Supporting Information

Improved Synthesis of Cyclic α -Hydrazino Acids of 5 to 9-Membered Rings and Optical Resolution of 5, 6, 7-Membered Ring Hydrazino Acids

Indranil Duttagupta,^[a] Koushik Goswami,^[a] Prathyusha Chatla,^[a] and Surajit Sinha*^[a]

*Department of Organic Chemistry, Indian Association for the Cultivation of Science,
Jadavpur, Kolkata 700 032, India*

ocss5@iacs.res.in

Supporting Information Contents:

<i>Contents</i>	S1
<i>Experimental Procedure</i>	S2
<i>¹H & ¹³C NMR spectra</i>	5-40

Experimental Procedure:

2-Allyl-2-(*N*, *N'*-di-*tert*-butoxycarbonyl-hydrazino)-malonic acid di-*tert*-butyl ester, 7a. The allyl substituted ditertiarybutylmalonate (10.4 g, 0.04 mol) was dissolved in THF (50 ml) and was added NaH (2.2 g, 0.092 mol) at 0 °C. DBAD (9.2 g, 0.04 mol) was added dropwise and the reaction mixture was then allowed to stir for 15 min at room temperature. After stirring for 15 min at room temperature the reaction mixture was quenched with 5 ml satd. NH_4Cl soln., THF was removed and extracted with EtOAc (150 ml). The EtOAc layer was washed with water and brine. Removal of organic solvent followed by silica gel column chromatography (15% EA in PE) yielded the product **7a** in almost quantitative yield (18.7 g, 0.038 mol, 96%) as colorless to faint yellow oil. Overall yield from di-*tert*-butyl malonate 69% (2 steps).

^1H NMR (500 MHz, CDCl_3) δ 6.36 (s, 0.66H), 6.02 – 6.08 (m, 1H), 5.96 (s, 0.34H), 5.03 – 5.10 (m, 2H), 3.003 (brm, 0.66H), 2.89 – 2.93 (dd, 1.34H, $J = 7, 7.5$ Hz), 1.43 – 1.46 (m, 32H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.3, 155.4, 154.8, 133.8, 117.8, 82.9, 82.6, 82.3, 80.8, 39.7, 28.4, 28.4, 28.2, 28.0, 27.9; IR ν max KBr, 2983.98, 1764.93, 1732.13, 1234.48, 1155.40; HRMS (ESI) ($M + \text{Na}$) $^+$ calculated for, $\text{C}_{24}\text{H}_{42}\text{N}_2\text{O}_8\text{Na}^+ = 509.2839$, found 509.2839.

2-Allyl-2-(*N*,*N'*-di-*tert*-butoxycarbonyl-hydrazino)-malonic acid di-benzyl ester, 7b. Yield, quantitative (9.88 g, 0.018 mol of **7b** from 5.97 g, 0.018 mol of dibenzyl 2-allylmalonate). Overall yield from di-benzyl malonate 66.6% (2 steps).

^1H NMR (500 MHz, CDCl_3) δ 7.32 – 7.38 (m, 10H), 6.95 (d, 1H, $J = 11.5$ Hz), 6.54 – 6.62 (m, 1H), 6.23 – 6.43 (brm, 1H), 5.93 (brs, 1H), 5.55 (d, 1H, $J = 16.5$ Hz), 5.44 (d, 1H, $J = 10.5$ Hz), 5.03 – 5.19 (m, 4H), 1.32 – 1.57 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.1, 153.3, 135.6, 131.8, 131.2, 128.6, 128.4, 128.4, 128.2, 124.3, 80.9, 67.3, 67.1, 28.2, 28.1; IR ν max KBr, 3327.32, 1737.92, 1714.77; HRMS (ESI) ($M + \text{Na}$) $^+$ calculated for, $\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_8\text{Na}^+ = 577.2526$, found 577.2524.

2-But-3-enyl-2-(*N*, *N'*-di-*tert*-butoxycarbonyl-hydrazino)-malonic acid di-*tert*-butyl ester, 7c. Yield, quantitative (12.6 g, 0.025 mol of **7c** from 7.1 g, 0.026 mol of di-*tert*-butyl 2-(but-3-enyl)malonate). Overall yield from di-*tert*-butyl malonate 67.5% (2 steps).

^1H NMR (500 MHz, CDCl_3) δ 6.42 (s, 0.70H), 6.02 (br s, 0.30 H), 5.77 – 5.84 (m, 1H), 5.02 (d, 1H, $J = 17$ Hz), 4.93 (d, 1H, $J = 10$ Hz), 2.54 (br m, 1H), 2.17 – 2.32 (m, 1 H), 1.45 – 1.49 (m, 36H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.7, 155.7, 154.8, 138.7, 114.5, 83.1, 82.5, 80.9, 34.6, 29.2, 28.4, 28.4, 28.2, 28.1, 27.9; IR ν max KBr, 3365.90, 1764.93, 1732.13; HRMS (ESI) ($M + \text{Na}$) $^+$ calculated for $\text{C}_{25}\text{H}_{44}\text{N}_2\text{O}_8\text{Na}^+ = 523.2995$ found 523.2996.

2-But-3-enyl-2-(*N*, *N'*-di-*tert*-butoxycarbonyl-hydrazino)-malonic acid di-benzyl ester, 7d. Yield, quantitative (12.2 g, 0.021 mol of **7d** from 7.4 g, 0.022 mol of di-benzyl 2-(but-3-enyl)malonate). Overall yield from di-*tert*-butyl malonate 68% (2 steps).

^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.37 (m, 10H), 6.42 (br s, 0.68H), 5.76 – 5.82 (m, 1H), 4.89 – 5.22 (m, 6H), 2.37 (br s, 1H), 2.23 (br s, 1H), 1.87 – 1.95 (m, 2H), 1.36 – 1.50 (m, 18H); ^{13}C NMR (500 MHz, CDCl_3) δ 172.0, 155.6, 137.4, 135.4, 128.6, 128.40, 128.1, 115.6, 115.4, 82.1, 81.9, 80.8, 67.0, 61.0, 59.3, 30.1, 28.1, 28.0, 27.7; HRMS (ESI) ($M + \text{Na}$) $^+$ calculated for $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_8\text{Na}^+ = 591.2682$, found 591.2680.

Synthesis of 4 and 5

3,3-Dibenzyl-1,2-di-*tert*-butyl-4,5-dihydro-1,2-diazocine-1,2,3,3(8H)-tetracarboxylate, 8b. Yield 77% (0.417 g, 0.72 mmol) of **8b** in 2 steps from (0.531 g, 0.93 mmol) of **7d**.

