19b</sup> were prepared based on the similar type of procedure described in the literature.

# Alkylation of Amines 4a-i with 5; General Procedure

To a mixture of an appropriate amine (2.5 mmol) and anhyd  $K_2CO_3$  (1.4 g, 10 mmol) in anhyd MeCN (10 mL) was added **5** (0.5 g, 2.5 mmol) and the mixture was stirred at reflux for 3 h. The mixture was cooled to r.t. and filtered through Celite. The solvent was evaporated from the filtrate and the resulting residue was purified by column chromatography (hexane–EtOAc) to afford **3a–i** in good yields (75–91%) (Tables 1 and 4).

# Addition of Grignard Reagents to 3a-i; General Procedure

To a solution of **3a–i** (2.5 mmol) in anhyd THF (20 mL) was added the appropriate Grignard reagent (7.5 mmol) in anhyd THF (10 mL) under N<sub>2</sub> at a suitable temperature (see Table 2). The mixture was then stirred for 1.5 h. The hydrolysis was achieved by the cautious addition of sat. aq NH<sub>4</sub>Cl solution (30 mL). After returning to r.t., the two phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic phases were combined, washed with brine (40 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography (hexane–EtOAc) to afford Ndisubstituted-β-amino ketones **1aa–1gg** in good yields (65–83%) (Tables 2 and 5).

# Tertiary 1-(3,3-Diarylpropyl)amines 7a-c; General Procedure

*N*,*N*-Disubstituted- $\beta$ -amino ketones **1ga–1ia** (75–81%) were prepared by the addition of phenylmagnesium bromide [prepared from bromobenzene (1.17 g, 7.5 mmol) and Mg (0.206 g, 8.5 mmol) in anhyd THF (20 mL) with stirring at reflux for 1 h under a N<sub>2</sub> atm] to a solution of **3g–i** (2.5 mmol) in THF (20 mL) at 0 °C. To a stirred



## Scheme 4

Synthesis 2001, No. 15, 2239-2246 ISSN 0039-7881 © Thieme Stuttgart · New York

Product	<sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> /TMS) $\delta$ , $J$ (Hz)	$^{13}$ C NMR (75 MHz, CDCl <sub>3</sub> /TMS) $\delta$
<b>3</b> a	2.60 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 2.82 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> CH <sub>2</sub> ), 3.08 (s, 3 H, NCH <sub>3</sub> ), 3.59 (s, 4 H, NCH <sub>2</sub> Ph), 3.64 (s, 3 H, OCH <sub>3</sub> ), 7.1–7.36 (m, 10 H, ArH)	30.29, 32.01, 49.21, 58.27, 61.02, 126.83, 128.15, 128.71, 139.51, 175.10
3b	2.75 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 2.80 (s, 3 H, NCH <sub>3</sub> ), 3.15 (s, 3 H, NCH <sub>3</sub> ), 3.34 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> CH <sub>2</sub> ), 3.68 (s, 3 H, OCH <sub>3</sub> ), 7.51–7.60 (m, 3 H, ArH), 7.77–7.79 (m, 2 H, ArH)	31.00, 31.47, 35.42, 45.62, 60.75, 126.84, 128.59, 132.10, 137.00, 171.15
3с	2.60 (t, 2 H, <i>J</i> = 7.4, CH <sub>2</sub> CO), 2.84 (t, 2 H, <i>J</i> = 7.4, NCH <sub>2</sub> CH <sub>2</sub> ), 3.11 (s, 3 H, NCH <sub>3</sub> ), 3.53 (s, 2 H, NCH <sub>2</sub> Ph), 3.55 (s, 2 H, NCH <sub>2</sub> ), 3.59 (s, 3 H, OCH <sub>3</sub> ), 3.84 (s, 3 H, ArOCH <sub>3</sub> ), 3.88 (s, 3 H, ArOCH <sub>3</sub> ), 6.88–7.36 (m, 8 H, ArH)	30.33, 32.55, 49.25, 54.85, 54.92, 58.25, 58.31, 61.05, 114,51, 114.82, 126.81, 128.21, 128.51, 128.72, 140.73, 139.71, 159.61, 159.91, 171.15
3d	1.52 {d, 12 H, $J = 7.4$ , [(CH <sub>3</sub> ) <sub>2</sub> CH] <sub>2</sub> }, 2.61 {m, 2 H, [(CH <sub>3</sub> ) <sub>2</sub> CH] <sub>2</sub> }, 2.71 (t, 2 H, $J = 7.3$ , CH <sub>2</sub> CO), 2.85 (t, 2 H, $J = 7.3$ , NCH <sub>2</sub> CH <sub>2</sub> ), 3.10 (s, 3 H, NCH <sub>3</sub> ), 3.59 (s, 4 H, NCH <sub>2</sub> Ph), 3.69 (s, 3 H, OCH <sub>3</sub> )	21.15, 31.25, 38.75, 48.30, 49.31, 61.50, 171.15
3e	1.35 [s, 9 H, (CH <sub>3</sub> ) <sub>3</sub> C], 2.34 [t, 4 H, $J = 6.8$ , N(CH <sub>2</sub> ) <sub>2</sub> ], 2.54 (t, 2 H, $J = 7.3$ , NCH <sub>2</sub> ), 2.63 (t, 2 H, $J = 7.3$ , CH <sub>2</sub> CO), 3.08 (s, 3 H, NCH <sub>3</sub> ), 3.33 [t, 4 H, $J = 6.8$ , N(CH <sub>2</sub> ) <sub>2</sub> ], 3.60 (s, 3 H, OCH <sub>3</sub> )	28.26, 29.37, 32.00, 43.11, 52.76, 53.30, 61.16, 79.47, 154.55, 170.54
3f	2.88 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 3.15 (s, 3 H, NCH <sub>3</sub> ), 3.57 (s, 3 H, OCH <sub>3</sub> ), 4.29 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> ) 6.98–7.06 (m, 2 H, ArH), 7.66 (s, 1 H, ArH)	31.92, 33.38, 41.95, 61.11, 121.57, 128.77, 137.14, 170.67
3g	2.42 (t, 2 H, <i>J</i> = 6.8, CH <sub>2</sub> CO), 2.62 (t, 2 H, <i>J</i> = 6.8, NCH <sub>2</sub> ), 2.66 [t, 4 H, <i>J</i> = 7.3, N(CH <sub>2</sub> ) <sub>2</sub> ], 3.11 (s, 3 H, NCH <sub>3</sub> ), 3.63 (s, 3 H, OCH <sub>3</sub> ), 3.64 [t, 4 H, <i>J</i> = 7.3, O(CH <sub>2</sub> ) <sub>2</sub> ]	28.83, 31.63, 44.32, 53.09, 60.80, 66.11, 172.46
3h	1.50–1.65 (m, 2 H, CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ), 1.82–1.99 (m, 4 H, CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ), 2.87 (t, 2 H, $J = 7.3$ , CH <sub>2</sub> CO), 3.06 (s, 3 H, NCH <sub>3</sub> ), 2.98–3.10 [m, 6 H, (CH <sub>2</sub> ) <sub>2</sub> NCH <sub>2</sub> ], 3.63 (s, 3 H, OCH <sub>3</sub> )	24.30, 26.33, 30.41, 32.11, 49.31, 56.71, 62.02, 171.30
3i	2.27 [s, 6 H, N(CH <sub>3</sub> ) <sub>2</sub> ], 2.65–2.78 (m, 4 H, CH <sub>2</sub> CO, NCH <sub>2</sub> ), 3.10 (s, 3 H, NCH <sub>3</sub> ), 3.70 (s, 3 H, OCH <sub>3</sub> )	31.10, 32.81, 35.40, 45.62, 60.85, 171.82