^1H NMR (500 MHz, CDCl_3) δ 7.26 – 7.41 (m, 10H), 5.43 – 5.48 (m, 1H), 5.24 – 5.29 (m, 2H), 5.06 – 5.21 (m, 3H), 4.65 – 4.68 (m, 1H), 3.60 – 3.81 (m, 1H), 2.67 – 2.72 (m, 1H), 2.39 – 2.66 (m, 2H), 2.13 – 2.18 (m, 1H), 1.32 – 1.48 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.4, 168.2, 155.3, 153.5, 135.7, 135.4, 128.4, 128.7, 128.5, 128.5, 128.4, 128.3, 128.0, 127.9, 72.6, 67.8, 67.8, 47.5, 31.7, 28.4, 28.0, 21.7; HRMS (ESI) ($M + \text{Na}$) $^+$ calculated for $\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_8\text{Na}^+ = 603.2682$, found 603.2683.

Tetra-*tert*-butyl-4,5-dihydro-1H-1,2-diazocine-1,2,3,3(8H,9H)-tetracarboxylate, 9a. Yield 69% (0.492 g, 0.93 mmol) of **9a** in 2 steps from (0.678 g, 1.3 mmol) of **7c**.

^1H NMR (500 MHz, CDCl_3) δ 5.60 – 5.69 (m, 2H), 3.826– 3.956 (m, 1H), 2.95 – 3.00 (m, 1H), 2.52 – 2.65 (m, 3H), 2.33 (d, 1H, J = 7 Hz), 2.09 (d, 1H, J = 4 Hz), 1.67 – 1.68 (m, 1H), 1.42 – 1.52 (m, 36H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.7, 166.9, 156.5, 153.2, 131.6, 131.4, 129.3, 128.8, 82.1, 82.1, 81.9, 81.9, 81.1, 80.8, 80.7, 77.2, 73.7, 54.0, 53.4, 33.4, 33.0, 29.8, 28.7, 28.5, 28.4, 28.3, 28.2, 28.1, 27.9, 25.8, 25.3, 25.2, 24.9; HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ calculated for $\text{C}_{27}\text{H}_{46}\text{N}_2\text{O}_8\text{Na}^+$ = 549.3152 found 549.3152.

3,3-Dibenzyl-1,2-di-*tert*-butyl-4,5-dihydro-1H-1,2-diazonine-1,2,3,3-(8H,9H)-tetracarboxylate, 9b. Yield 76% (0.323 g, 0.54 mmol) of **9b** in 2 steps from (0.407 g, 0.75 mmol of **7d**).

^1H NMR (500 MHz, CDCl_3) δ 7.28 – 7.34 (m, 10H), 6.54 – 5.58 (q, 1H), 5.46 (brs, 1H), 5.08 – 5.25 (m, 4H), 3.93 (d, 1H, J = 13.5 Hz), 3.07 – 2.89 (brs, 1H), 2.57 – 2.63 (m, 3H), 2.45 (d, 1H, J = 8 Hz), 2.02 – 2.13 (m, 1H), 1.81 (brs, 1H), 1.42 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.0, 167.9, 155.6, 153.2, 135.2, 134.6, 129.0, 128.2, 128.0, 127.9, 127.7, 127.5, 81.2, 80.6, 72.1, 67.3, 52.9, 32.1, 27.7, 27.4, 24.5, 24.5; HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ calculated for $\text{C}_{33}\text{H}_{42}\text{N}_2\text{O}_8\text{Na}^+$ = 617.2839 found 617.2836.

Tetra-*tert*-butyl-1,2-diazonane-1,2,3,3-tetracarboxylate, 10b: Yield, quantitative (0.45 g, 0.85 mmol) from 0.452 g, 0.86 mmol of **9a**.

^1H NMR (500 MHz, CDCl_3) δ 4.03 (br m, 0.50H), 3.85 (br s, 0.50H), 3.14 (br m, 1H), 1.99 – 2.16 (m, 3H), 1.31 – 1.67 (m, 43H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.6, 166.8, 156.0, 153.4, 82.4, 82.1, 81.9, 80.7, 80.5, 75.5, 74.1, 54.7, 54.2, 30.8, 29.8, 29.1, 28.4, 28.4, 28.3, 28.2, 28.1, 28.16, 28.0, 27.4, 22.7, 22.2, 21.3, 20.6. HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ calculated for $\text{C}_{27}\text{H}_{48}\text{N}_2\text{O}_8\text{Na}^+$ = 551.3308 found 551.3309.

1,2-Bis(*tert*-butoxycarbonyl)-1,2-diazocane-3-carboxylic acid, 11. Yield, quantitative (0.242 g, 0.67 mmol) from 0.393 g, 0.67 mmol of **8b**.

^1H NMR (500 MHz, CDCl_3) δ 3.91 – 4.33 (m, 1H), 3.76 – 3.86 (m, 1H), 3.11 – 3.30 (m, 1H), 2.05 – 2.17 (m, 2H), 1.60 – 2.04 (m, 3H), 1.62 – 1.67 (m, 1H), 1.53 – 1.57 (m, 1H), 1.42 – 1.45 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.1, 171.3, 158.3, 157.6, 156.1, 155.7, 155.5, 153.5, 152.0, 84.9, 84.3, 84.1, 83.5, 82.7, 82.4, 81.8, 81.3, 67.5, 65.6, 62.4, 61.3, 49.7, 49.6, 48.9, 48.2, 30.5, 29.8, 29.1, 28.5, 28.4, 28.3, 28.1, 28.0, 27.7, 27.6, 27.5, 26.6, 26.5, 26.4, 26.3, 25.9. HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ calculated for $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}_6\text{Na}^+$ = 381.2002 found 381.2002.

1,2-Bis(*tert*-butoxycarbonyl)-1,2-diazonane-3-carboxylic acid, 12. Yield, 99% (0.211 g, 0.56 mmol) from 0.341 g, 0.57 mmol of **9b**.

^1H NMR (500 MHz, CDCl_3) δ 12.90 (brs, 1H), 4.32 – 4.41 (m, 0.34H), 4.12 – 4.16 (m, 0.55H), 4.02 – 4.11 (m, 0.93H), 3.93 – 3.97 (m, 0.18H), 3.30 – 3.40 (m, 0.74H), 3.09 – 3.17 (m, 0.26), 2.24 – 2.36 (m, 1H), 1.84 – 2.02 (m, 2.5H), 1.70 – 1.76 (m, 1.5H), 1.56 – 1.67 (m, 3Hs), 1.44 – 1.53 (m, 21H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 158.7, 152.4, 84.4, 84.2, 66.9, 66.8, 66.6, 53.4, 52.2, 51.6, 28.7, 28.5, 28.3, 28.2, 28.1, 28.1, 28.0, 27.7, 27.6, 26.1, 26.1, 25.9, 25.4, 24.9, 24.7, 24.3, 24.0; HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ calculated for $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_6\text{Na}^+$ = 395.2158 found 395.2159

1,2-Diazocane-3-carboxylic acid, 4. Yield, quantitative (0.229 g, 0.59 mmol) from **11** (0.213 g, 0.59 mmol).

^1H NMR (500 MHz, CD_3OD) δ 3.70 – 3.73 (q, 1H, J = 6.5), 3.05 – 3.11 (m, 2H), 2.19 (s, 1H), 1.89 – 1.96 (brm, 3H), 1.81 (brs, 2H), 1.64 (s, 2H), 1.26 – 1.31 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.6, 59.4, 49.4, 48.14, 47.9, 47.8, 47.6, 47.5, 47.3, 47.1, 26.1, 24.9, 24.4, 22.2; HRMS (ESI) ($\text{M} + \text{H}$) $^+$ calculated for $\text{C}_7\text{H}_{15}\text{N}_2\text{O}_2^+$ = 159.1134 found 159.1127.

1,2-Diazonane-3-carboxylic acid, 5. Yield, quantitative, (0.185 g, 0.46 mmol) from **12** (0.172 g, 0.46 mmol).

^1H NMR (500 MHz, CD_3OD) δ 3.71 – 3.73 (m, 1H), 3.05 – 3.15 (m, 2Hs), 2.15 (brs, 1H), 2.01 (brs, 1H), 1.84 – 1.87 (m, 2Hs), 1.79 – 1.82 (m, 4Hs), 1.58 – 1.78 (m, 2Hs); ^{13}C NMR (125 MHz, CD_3OD) δ 173.6, 59.6, 48.9, 47.7, 47.5, 47.3, 47.2, 47.0, 46.8, 46.7, 25.0, 22.4, 22.3, 20.4; HRMS (ESI) $(\text{M} + \text{H})^+$ calculated for $\text{C}_8\text{H}_{18}\text{N}_2\text{O}_2^+ = 173.1290$ found 173.1283.

((*Tert*-butoxycarbonylamino)-3-phenylpropyl) 1,2-di-*tert*-butyl piperazine-1,2,3-tricarboxylate, 17a. Yield 33% (0.018 g, 0.033 mmol of **17a**) from **14** (0.033 g, 0.1 mmol). Overall yield 73% (3 mg, 0.0053 mmol mixture).

$[\alpha]_{\text{D}}^{25} - 8.12$ (c 2.57, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.17 – 7.29 (m, 5H), 6.48 (d, 0.74H, $J = 8.5$ Hz), 6.36 (d, 0.26H, $J = 8.5$ Hz), 5.00 – 5.15 (m, 0.5H), 4.90 (brs, 0.24H), 4.65 – 4.77 (m, 0.26H), 3.86 – 4.12 (m, 4H), 2.98 – 3.06 (m, 1H), 2.76 – 2.90 (m, 2H), 2.03 – 2.13 (m, 1H), 1.60 – 1.83 (m, 3H), 1.33 – 1.54 (m, 28H); ^{13}C (125 MHz, CDCl_3) δ 170.6, 170.3, 168.6, 156.1, 155.3, 154.8, 154.2, 153.2, 152.9, 138.6, 137.3, 129.6, 129.4, 128.7, 128.5, 126.8, 126.3, 82.6, 81.8, 81.3, 80.6, 79.8, 78.8, 66.0, 65.6, 65.4, 65.2, 54.5, 54.0, 51.3, 45.8, 38.4, 38.1, 37.9, 37.6, 28.7, 28.5, 28.3, 24.7, 24.2, 20.6, 19.9; HRMS (ESI) $(\text{M} + \text{Na})^+$ calculated for $\text{C}_{29}\text{H}_{45}\text{N}_3\text{O}_8\text{Na}^+ = 586.3104$ found 586.3100.

((*Tert*-butoxycarbonylamino)-3-phenylpropyl) 1,2-di-*tert*-butyl piperazine-1,2,3-tricarboxylate, 17b. Yield 35% (0.02 g, 0.035 mmol of **17b**) from **14** (0.033 g, 0.1 mmol).

$[\alpha]_{\text{D}}^{25} - 1.34$ (c 2.4, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.19 – 7.28 (m, 5H), 5.79 – 5.84 (brm, NH proton), 5.00 (brs, 0.54H), 4.82 (brs, 0.21H), 4.65 (brs, 0.25H), 3.90 – 4.29 (m, 4H), 2.69 – 3.12 (m, 3H), 2.04 – 2.13 (m, 1H), 1.70 – 1.87 (m, 2H), 1.40 – 1.56 (m, 28H); ^{13}C (125 MHz, CDCl_3) δ 170.7, 169.7, 155.8, 155.3, 154.7, 153.0, 138.2, 137.2, 129.6, 129.4, 128.7, 128.6, 128.6, 126.8, 126.5, 82.0, 81.9, 81.2, 80.6, 79.7, 79.6, 79.0, 65.6, 65.5, 55.1, 54.7, 51.6, 51.1, 45.4, 45.0, 42.8, 38.3, 38.0, 24.2, 24.0, 20.7, 20.1; HRMS (ESI) $(\text{M} + \text{Na})^+$ calculated for $\text{C}_{29}\text{H}_{45}\text{N}_3\text{O}_8\text{Na}^+ = 586.3104$ found 586.3100.

3-(2-(*Tert*-butoxycarbonylamino)-3-phenylpropyl) 1,2-di-*tert*-butyl 1,2-diazepane-1,2,3-tricarboxylate, 18a. Yield 28% (0.012 g, 0.022 mmol of **18a**) from 0.027 g, 0.078 mmol, of **15**. Overall yield 78% (9.4 mg, 0.016 mmol mixture).