Table 4 NMR Data for Compounds 3a-i

solution of 1ga-1ia (2.5 mmol) in anhyd THF (20 mL) was added the appropriate aryl Grignard reagent (7.5 mmol) under N2 at 0 °C and the mixture was stirred for 2.5 h period. After quenching the excess of the Grignard reagent with sat. aq NH<sub>4</sub>Cl (30 mL), the crude product was extracted with EtOAc ( $3 \times 20$  mL). The solvent was evaporated from the combined organic layers and the resulting residue was dried in vacuo. The residue was then dissolved in benzene (10 mL) and a little excess of p-toluenesulphonic acid monohydrate was added. The mixture was stirred at reflux for 3 h. After cooling to r.t., the solvent was evaporated under reduced pressure. The resulting material was dissolved in MeOH (20 mL) and a catalytic amount of Pd 10% (on activated charcoal) was added. The mixture was stirred at r.t. under a H<sub>2</sub> atm (ballon pressure was used). After 12 h, the mixture was filtered through Celite. The solvent was evaporated from the filtrate and the resulting residue was purified by column chromatography (hexane-EtOAc) to afford tertiary 1-(3,3diarylpropyl)amines 7a-c as colourless syrups in good yields (68–70%).

**1-[3-(4-Methoxyphenyl)-3-phenylpropyl]morpholine (7a)** Yield: 0.52 g (68%); mp (hydrochloride salt) 58–62 °C.

IR (KBr): 3098, 3032, 2855, 1590, 1432 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 2.11-2.28$  (m, 4 H,  $CH_2CH_2$ ), 2.30 [t, 4 H, J = 6.8 Hz, N(CH<sub>2</sub>)<sub>2</sub>], 3.59 (s, 3 H, ArOCH<sub>3</sub>), 3.82 [t, 4 H, J = 6.8 Hz, O(CH<sub>2</sub>)<sub>2</sub>], 4.01 (t, 1 H, J = 7.4 Hz, CHCH<sub>2</sub>), 6.69 (d, 2 H, J = 8.3 Hz, ArH), 7.04 (d, 2 H, J = 8.3 Hz, ArH), 7.10–7.51 (m, 5 H, ArH).

 $^{13}\text{C}$  NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 33.47, 46.32, 48.83, 53.55, 54.85, 66.81, 114.12, 120.71, 125.51, 128.41, 129.20, 129.55, 137.88, 154.87.

Anal. Calcd for  $C_{20}H_{25}NO_2$ : C, 77.14; H, 8.09; N, 4.50. Found: C, 77.30; H, 7.98; N, 4.34.