$[\alpha]_{\text{D}}^{25} - 18.44$ (c 4.1, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.14 – 7.33 (m, 5H), 6.53 (d, 0.71H, $J = 9$ Hz), 6.27 – 6.35 (m, 0.13H), 5.08 – 5.20 (br m, 0.16H), 4.63 (dd, 0.67H, $J = 12.3$, 4.8 Hz), 4.44 – 4.55 (m, 0.33H), 4.22 – 4.31 (m, 0.35H), 3.93 – 4.14 (m, 3.65H), 2.71 – 3.11 (m, 3H), 2.22 – 2.31 (m, 1H), 2.01 – 2.11 (m, 1H), 1.56 – 1.85 (m, 3H), 1.26 – 1.52 (m, 27H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.4, 170.3, 156.1, 154.4, 154.2, 138.9, 129.8, 129.5, 128.6, 128.4, 128.3, 126.2, 81.5, 81.3, 81.0, 78.8, 65.5, 61.06, 60.8, 51.8, 51.7, 37.5, 28.7, 28.6, 28.5, 28.4, 28.3, 28.2, 28.6, 25.4; HRMS (ESI) $(\text{M} + \text{Na})^+$ calculated for $\text{C}_{30}\text{H}_{47}\text{N}_3\text{O}_8\text{Na}^+ = 600.3261$ found 600.3259.

3-(2-(*Tert*-butoxycarbonylamino)-3-phenylpropyl) 1,2-di-*tert*-butyl 1,2-diazepane-1,2,3-tricarboxylate, 18b. Yield 30% (0.0136 g, 0.023 mmol of **18b**) from 0.27 g, 0.078 mmol, of **15**.

$[\alpha]_{\text{D}}^{25} - 14.14$ (c 4.9, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.17 – 7.27 (m, 5H), 6.57 (d, 0.21H, $J = 9.3$ Hz), 6.44 (d, 0.52H, $J = 9.3$ Hz), 4.78 – 4.90 (br m, 0.27H), 4.41 – 4.56 (m, 1H), 3.90 – 4.27 (m, 5H), 2.74 – 2.93 (m, 3H), 2.20 – 2.26 (m, 0.68H), 2.03 – 2.11 (m, 1.32H), 1.57 – 1.87 (m, 3H), 1.36 – 1.52 (m, 27H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.8, 171.3, 170.4, 156.0, 155.2, 154.6, 154.0, 153.8, 138.6, 138.4, 137.6, 129.6, 129.5, 129.4, 128.6, 128.5, 128.5, 128.4, 126.6, 126.4, 126.3, 82.4, 81.6, 81.5, 81.3, 81.2, 81.0, 78.7, 66.0, 65.4, 65.1, 62.7, 61.2, 52.2, 51.0, 50.3, 38.1, 29.7, 29.1, 28.5, 28.4, 28.4, 28.3, 28.1, 27.5, 26.8, 26.3, 25.9; HRMS (ESI) $(\text{M} + \text{Na})^+$ calculated for $\text{C}_{30}\text{H}_{47}\text{N}_3\text{O}_8\text{Na}^+ = 600.3261$ found 600.3260.

(S)-Piperazine-3-carboxylic acid mono TFA Salt, 2a.^[1,2c] $[\alpha]_D^{25}$ 10.07 (c 1.00, CH₃OH). Yield, 89% over 2 steps (6.95 mg, 0.028 mmol) from **17a** (0.018 g, 0.032 mmol).

(R)-Piperazine-3-carboxylic acid mono TFA Salt, 2b.^[1,2d] $[\alpha]_D^{25}$ -10.9 (c 1.10, CH₃OH). Yield, 92% over 2 steps (7.85 mg, 0.032 mmol) from 0.02 g, 0.035 mmol of **17b**.

1,2-Diazepane-3-carboxylic acid mono TFA Salt, 3a (hydrolysis was carried out in THF-water (2:1) mixture).^[1] $[\alpha]_D^{25}$ -4.13 (c, 1.54, CH₃OH). Yield, 38%, (1.67 mg, 0.0065 mmol of **3a**) from **18a** (0.01 g, 0.017 mmol).

1,2-Diazepane-3-carboxylic acid mono TFA Salt, 3b (hydrolysis was carried out in THF-water (2:1) mixture).^[1] $[\alpha]_D^{25}$ 3.98 (c, 1.75, CH₃OH). Yield, 36%, (1.39 mg, 0.0054 mmol of **3b**) from **18b** (9 mg, 0.015 mmol).

Hydrolysis of **18** was completed when the reaction was carried out in MeOH-water (2:1) mixture with the same set of reagents.

(S)-Di-tert-butyl-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbam-oyl) piperazine-1,2-dicarboxylate, 22a. Overall yield of the diastereomers **22a/b** was 61% (0.544 g, 1.1 mmol). Yield 31%, (0.28 g, 0.56 mmol of **22a**) from 0.60 g, 1.8 mmol of **14**.

$[\alpha]_D^{25}$ -4.51 (c 8.63, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.33 (brs, 0.54H), 7.53 (brs, 0.46 H), 7.14 – 7.31 (m, 5H), 5.02 – 5.09 (m, 0.52H), 4.85 (brs, 0.48H), 4.72 (q, 1H, *J* = 7.8 Hz), 3.86 – 3.90 (m, 1H), 3.73 (s, 1.5H), 3.62 (s, 1.5H), 3.11 – 3.29 (m, 1H), 2.72 – 2.98 (m, 2H), 2.14 (dd, 1H, *J* = 13.5, 3 Hz), 1.49 – 1.74 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 171.8, 171.6, 156.7, 153.8, 136.9, 136.0, 129.3, 129.1, 128.3, 128.2, 126.8, 126.7, 82.9, 82.3, 81.8, 57.9, 56.8, 54.0, 53.4, 53.4, 52.2, 51.9, 44.3, 42.0, 39.2, 38.1, 28.27, 28.1, 28.0, 24.0, 23.3, 20.4, 19.9; HRMS (ESI) (M+Na)⁺ calculated for C₂₅H₃₇N₃O₇Na⁺ = 514.2529 found 514.2529.

(R)-Di-tert-butyl-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbam-oyl) piperazine-1,2-dicarboxylate, 22b. Yield 30% (0.26 g, 0.54 mmol of **22b**) from 0.60 g, 1.8 mmol of **14**.

$[\alpha]_D^{25}$ 10.82 (c 4.45, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.54 – 8.65 (brm, 1H), 7.13 – 7.29 (m, 5H), 4.93 – 5.04 (m, 0.1H), 4.78 (brm, 1H) 4.48 – 4.56 (m, 0.9H), 3.96 – 4.02 (m, 1H), 3.67 (s, 0.9H), 3.65 (s, 2.1H), 3.12 – 3.27 (m, 1H), 2.89 – 3.03 (m, 2H), 2.28 – 2.31 (m, 1H), 1.62 – 1.75 (m, 3H), 1.56 – 1.52 (m, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 172.2, 171.1, 154.6, 154.5, 137.0, 129.3, 128.6, 126.9, 82.3, 81.9, 55.2, 53.5, 52.1, 44.7, 38.2, 37.1, 28.4, 28.2, 24.2, 20.9; HRMS (ESI) (M+Na)⁺ calculated for C₂₅H₃₇N₃O₇Na⁺ = 514.2529 found 514.2529.

(S)-Di-tert-butyl-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbam-oyl)-1,2-diazepane-1,2-dicarboxylate, 23a. Overall yield of the mixture of diastereomers (1.36 g, 2.7 mmol, 73%). Yield 32%, (0.60 g, 1.2 mmol of **23a**) from 1.27 g, 3.7 mmol of **15**.

$[\alpha]_D^{25}$ -12.85 (c 8.03, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.40 (d, 0.55H, *J* = 7.8 Hz), 9.25 (d, 0.45H, *J* = 8.7 Hz), 7.15 – 7.23 (m, 5H), 4.76 – 4.93 (m, 1H), 4.05 – 4.25 (m, 2H), 3.67 (s, 3H), 3.23 (dd, 1H, *J* = 14.25, 5.4 Hz), 2.77 – 2.98 (m, 2H), 1.95 – 2.10 (m, 3H), 1.37 – 1.58 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 172.2, 172.0, 171.5, 156.7, 156.4, 153.9, 153.4, 137.2, 137.0, 129.4, 129.3, 128.2, 128.1, 126.6, 126.5, 82.8, 82.2, 82.1, 81.8, 67.2, 65.5, 53.3, 52.9, 52.0, 52.0, 52.0, 38.1, 37.7, 29.7, 29.1, 28.4, 28.2, 28.0, 27.6, 27.5, 27.2, 26.7; HRMS (ESI) (M+Na)⁺ calculated for C₂₆H₃₉N₃O₇Na⁺ = 528.2686 found 528.2684.

(R)-Di-tert-butyl-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbam-oyl)-1,2-diazepane-1,2-dicarboxylate, 23b. Yield 39% (0.73 g, 1.44 mmol of **23b**) from 1.27 g, 3.7 mmol of **15**.

$[\alpha]_D^{25}$ 1.29 (c 4.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.69 (d, 0.51H, *J* = 6.9 Hz), 9.46 (d, 0.49H, *J* = 7.5 Hz), 7.15 – 7.32 (m, 5H), 4.76 – 4.94 (m, 0.13H), 4.57 – 4.70 (m, 0.87H), 4.32 (dd, 0.44H, *J* = 12.6, 3.9 Hz), 4.04 – 4.20 (m, 1.56H), 3.62 – 3.67 (m, 3H), 2.83 – 3.18 (m, 3H), 2.23 – 2.31 (m, 1H), 1.80 – 2.11 (m, 2H), 1.26 – 1.66 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 173.4,

172.5, 172.4, 172.4, 156.8, 156.6, 154.0, 153.4, 137.2, 137.1, 129.3, 129.5, 128.4, 126.8, 126.7, 82.6, 82.5, 82.3, 81.7, 67.4, 65.1, 54.9, 54.3, 52.1, 52.0, 51.9, 51.9, 37.7, 37.6, 30.0, 29.5, 28.4, 28.4, 28.3, 28.3, 28.1, 28.1, 27.6, 27.5, 27.1, 26.3; HRMS (ESI) (M+Na)⁺ calculated for C₂₆H₃₉N₃O₇Na⁺ = 528.2686 found 528.2685.

(S)-Di-*tert*-butyl-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbam-oyl)-1,2-diazocane-1,2-dicarboxylate, 24a. Overall yield of the diastereomeric mixture 63% (0.043 g, 0.083 mmol) from **19**. Yield 34% (0.023 g, 0.044 mmol of **24a**) from 0.047g, 0.13 mmol of **19**.

[α]_D²⁶ = 5.8 (c 1.88, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.21 (d, 0.27H, *J* = 7.5 Hz), 8.90 (d, 0.06H, *J* = 12 Hz), 8.17 (d, 0.25H, *J* = 12 Hz), 7.10 – 7.32 (m, 5H), 6.35 – 6.51 (m, 0.42H), 4.79 – 4.97 (m, 1H), 4.47 – 4.53 (m, 0.42H), 4.17 – 4.23 (m, 0.58H), 3.76 – 3.98 (m, 2H), 3.62 – 3.72 (m, 3H), 3.00 – 3.34 (m, 4H), 2.00 – 2.09 (m, 2H), 1.14 – 1.75 (m, 22H); ¹³C NMR (100 MHz, CDCl₃) δ 172.8, 172.6, 172.3, 170.9, 170.3, 170.2, 156.7, 156.4, 156.0, 155.3, 152.5, 136.9, 136.7, 136.3, 129.6, 129.5, 129.3, 128.9, 128.7, 128.6, 128.5, 127.1, 127.0, 126.9, 82.6, 82.5, 82.0, 81.9, 81.5, 81.4, 66.8, 65.5, 64.0, 55.7, 54.2, 53.4, 52.3, 52.1, 52.0, 49.6, 48.4, 48.0, 38.5, 38.4, 38.0, 28.5, 28.4, 28.3, 28.2, 28.1, 27.7, 27.5, 27.3, 27.0, 26.9, 26.7, 26.4, 25.9, 25.8, 25.7, 25.4, 25.1; HRMS (ESI) (M + H)⁺ calculated for C₂₇H₄₂N₃O₇H⁺ = 520.3047, found 520.3018.

(R)-Di-*tert*-butyl-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbam-oyl)-1,2-diazocane-1,2-dicarboxylate, 24b. Yield 27% (0.018 g, 0.035 mmol of **24b**) from 0.047g, 0.13 mmol of **19**.