Table 5 NMR Data for Compounds 1aa-1ia

Product	<sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> /TMS) $\delta$ , <i>J</i> (Hz)	$^{13}$ C NMR (75 MHz, CDCl <sub>3</sub> /TMS) $\delta$
1aa	2.89 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 3.04 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> ), 3.56 (s, 4 H, NCH <sub>2</sub> Ph), 7.13–7.41 (m, 13 H, ArH), 7.78–7.89 (d, 2 H, <i>J</i> = 7.2, ArH)	36.21, 47.18, 58.17, 126.81, 128.10, 128.21, 128.40, 128.65, 132.91, 134.21, 139.08, 198.31
1ab	2.87 (t, 2 H, <i>J</i> = 6.8, CH <sub>2</sub> CO), 3.01 (t, 2 H, <i>J</i> = 6.8, NCH <sub>2</sub> ), 3.56 (s, 4 H, NCH <sub>2</sub> Ph), 3.70 (s, 3 H, ArOCH <sub>3</sub> ) 6.80–6.85 (m, 2 H, ArH), 7.13–7.29 (m, 10 H, ArH), 7.71–7.74 (m, 2 H, ArH)	36.13,49.23,55.41,58.74,117.25,126.69,127.94128.93,129.1 4, 131.87, 129.56, 163.05, 197.56
1ac	2.35 (s, 3 H, ArCH <sub>3</sub> ), 2.92 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 3.06 (t, 2 H, 7.3, NCH <sub>2</sub> ), 3.56 (s, 4 H, NCH <sub>2</sub> Ph), 6.81–7.01 (m, 2 H, ArH), 7.21–7.41 (m, 12 H, ArH)	32.31,34.21,47.11,58.21,125.31,126.93,128.21128.43,129.1 1,132.71,133.21,139.05,197.61
1ad	0.88 (t, 3 H, $J$ = 7.3, CH <sub>3</sub> ), 1.21–1.27 (m, 2 H, CH <sub>2</sub> CH <sub>3</sub> ), 1.46–1.50 (m, 2 H, CH <sub>2</sub> CH <sub>2</sub> ), 2.22 (t, 2 H, $J$ = 7.3, CH <sub>2</sub> CO), 2.54 (t, 2 H, $J$ = 6.8, CH <sub>2</sub> CO), 2.76 (t, 2 H, $J$ = 6.8, NCH <sub>2</sub> ), 3.50 (s, 4 H, NCH <sub>2</sub> Ph), 7.20–7.34 (m, 10 H, ArH)	13.68, 22.11, 25.52, 40.66, 42.10, 48.47, 58.19, 126.78, 128.01, 128.65, 139.08, 209.71
1ae	1.10 [d, 6 H, $J$ = 7.10, (CH <sub>3</sub> ) <sub>2</sub> CH], 2.50–2.60 (m, 1 H-, CHCO), 2.60 (t, 2 H, $J$ = 6.8, CH <sub>2</sub> CO), 2.75 (t, 2 H, $J$ = 6.8, NCH <sub>2</sub> ) 3.60 (s, 4 H, NCH <sub>2</sub> Ph), 7.21–7.34 (m, 10 H, ArH)	18.05, 38.36, 40.69, 48.68, 58.41, 126.93, 127.40, 127.90, 139.30, 213.80
1af	1.78 (dd, 3 H, $J = 7.8$ , 1.9, CH <sub>3</sub> ), 2.72 (t, 2 H, $J = 6.8$ , CH <sub>2</sub> CO), 2.85 (t, 2 H, $J = 6.8$ , NCH <sub>2</sub> ), 3.56 (s, 4 H, NCH <sub>2</sub> Ph), 5.99 (d, 1 H, $J = 16.3$ , CH=CHCH <sub>3</sub> ), 6.62–6.75 (m, 1 H, CH=CHCH <sub>3</sub> ), 7.20–7.34 (m, 10 H, ArH)	19.34, 42.58, 48.64, 58.19, 122.21, 127.78, 128.41, 128.65, 139.08, 141.18, 196.91
1ag	2.85 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 3.04 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> ), 3.56 (s, 4 H, NCH <sub>2</sub> Ph), 7.10–7.90 (m, 17 H, ArH)	38.73, 49.71, 59.14, 126.78, 126.81, 127.70, 127.75, 127.77, 127.96, 128.16, 128.79, 129.76, 130.10, 132.79, 132.87, 134.21, 139.08, 199.79