[α]_D²⁶ = 10.1 (c 1.66, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.90 (br s, 0.22H), 7.90 (d, 0.23H, *J* = 7.5 Hz), 7.09 – 7.32 (m, 5H), 6.27 – 6.42 (m, 0.55H), 4.87 – 4.97 (m, 0.57H), 4.68 – 4.84 (m, 0.43H), 4.16 – 4.25 (m, 0.6H), 3.82 – 3.97 (m, 1.2H), 3.60 – 3.79 (m, 4.2H), 2.97 – 3.22 (m, 4H), 0.86 – 1.74 (m, 24H); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 172.1, 170.3, 170.0, 156.2, 155.3, 136.9, 136.8, 136.1, 129.5, 129.5, 129.4, 129.3, 129.3, 129.0, 128.7, 128.6, 128.6, 128.5, 127.3, 126.9, 82.8, 82.3, 82.0, 81.9, 81.7, 81.6, 66.6, 65.4, 64.1, 54.2, 53.4, 53.0, 52.1, 52.0, 49.6, 48.3, 48.0, 38.5, 38.3, 38.3, 28.5, 28.4, 28.4, 28.3, 28.3, 28.2, 28.1, 27.8, 27.6, 27.6, 26.8, 26.7, 26.4, 25.9, 25.8, 25.7, 25.2, 25.0; HRMS (ESI) (M + Na)⁺ calculated for C₂₇H₄₂N₃O₇Na⁺ = 542.2842, found 542.2843.

(S)-Di-*tert*-butyl-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbam-oyl)-1,2-diazonane-1,2-dicarboxylate, 25a, and **(R)-Di-*tert*-butyl 3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbamoyl)-1,2-diazonane-1,2-di carboxylate, 25b.** Yield (from 0.033g, 0.088 mmol of **20**) 68%, (0.032 g, 0.06 mmol of **25a,b**).

¹H NMR (500 MHz, CDCl₃) δ 9.77 (d, 0.33H, *J* = 5.5 Hz), 9.63 (d, 0.35H, *J* = 7 Hz), 9.49 (d, 0.13H, *J* = 6.5 Hz), 9.39 (d, 0.19H, *J* = 8 Hz), 7.17 – 7.31 (m, 5H), 4.84 – 4.89 (m, 0.22H), 4.72 – 4.77 (q, 0.5H, *J* = 7 Hz), 4.44 – 4.48 (m, 0.28H), 4.21 (dd, 0.32H, *J* = 11.5, 5.5 Hz), 4.13 (dd, 0.18H, *J* = 12, 6 Hz), 4.02 – 4.06 (m, 1H), 3.91 – 3.96 (m, 0.5H), 3.58 – 3.67 (m, 3H), 3.28 – 3.40 (m, 1H), 3.00 – 3.18 (m, 2H), 2.28 (br m, 1H), 1.18 – 1.90 (m, 27H); ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 172.1, 171.4, 170.8, 157.2, 157.2, 152.9, 152.8, 137.2, 137.1, 129.5, 129.4, 128.6, 128.4, 128.4, 128.3, 128.5, 126.9, 126.7, 126.6, 82.8, 82.5, 82.3, 82.2, 81.9, 81.6, 81.6, 66.6, 65.5, 66.2, 56.0, 54.7, 54.0, 53.0, 52.1, 52.0, 51.9, 51.9, 38.5, 38.4, 38.4, 38.0, 28.5, 28.4, 28.3, 28.3, 28.1, 28.1, 28.0, 27.3, 24.5, 24.4, 24.4, 24.2, 24.2, 24.1, 24.0; HRMS (ESI) (M + Na)⁺ calculated for C₂₈H₄₃N₃O₇Na⁺ = 556.2999, found 556.2994.

Synthesis of 5-Membered Ring.

1,2-Di-*tert*-butyl 3,3-di-*tert*-butyl pyrazolidine-1,2,3,3-tetracarboxylate, 27. To a solution of **7a** (1.36 g, 2.79 mmol) in THF/H₂O (2:1, 20 ml) was added OsO₄ (0.035 g, 0.14 mmol, in *tert*-butanol) and the reaction mixture was allowed to stir for 5 min. NaIO₄ (1.8 g, 8.3 mmol) was then added portion wise over a period of 30 min; the resulting mixture was allowed to stir overnight (12 h). The reaction mixture was then filtered through Celite, THF was removed, and extracted with EtOAc (60 ml), washed with Na₂SO₃ solution, satd. NaHCO₃, and brine. Removal of the organic solvent in vacuo yielded the corresponding aldehyde **26** (1.13 g, 2.3 mmol, 83%), which was used in the next step without further purification.

The aldehyde (1.13 g, 2.3 mmol) hence obtained was dissolved in dry DCM (90 ml). Triethylsilane (0.738 ml, 4.6 mmol) was added. The reaction mixture was cooled to -78 °C followed by the addition of BF₃.Et₂O (0.645 ml, 5.1 mmol) and was stirred for 30 min after which another set of triethylsilane (0.738 ml, 4.6 mmol) and BF₃.Et₂O (0.645 ml, 5.1 mmol) was added and the reaction mixture was stirred for another 3 h. The reaction was then quenched with satd. sodium bicarbonate solution. The mixture was diluted with DCM (30 ml), dried over anhyd. Na₂SO₄, aqueous workup was avoided as it resulted in complete loss of product or low yield.

Removal of organic solvent followed by silica gel column chromatography (30% EA in PE) yielded the pure product **27** in 68% (0.746 g, 1.56 mmol) yield.

^1H NMR (500 MHz, CDCl_3) δ 4.11 – 4.15 (dd, 1H, $J = 7, 7.5$ Hz), 3.26 – 3.32 (dt, 1H, $J = 6, 5.5, 5.5$ Hz), 2.50 – 2.567 (m, 1H), 2.34 – 2.38 (dd, 1H, $J = 5.5, 3.5$ Hz), 1.45 – 1.49 (m, 36H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.3, 167.2, 157.1, 152.8, 83.1, 82.1, 81.6, 81.3, 72.9, 47.0, 38.6, 28.3, 28.2, 28.2, 27.9, 27.9; IR ν max KBr, 2980.12, 1732.13, 1714.77, 1367.58, 1155.40; HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ calculated for $\text{C}_{23}\text{H}_{40}\text{N}_2\text{O}_8\text{Na}^+$ = 495.2682, found 495.2682.

Synthesis of aza-proline, 1. The solution of ester **27** (0.746 g, 1.5 mmol) in 30% TFA in DCM (4 ml) was stirred at 0 °C for 5 h. Removal of organic solvent gave deprotected amino acid in almost quantitative yield (0.345 g, 1.5 mmol).

Synthesis of 6-Membered Ring.

Synthesis of 7-Membered Ring.