1ba	2.81 (s, 3 H, NCH <sub>3</sub> ), 3.30 (t, 2 H, <i>J</i> = 6.8, CH <sub>2</sub> CO), 3.42 (t, 2 H, <i>J</i> = 6.8, NCH <sub>2</sub> ), 7.42–7.58 (m, 6 H, ArH), 7.77–7.79 (m, 2 H, ArH), 7.91–7.93 (m, 2 H, ArH)	36.33, 38.30, 45.95, 128.22, 128.68, 129.14, 132.61, 133.34, 133.43, 136.54, 137.71, 197.68
1bb	2.82 (s, 3 H, NCH <sub>3</sub> ), 3.28 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 3.46 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> ), 3.87 (s, 3 H, ArOCH <sub>3</sub> ), 6.92–6.95 (m, 2 H, ArH), 7.51–7.62 (m, 2 H, ArH), 7.91–8.01 (m, 5 H, ArH)	36.11, 37.70, 46.05, 55.60, 113.76,127.20, 129.09, 129.52,130.20, 132.65, 137.34,163.72, 196.55
1bc	2.77 (s, 3 H, ArC <i>H</i> <sub>3</sub> ), 2.80 (d, 3 H, NCH <sub>3</sub> ), 3.21 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 3.42 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> ), 7.2–7.3 (m, 2 H, ArH), 7.12–7.25 (m, 2 H, ArH), 7.51–7.62 (m, 5 H, ArH)	32.35, 36.33, 38.41, 45.98, 125.81, 126.93, 128.72, 129.56, 132.31, 133.34, 137.71, 139.11, 197.34
1bd	0.89 (t, 3 H, $J$ = 7.3, CH <sub>3</sub> ), 1.24–1.34 (m, 2 H, CH <sub>2</sub> CH <sub>3</sub> ), 1.49–1.56 (m, 2 H, CH <sub>2</sub> CH <sub>2</sub> ), 2.40 (t, 2 H, $J$ = 7.3, CH <sub>2</sub> CO), 2.72 (t, 2 H, $J$ = 6.8, CH <sub>2</sub> CO), 2.73 (s, 3 H, NCH <sub>3</sub> ), 3.24 (t, 2 H, $J$ = 6.8, NCH <sub>2</sub> ), 7.50–7.60 (m, 3 H, ArH), 7.76 (dd, 2 H, $J$ = 7.3, 1.0, ArH)	13.81, 22.23, 25.63, 36.41, 40.71, 42.41, 46.11, 128.64, 129.56, 133.91, 137.05, 209.81
1be	1.21 [d, 6 H, $J$ = 7.0, (C $H_3$ ) <sub>2</sub> CH], 2.48–2.55 (m, 1 H, CHCO), 2.75 (t, 2 H, $J$ = 6.8, CH <sub>2</sub> CO), 2.80 (s, 3 H, NCH <sub>3</sub> ), 3.30 (t, 2 H, $J$ = 6.8, NCH <sub>2</sub> ), 7.50–7.70 (m, 5 H, ArH)	18.20, 38.35, 40.75, 42.40, 46.10, 128.56, 129.63, 130.01, 137.10, 210.10
1bf	1.75 (dd, 3 H, $J = 7.8$ , 1.9, CH <sub>3</sub> ), 2.72 (t, 2 H, $J = 6.8$ , CH <sub>2</sub> CO), 2.78 (s, 3 H, NCH <sub>3</sub> ), 3.26 (t, 2 H, $J = 6.8$ , NCH <sub>2</sub> ), 5.87 (d, 1 H, $J = 16.3$ , CH=CHCH <sub>3</sub> ), 6.68–6.79 (m, 1 H, CH=CHCH <sub>3</sub> ), 7.50–7.76 (m, 5 H, ArH)	19.37, 36.38, 38.90, 46.15, 122.11, 127.68, 128.60, 129.76, 133.99, 137.15, 199.91
1bg	2.80 (s, 3 H, NCH <sub>3</sub> ), 3.35 (t, 2 H, <i>J</i> = 6.8, CH <sub>2</sub> CO), 3.45 (t, 2 H, <i>J</i> = 6.8, NCH <sub>2</sub> ), 7.42–7.90 (m, 12 H, ArH)	36.05, 38.01, 45.84, 127.56, 128.22, 128.68, 128.72, 128.92, 129.14, 129.56, 129.80, 132.61, 133.34, 133.43, 136.54, 137.71, 137.90, 197.96
1ca	2.96 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 3.14 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> ), 3.57 (s, 2 H, NCH <sub>2</sub> Ph), 3.61 (s, 2 H, NCH <sub>2</sub> ), 3.84 [s, 6 H, Ar(OCH <sub>3</sub> ) <sub>2</sub> ], 6.75–7.95 (m, 13 H, ArH)	36.21, 47.18, 55.88, 58.11, 58.18, 114.17, 114.15, 126.82, 128.16, 128.43, 128.48, 128.76, 129.15, 131.65, 136.65, 139.19, 139.71, 159.90, 159.24, 197.62