1,2-Di-tert-butyl 3,3-di-tert-butyl piperazine-1,2,3,3-tetracarboxylate, 28a. To a solution of **7a** (1.47 g, 3 mmol) in dry THF (20 ml) was added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (0.46 g, 6 mmol, 6 ml of 1 M in THF) at 0 °C and the mixture was then allowed to stir at the same temperature for 1.5 h. Aqueous satd. solution of NaOAc (4 ml) and 30% H_2O_2 (2 ml) were then added dropwise to quench the reaction mixture and was stirred for 1 h. THF was removed, extracted with EtOAc (60 ml), washed with brine, and dried over anhyd Na_2SO_4 . Removal of organic solvent and followed by silica gel column purification (50% EA and PE) yielded the alcohol in 86% (1.31 g, 2.7 mmol) yield.

To the solution of alcohol obtained from the hydroboration oxidation of **7a** (1.23 g, 2.44 mmol), DMAP (0.03 g, 0.25 mmol, 10 mol %) and mesyl chloride (0.42 g, 0.28 ml, 3.66 mmol) in dry DCM (15 ml), triethylamine (0.74 g, 1.1 ml, 7.3 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 2 h. After removing DCM, the reaction mixture was quenched with satd. NH_4Cl solution (1 ml), extracted with EtOAc (60 ml), and washed with satd. NaHCO_3 followed by brine. The organic layer was dried over anhyd Na_2SO_4 . After removing the solvent in vacuo, the crude product (1.24 g, 2.38 mmol) was used in the next step without further purification. The crude mesylate (1.24 g, 2.38 mmol) was dissolved in THF (65 ml). Solution of TBAF (1 M) in THF (1.11 g, 4.2 ml, 4.25 mmol) was added and the resulting mixture was allowed to stir for 4 h at room temperature. THF was removed and 3 ml satd. NH_4Cl solution was added; the reaction mixture was then extracted with EtOAc (70 ml), repeatedly washed with small volume of water (4×15 ml), followed by brine. The organic layer was dried over anhyd Na_2SO_4 and removed in vacuo. The crude product was subjected for silica gel column chromatography purification (20% EtOAc in PE) and obtained the cyclized product **12a** in 81% (0.963 g, 1.98 mmol) yield.

^1H NMR (500 MHz, CDCl_3) δ 4.03 – 4.07 (m, 0.65H), 3.83 (br s, 0.35H), 2.88 (br s, 1H), 1.95 – 2.52 (m, 3H), 1.66 (m, 2 H), 1.40 – 1.43 (m, 36H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.3, 167.2, 157.1, 152.8, 83.1, 82.1, 81.6, 81.3, 72.9, 47.0, 38.6, 28.3, 28.2, 28.2, 27.9, 27.9; IR ν max KBr, 1749.49, 1722.49; melting point = 103 – 107 °C; HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ calculated for, $\text{C}_{24}\text{H}_{42}\text{N}_2\text{O}_8\text{Na}^+$ = 509.2839, found 509.2838. Same procedure was followed in case of **28b**, **29a** and **29b**.

1,2-Di-tert-butyl 3,3-dibenzyl piperazine-1,2,3,3-tetracarboxylate, 28b. Yield 74%, 2 steps, (1.49 g, 2.7 mmol of **28b** from 2.04 g, 3.68 mmol of **7b**).

^1H NMR (500 MHz, CDCl_3) δ 7.24 – 7.34 (m, 10H), 5.04 – 5.29 (m, 4H), 4.07 (brs, 1H), 2.95 (br s, 1H), 2.28 (br s, 1H), 2.06 – 2.10 (br m, 1H), 1.65 (s, 1H), 1.52 (s, 1H), 1.25 – 1.48 (m, 18H); IR ν max KBr, 2978.19, 1726.35, 1712.85; HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ calculated for $\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_8\text{Na}^+$ = 577.2526, found 577.2526.

1,2-Di-*tert*-butyl-3,3-di-*tert*-butyl-1,2-diazepane-1,2,3,3-tetracarboxylate, 29a. Yield 66%, 2 steps, (1.12 g, 2.24 mmol of **29a** from 1.7 g, 3.39 mmol of **7c**).

^1H NMR (500 MHz, CDCl_3) δ 3.92 – 4.26 (dt, 2H, $J = 14, 9$ Hz), 2.82 – 2.95 (m, 2H), 2.30 – 2.82 (dd, 1H, $J = 7.5, 7$ Hz), 2.18 – 2.25 (m, 1H), 1.93 – 1.99 (m, 2H), 1.39 – 1.41 (m, 36H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.3, 166.7, 166.6, 166.0, 155.0, 153.1, 82.3, 82.1, 82.0, 81.3, 80.7, 80.6, 80.6, 80.3, 80.1, 74.3, 73.7, 51.7, 50.6, 50.2, 35.0, 33.8, 28.4, 28.3, 28.2, 28.2, 28.1, 28.0, 27.9, 27.8, 27.6, 26.8, 26.6, 23.7, 23.0, 22.8; IR ν max KBr, 2980.12, 1734.06; HRMS (ESI) $(\text{M} + \text{Na})^+$ calculated for $\text{C}_{25}\text{H}_{44}\text{N}_2\text{O}_8\text{Na}^+$ = 523.2995, found 523.2995.

1,2-Di-*tert*-butyl-3,3-di-benzyl-1,2-diazepane-1,2,3,3-tetracarboxylate, 29b. Yield (from 0.89 g, 1.56 mmol of **7d**, 69% , 2 steps, 0.61 g, 1.08 mmol of **29b**).

^1H NMR (500 MHz, CDCl_3) δ 7.28 – 7.44 (m, 10H), 5.15 – 5.31 (m, 4Hs), 4.33 (d, 0.25H, $J = 14.5$ Hz), 4.12 – 4.20 (m, 0.60H), 4.05 (d, 0.15H, $J = 15.5$ Hz), 2.90 – 3.06 (m, 1H), 2.34 – 2.44 (m, 1H), 2.13 – 2.27 (m, 1H), 1.74 – 1.84 (m, 2H), 1.59 – 1.67 (m, 2H), 1.32 – 1.51 (m, 18Hs); ^{13}C NMR (125 MHz, CDCl_3) δ 168.1, 167.7, 167.5, 154.5, 153.2, 135.9, 135.3, 135.1, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.7, 127.7, 82.6, 81.5, 81.4, 81.0, 80.9, 80.8, 73.6, 72.6, 67.8, 67.6, 67.6, 67.5, 67.3, 51.7, 50.4, 50.2, 34.7, 34.5, 33.8, 33.6, 28.4, 28.3, 28.3, 28.2, 27.9, 27.9, 26.7, 26.6, 23.4, 22.9, 22.5; IR ν max KBr, 1734.06, 1705.13, 1367.58, 1153.47; HRMS (ESI) $(\text{M} + \text{Na})^+$ calculated for $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_8\text{Na}^+$ = 591.2682, found 591.2681.

Synthesis of **2** and **3**.

Piperazine-3-carboxylic acid, 2.TFA. The cyclized product **28a** (0.905 g, 1.84 mmol) was treated with 30% TFA in DCM (10 ml) at 0 °C for 6 h. TFA and DCM were removed to obtain the deprotected amino acid in almost quantitative yield (0.449 g, 1.84 mmol).

1,2-Diazepane-3-carboxylic acid, 3.TFA. Same procedure was employed as that of **28a**, (yield, quantitative, 0.062 g of **3** from 0.12 g, 0.24 mmol of **29a**).

Synthesis of **2** and **3**.

To a solution of **28b** (0.08 g, 0.14 mmol) in methanol (2 ml) was added 10% Pd/C (10 mg) and the resulting mixture was then stirred under hydrogen atmosphere (1 atm) for 4 h. The reaction was monitored by TLC. Methanol was removed followed by celite filtration with DCM provided the pure NBoc protected free acid. It was then treated with 20% TFA in DCM (10 ml) at 0 °C for 4 h. TFA and DCM were removed to obtain **2** in quantitative yield (34 mg, 0.14 mmol).

Same procedure was followed when **29b** was used as starting material, (yield, quantitative 22.45 mg, 0.087 mmol of **3** from 0.053 g, 0.09 mmol of **29b**).

¹H of Di-*tert*-butyl 2-allylmalonate.

¹³C of Di-*tert*-butyl 2-allylmalonate.

¹H of Dibenzyl 2-allylmalonate.

¹³C of Dibenzyl 2-allylmalonate.

¹H of Di-*tert*-butyl 2-(but-3-enyl)malonate.

¹³C of Di-*tert*-butyl 2-(but-3-enyl)malonate.

¹H of Dibenzyl 2-(but-3-enyl)malonate.

¹³C of Dibenzyl 2-(but-3-enyl)malonate.

¹H of 7a

¹³C of 7a

¹H of 7b.

¹³C of 7b.

¹H of 7c.

¹³C of 7c.

¹H of 7d.

¹³C of 7d.

¹H of 8a.

¹³C of 8a.

¹H of 8b.

¹³C of 8b.

¹H of 9a.

¹³C of 9a.

¹H of 9b.

¹³C of 10a.

¹H of 10b.

¹³C of 10b.

¹H of 11.

¹³C of 11.

¹H of 12.

¹³C NMR of 16a.

¹H of 16b.

¹³C of 16b.

Current Data Parameters
NAME IDG-CR-5-PA-L-13C
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20130819
Time 11.07
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 2417
DS 4
SWH 18028.846 Hz
FIDRES 0.550197 Hz
AQ 0.9087659 sec
RG 210.78
DW 27.733 usec
DE 6.50 usec
TE 298.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 75.4752949 MHz
NUC1 13C
P1 9.25 usec
PLW1 34.00000000 W

===== CHANNEL f2 =====
SFO2 300.1312005 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 90.00 usec
PLW2 6.99840021 W
PLW12 0.17545000 W
PLW13 0.14211001 W

F2 - Processing parameters
SI 32768
SF 75.4677396 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹H of 17a.

¹³C of 17b.

¹H of 18a.

18a

¹H of 18b.

F2 - Processing parameters	
SI	32768
SF	75.4677396 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

¹³C of 21a.

¹H of 21b.

Current Data Parameters
NAME IDG-JB-1-210-U-13C
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20130509
Time 14.57
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 223
DS 4
SWH 18028.846 Hz
FIDRES 0.550197 Hz
AQ 0.9087659 sec
RG 210.78
DW 27.733 usec
DE 6.50 usec
TE 299.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

***** CHANNEL f1 *****
SFO1 75.4752949 MHz
NUC1 13C
P1 9.25 usec
PLW1 34.00000000 W

***** CHANNEL f2 *****
SFO2 300.1312005 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 90.00 usec
PLA2 6.99840021 W
PLW2 0.17545000 W
PLW3 0.14211001 W

F2 - Processing parameters
SI 32768
SF 75.4677495 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

33

¹H of 22b.

¹³C of 22b.

¹H of 23a.

¹³C of 23a.

¹H of 23b.

¹³C of 23b.

¹H of 24a.

1H of 25a,25b.

Current Data Parameters

NAME	KG-3065M-13C
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20130606
Time	8.55
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	16976
DS	4
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9087659 sec
RG	210.78
DW	27.733 usec
DE	6.50 usec
TE	299.9 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

===== CHANNEL f1 =====

SFO1	75.4752949 MHz
NUC1	13C
P1	9.25 usec
PLW1	34.00000000 W

===== CHANNEL f2 =====

SFO2	300.1312005 MHz
NUC2	1H
CPDPRG2	waltz16
PCPD2	90.00 usec
PLW2	6.99840021 W
PLW12	0.17545000 W
PLW13	0.14211001 W

F2 - Processing parameters

SI	32768
SF	75.4677379 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

¹³C of 27.

¹H of 28a.

NAME PTU-1086-13C
 EXPNO 1
 PROCNO 1
 Date_ 20120312
 Time_ 15.23
 INSTRUM spect
 PROBHD 5 mm PABBO BB-
 PULPROG zgpg30
 TO 32768
 SOLVENT CDCl3
 NS 1024
 DS 4
 SWH 29761.904 Hz
 FIDRES 0.908261 Hz
 AQ 0.5505524 sec
 RG 57
 DW 16.800 usec
 DE 6.50 usec
 TE 298.2 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1

===== CHANNEL f1 =====
 NUC1 13C
 P1 9.88 usec
 PL1 0.50 dB
 PL1W 82.16106415 W
 SFO1 125.7703643 MHz

===== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 80.00 usec
 PL2 1.00 dB
 PL12 16.50 dB
 PL13 20.00 dB
 PL2W 15.50318813 W
 PL12W 0.43693921 W
 PL13W 0.19517358 W
 SFO2 500.1320005 MHz
 SI 16384
 SF 125.7577792 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.00