Downloaded by: UC Santa Barbara. Copyrighted material.

Table 5 NMR Data for Compounds 1aa-1ia (continued)

Product	<sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> /TMS) δ, <i>J</i> (Hz)	$^{13}$ C NMR (75 MHz, CDCl <sub>3</sub> /TMS) $\delta$
1cb	2.96 (t, 2 H, $J = 6.8$ , CH <sub>2</sub> CO), 3.14 (t, 2 H, $J = 6.8$ , NCH <sub>2</sub> ), 3.57 (s, 2 H, NCH <sub>2</sub> Ph), 3.61 (s, 2 H, NCH <sub>2</sub> ), 3.84 (s, 3 H, ArOCH <sub>3</sub> ), 3.88 (s, 3 H, ArOCH <sub>3</sub> ), 3.89 (s, 6 H, ArOCH <sub>3</sub> ), 6.81–8.01 (m, 12 H, ArH)	35.89, 49.86, 54.23, 58.11, 58.64, 113.15, 114.15, 114.75, 126.87, 128.21, 128.43, 128.48, 128.76, 129.10, 136.66, 139.78, 158.54, 158.68, 159.10, 198.16
1cc	2.22 (s, 3 H, ArCH <sub>3</sub> ), 2.78 (t, 2 H, $J$ = 7.3, CH <sub>2</sub> CO), 3.17 (t, 2 H, $J$ = 7.3, NCH <sub>2</sub> ), 3.56 (s, 2 H, NCH <sub>2</sub> Ph), 3.59 (s, 2 H, NCH <sub>2</sub> ), 3.83 [s, 6 H, Ar(OCH <sub>3</sub> ) <sub>2</sub> ], 6.81–7.31 (m, 12 H, ArH)	23.33, 34.43, 46.77, 58.22, 58.63, 114.21, 114.25, 126.78, 128.33, 128.49, 128.58, 128.76, 129.02, 136.65, 136.81, 137.87, 139.19, 154.20, 154.44, 197.62
1cd	0.91 (t, 3 H, $J = 7.3$ , CH <sub>3</sub> ), 1.22–1.29 (m, 2 H, CH <sub>2</sub> CH <sub>3</sub> ), 1.47–1.51 (m, 2 H, CH <sub>2</sub> CH <sub>2</sub> ), 2.23 (t, 2 H, $J = 7.3$ , CH <sub>2</sub> CO) 2.55 (t, 2 H, $J = 6.8$ , CH <sub>2</sub> CO), 2.78 (t, 2 H, $J = 6.8$ , NCH <sub>2</sub> ), 3.50 (s, 2 H, NCH <sub>2</sub> Ph), 3.54 (s, 2 H, NCH <sub>2</sub> ), 3.85 [s, 6 H, Ar(OCH <sub>3</sub> ) <sub>2</sub> ], 6.77–7.36 (m, 8 H, ArH)	13.78, 22.78, 25.82, 41.76, 42.70, 48.57, 58.29, 58.63, 113.12, 114.11, 126.82, 128.12, 128.75, 129.34, 139.32, 139.74, 152.76, 152.86, 208.89
1ce	1.11 [d, 6 H, $J$ = 7.1, C(CH <sub>3</sub> ) <sub>2</sub> ], 2.50–2.60 (m, 1 H -, CHCO), 2.62 (t, 2 H, $J$ = 6.8, CH <sub>2</sub> CO), 2.78 (t, 2 H, $J$ = 6.8, NCH <sub>2</sub> ), 3.52 (s, 2 H, NCH <sub>2</sub> Ph), 3.56 (s, 2 H, NCH <sub>2</sub> ), 3.86 (s, 3 H, ArOCH <sub>3</sub> ), 3.89 (s, 3 H, ArOCH <sub>3</sub> ), 6.76–7.40 (m, 8 H, ArH)	18.07, 38.18, 40.69, 48.62, 55.88, 58.11 58.18, 110.87, 112.04, 126.83, 128.25, 128.82, 129.50, 139.23, 139.43, 158.12, 158.45, 201.11
1da	1.55 {d, 12 H, $J = 7.4$ , [(CH <sub>3</sub> ) <sub>2</sub> CH] <sub>2</sub> }, 2.65 {m, 2 H, [(CH <sub>3</sub> ) <sub>2</sub> CH] <sub>2</sub> }, 2.81 (t, 2 H, $J = 6.9$ , CH <sub>2</sub> CO), 3.10 (t, 2 H, $J = 6.9$ , NCH <sub>2</sub> ), 7.31–7.59 (m, 3 H, ArH), 7.88–8.05 (m, 2 H, ArH)	21.18, 32.85, 38.78, 48.35, 127.86, 129.18, 131.87, 135.63, 196.16
1eb	1.50 [s, 9 H, (CH <sub>3</sub> ) <sub>3</sub> C], 3.25 [m, 6 H, N(CH <sub>2</sub> ) <sub>2</sub> , CH <sub>2</sub> CO], 3.40 [br s, 4 H, N(CH <sub>2</sub> ) <sub>2</sub> ], 3.98 (s, 3 H, OCH <sub>3</sub> ), 6.92 (d, 2 H, $J = 5.5$ , ArH), 7.98 (d, 2 H, $J = 5.5$ , ArH)	28.20, 32.30, 43.28, 55.27, 55.45, 55.57, 81.26, 113.71, 129.92, 130.37, 153.90, 163.50, 197.44
1fc	2.35 (s, 3 H, ArCH <sub>3</sub> ), 2.92 (t, 2 H, J = 7.3, CH <sub>2</sub> CO), 4.35 (t, 2 H, J = 7.3, NCH <sub>2</sub> ), 6.98–7.16 (m, 4 H, ArH), 7.41–7.66 (m, 3 H, ArH)	21.30, 32.31, 42.85, 120.30, 125.50, 128.47 129.22, 129.60, 137.85, 138.35, 198.18
1gg	2.58 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 2.75 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> ), 2.85 [t, 2 H, <i>J</i> = 6.9, N(CH <sub>2</sub> ) <sub>2</sub> ], 3.68 [t, 4 H, <i>J</i> = 6.9, O(CH <sub>2</sub> ) <sub>2</sub> ], 7.31–7.97 (m, 7 H, ArH)	32.63, 46.32, 53.55, 66.81, 123.32, 127.86, 127.95,128.52,128.82, 129.10, 129.18, 131.10, 131.87, 135.63, 196.17
1ga	2.56 (t, 2 H, <i>J</i> = 7.3, CH <sub>2</sub> CO), 2.75 (t, 2 H, <i>J</i> = 7.3, NCH <sub>2</sub> ), 2.80 [t, 4 H, <i>J</i> = 7.3, N(CH <sub>2</sub> ) <sub>2</sub> ], 3.78 [t, 4 H, <i>J</i> = 7.3, O(CH <sub>2</sub> ) <sub>2</sub> ], 7.36–7.48 (m, 3 H, ArH), 7.59–7.97 (m, 2 H, ArH)	32.65, 45.22, 52.52, 65.80, 128.43, 128.46, 131.65, 136.67, 195.75
1ha	1.18–1.27 (m, 2 H, CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ), 1.32–1.58 (m, 4 H, CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ), 2.16 [m, 4 H, N(CH <sub>2</sub> ) <sub>2</sub> ], 2.49 (t, 2 H, J = 7.3 Hz, NCH <sub>2</sub> ), 2.90 (t, 2 H, CH <sub>2</sub> CO), 7.07–7.27 (m, 3 H, ArH), 7.68–7.70 (m, 2 H, ArH)	23.54, 25.05, 35.70, 52.77, 53.54, 125.80, 126.33, 131.97, 136.28, 198.36
1ia	2.41 [s, 6 H, N(CH <sub>3</sub> ) <sub>2</sub> ], 2.91 (t, 2 H, NCH <sub>2</sub> ), 3.37 (t, 2 H, CH <sub>2</sub> CO), 7.41–7.63 (m, 3 H, ArH), 7.68–7.78 (m, 2 H, ArH)	32.15, 34.32, 46.62, 128.28, 128.34, 132.45, 136.66, 194.65

# 1-(3,3-Diphenylpropyl)piperidine (7b)

Yield: 0.48 g (70%); mp (hydrochloride salt) 216-218 °C (Lit.<sup>14</sup> mp 215-216 °C). Spectral properties were in agreement with literature<sup>14</sup> values.

# 1-[3-(4-Methylphenyl)-3-phenylpropyl]-*N*,*N*-dimethylamine (7c)

Yield: 0.43 g (69%); mp (hydrochloride salt) 154–157 °C (Lit.<sup>14</sup> mp 156–158 °C). Spectral properties were in agreement with literature<sup>14</sup> values.

# Reaction of 3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyllithium<sup>15</sup> with 3a; 3-(*N*,*N*-Dibenzyl)-1-(3,4,6-tri-*O*benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)propan-1-one (8)

To a solution of **3a** (0.5 g, 1.6 mmol) in anhyd THF (10 mL) was added 3,4,6-tri-*O*-benzyl-2-deoxy- $\alpha$ -D-*arabino*-hexopyranosyllithium (2.0 g, 4.8 mmol) at -78 °C under Ar. The mixture was stirred for 1.5 h. The hydrolysis was achieved by the cautious addition of sat. aq NH<sub>4</sub>Cl solution (30 mL) at -40 °C. After returning to r.t., the

two phases were separated and the aqueous phase was extracted with EtOAc (3  $\times$  20 mL). The organic phases were combined, washed with brine (40 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent under reduced pressure gave the crude product which was purified by column chromatography (hexane–EtOAc) to afford **8** as a colourless syrup; yield: 61% (0.65 g); [ $\alpha$ ]<sub>D</sub><sup>27</sup> +49.9 (c = 1, CHCl<sub>3</sub>).

Downloaded by: UC Santa Barbara. Copyrighted material

IR (CHCl<sub>3</sub>): 2933, 2869, 1718, 1611, 1454 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.80 (ddd, 1 H,  $J_{2ax,2eq}$  = 13 Hz,  $J_{2ax,3}$  = 8.5 Hz,  $J_{2ax,1}$  = 3.4 Hz, H-2ax), 2.37 (dd, 1 H,  $J_{2eq,2ax}$  = 13.1 Hz,  $J_{2eq,3}$  = 4.8 Hz, H-2eq), 2.97 (t, 2 H, J = 7.3 Hz, CH<sub>2</sub>CO), 3.15 (t, 2 H, J = 7.3 Hz, NCH<sub>2</sub>), 3.67–3.72 (m, 5 H, NCH<sub>2</sub>Ph, H-6), 3.70 (dd, 1 H,  $J_{6;6}$  = 10.7 Hz,  $J_{6;5}$  = 3.9 Hz, H-6'), 4.06–4.13 (m, 1 H, H-5), 4.48 (dd, 1 H,  $J_{4,3}$  = 12.7 Hz,  $J_{4,5}$  = 11.8 Hz, H-4), 4.59–4.69 (m, 6 H, OCH<sub>2</sub>Ph), 4.86 (dd, 1 H,  $J_{3,4}$  = 12.7 Hz,  $J_{2,3}$  = 8 Hz, H-3), 4.98 (d, 1 H,  $J_{1,2ax}$  = 3.4 Hz, H-1), 7.22–7.87 (m, 25 H, ArH).

<sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>): δ = 35.06 (C-2), 36.45 (CH<sub>2</sub>), 48.84 (CH<sub>2</sub>), 58.08 (NCH<sub>2</sub>Ph), 68.45 (C-5), 70.57 (C-6), 71.42 (C-3),

73.06 (C-4), 74.61 (PhCH<sub>2</sub>O), 77.30 (PhCH<sub>2</sub>O), 77.88 (PhCH<sub>2</sub>O), 96.38 (C-1), 126.59–138.79 (several peaks, C<sub>6</sub>H<sub>5</sub>), 199.22 (C=O).

Anal.Calcd for C<sub>44</sub>H<sub>47</sub>NO<sub>5</sub>: C, 78.89; H, 7.07; N, 2.09. Found: C, 78.78; H, 7.18; N, 2.24.

# 4-Bromo-N-methoxy-N-methylbutanamide (9a)

To a stirred and cooled solution (0 °C) of 4-bromobutanoyl chloride (3 g, 16.1 mmol) and *N*,*O*-dimethlyhydroxylamine hydrochloride (1.5 g, 16.1 mmol) in anhyd CH<sub>2</sub>Cl<sub>2</sub> (40 mL), was added dropwise a solution of anhyd pyridine (2.8 g, 35.4 mmol) dissolved in anhyd CH<sub>2</sub>Cl<sub>2</sub> (15 mL). The reaction mixture was stirred for 1 h. After returning to r.t., the mixture was washed with 2 N HCl (2 × 50 mL), then with sat aq NaHCO<sub>3</sub> solution (50 mL) followed by brine (50 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford **9a** as a colourless oil (1.35 g, 40%) which was readily decomposed to  $\gamma$ -butyrolactone was identical with that of the authentic sample.

## 4-Chloro-N-methoxy-N-methylbutanamide (9b)

According to the same reaction conditions and workup procedure as previously described for **9a**, compound **9b** was obtained as a colourless oil from vacuum distilled 4-chlorobutanoyl chloride<sup>20</sup> (3 g, 21.2 mmol), *N*,*O*-dimethlyhydroxylamine hydrochloride (2 g, 21.2 mmol) in anhyd CH<sub>2</sub>Cl<sub>2</sub> (50 ml), and anhyd pyridine (3.6 g, 46.6 mmol) dissolved in anhyd CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The compound **9b** was directly used without further purification for alkylation with morpholine; yield: 2.8 g (80%).

IR (CHCl<sub>3</sub>): 2965, 1661, 1442, 1179, 1021 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.22 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.74 (t, 2 H, *J* = 6.8 Hz, CH<sub>2</sub>CO), 3.30 (s, 3 H, NCH<sub>3</sub>), 3.75 (t, 2 H, *J* = 6.8 Hz, CICH<sub>2</sub>), 3.82 (s, 3 H, OCH<sub>3</sub>)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 27.0, 28.4, 44.1, 44.3, 60.9, 172.9.

# N-Methoxy-N-methyl-4-morpholinobutanamide 10

Following the general procedure, **10** was prepared as colourless syrup from **9b** (0.94 g, 5.7 mmol), **1g** (0.5 g, 5.7 mmol) and anhyd  $K_2CO_3$  in anhyd MeCN (20mL); yield: 1.1 g (89%).

IR (CHCl<sub>3</sub>): 2990, 1678, 1455, 1478, 1375 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.83 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.38 (t, 2 H, *J* = 7.3 Hz, CH<sub>2</sub>CO), 2.47 [m, 6 H, N(CH<sub>2</sub>)<sub>2</sub>, NCH<sub>2</sub>], 3.18 (s, 3 H, NCH<sub>3</sub>), 3.69 (s, 3 H, OCH<sub>3</sub>), 3.70 [t, 4 H, *J* = 6.8 Hz, O(CH<sub>2</sub>)<sub>2</sub>].

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 21.29, 29.52, 32.18, 48.22, 53.58, 61.18, 66.95, 172.10.

Anal. Calcd for  $C_{10}H_{20}N_2O_3$ : C, 55.53; H, 9.32; N, 12.95. Found: C, 55.40; H, 9.48; N, 13.11.

# 4-Morpholino-1-(2-naphthyl)butan-1-one (11)

Following the general procedure, **11** was prepared as a colourless solid by the addition of 2-naphthylmagnesium bromide [prepared from 2-bromonaphthalene (1.71 g, 8.3 mmol) and Mg (0.226 g, 9.3 mmol) in THF (20 mL) with stirring at reflux for 1 h under a  $N_2$  atm] to the stirred solution of **10** (0.6 g, 2.7 mmol) in THF (10 mL) at 0 °C; yield: 0.62 g (82%); mp 76–78 °C (Lit.<sup>16</sup> mp 77–80 °C).

IR (CHCl<sub>3</sub>): 2998, 1690, 1450, 1485, 1380 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.94 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.40 (t, 2 H, *J* = 7.3 Hz, NCH<sub>2</sub>), 2.42 [t, 4 H, *J* = 7.4 Hz, N(CH<sub>2</sub>)<sub>2</sub>], 2.99 (t, 2 H, *J* = 7.3Hz, CH<sub>2</sub>CO), 3.64 [t, 4 H, *J* = 7.4 Hz, O(CH<sub>2</sub>)<sub>2</sub>], 7.19–7.96 (m, 7 H, ArH).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 21.32, 31.12, 48.11, 53.18, 65.85, 123.12, 126.76, 127.95 128.50, 128.90, 129.09, 129.28, 131.50, 131.87, 135.56, 193.15.

# Acknowledgement

We are grateful to DST, New Delhi for the financial support (Project No: SP/S1/G-06/2000) of this research and RSIC (IIT), Chennai for the spectral data. One of us (VS) thanks IIT, Chennai for the scholarship and Dr. Jaimala Singh, CLRI, Chennai for constant support. We also thank Dr. S. Ganesh, Sygene Internationeal (P) Ltd., Banglore, for helping with the NMR data.

# References

- (a) Tramontini, M.; Angiolini, L. Mannich Bases, Chemistry and Uses; CRC: Boca Raton, **1994**. (b) Tramontini, M.; Angiolini, L. Tetrahedron **1990**, 46, 1791.
- (2) Arend, M.; Risch, N. *Synlett* **1997**, 974; and references cited therein.
- (3) (a) Kobayashi, S.; Iwamota, S.; Nagayama, S. Synlett 1997, 1099. (b) Loh, T. P.; Wei, L. L. Tetrahedron Lett. 1998, 39, 323.
- (4) Davies, S. G.; Ichihara, O. Tetrahedron Lett. 1998, 39, 6045.
- (5) Loh, T. P.; Wei, L. Synlett **1998**, 975.
- (6) Davies, S. G.; McCarthy, T. D. Synlett 1995, 700.
- (7) Katritzky, A. R.; Yang, Z.; Lam, J. N. J. Org. Chem. 1993, 58, 1970.
- (8) (a) Mechelke, M. F.; Meyers, A. I. *Tetrahedron Lett.* 2000, *41*, 4339. (b) Yang, C.; Yasuda, N. *Bioorg. Med. Chem. Lett.* 1998, 8, 255. (c) Lee, J. S.; Pyun, D. K.; Lee, W. K.; Lee, C. H. *Bull. Korean Chem. Soc.* 1998, *19*, 1294.
- (9) For an isolated example in the total synthesis of norsecurinine, see: Jacobi, P. A.; Blum, C. A.; Desimone, R. W.; Udodong, U. E. S. J. Am. Chem. Soc. 1991, 113, 5384.
- (10) For reviews concerning chemistry of Weinreb amide, see:
  (a) Sibi, M. P. Org. Prep. Proc. Int. 1993, 25, 15.
  (b) Mentzel, M. P.; Hoffmann, H. M. R. J. Prakt. Chem. 1997, 339, 517. (c) Singh, J.; Satyamurthi, N.; Aidhen, I. S. J. Prakt. Chem. 2000, 342, 340.
- (11) Kendall, E. C.; McKenzie, B. Org. Synth. **1951**, Coll. Vol. I, 131.
- (12) Greene, T. W.; Wuts, P. G. M. Protecting Groups in Organic Synthesis, 3rd ed.; Wiley: NewYork, **1999**, Chap. 10.
- (13) Sabitha, G.; Reddy, B. V. S.; Abraham, S.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 1569.
- (14) Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 1915; and references cited therein.
- (15) Lancelin, J.-M.; Morin-Allory, L.; Sinay, P. J. Chem. Soc., Chem. Commun. **1984**, 355.
- (16) Brown, G. R.; Bamford, A. M.; Bowyer, J.; James, D. S.; Rankine, N.; Tang, E.; Torr, V.; Culbert, E. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 575.
- (17) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. J. Am. Chem. Soc. **1995**, *117*, 2675.
- (18) (a) Robertson, D. W.; Kruhinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412. (b) Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339.
  (c) Carlier, P. R.; Lo, K. M.; Lo, M. M.-C.; Williams, I. D. J. Org. Chem. **1995**, *60*, 7511.
- (19) (a) 3b: Cairns, T. L.; Sauer, J. C. J. Org. Chem. 1955, 20, 627. (b) Compound 3c was prepared by refluxing a mixture of benzylamine (1 g, 9.33 mmol) and veratraldehyde (1.55 g, 9.33 mmol) in benzene (10 mL) for 2 h. The solvent was evaporated and dissolved in anhyd EtOH (8 mL), treated with NaBH<sub>4</sub> (0.68 g, 18 mmol) at 0 °C for 1 h to afford 3c as a colourless oil in quantitative yield (2.5 g, 96%). The product was directly used for further alkylation.
- (20) Goel, O. P.; Seamans, R. E. Synthesis 1973, 538.