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# A Parallel Solution-Phase Synthesis of Substituted 3,7-Diazabicyclo[3.3.1]nonanes

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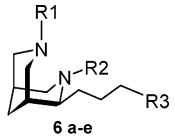
The parallel solution-phase synthesis of a series of building blocks and combinatorial libraries based on natural bispidine scaffold has been accomplished. Key reactions include catalytic hydrogenation of the (−)-cytisine heterocyclic system, followed by alkali-mediated ring cleavage. Using this approach, a series of new bispidine core building blocks for combinatorial synthesis with three points of diversity were effectively synthesized. The libraries from libraries were then obtained in good yields and purities using solution-phase acylation reactions. Obtained combinatorial libraries of 3,4,7-trisubstituted bispidines are potentially useful in the discovery of novel physiologically active compounds.

## Introduction

Combinatorial libraries based on natural product scaffolds—core structures around which analogues and derivatives are produced—represent a valuable source of exploratory chemistry for novel drug discovery and development. In this work, we report synthesis of libraries containing bispidine (3,7-diazabicyclo[3.3.1]nonane) moiety as a core fragment. The bispidine skeleton constitutes the B and C rings of a variety of lupanine alkaloids, for example, sparteine,[1] which is a tetracyclic alkaloid with antiarrhythmic properties.[2] Due to this structural relationship, compounds belonging to the ring system of bispidines have been the subject of considerable interest. Several natural and synthetic bispidine derivatives were described as potent and selective effectors of ion channel receptor complexes. For instance, antiarrhythmic properties have been demonstrated for bispidine derivatives ambasilide,[3] tedisamil,[4] and bisaramil.[5] Alkaloid (−)-cytisine and its derivatives are selective nAChR ligands.[6] Studies of crystal structures, stereochemistry, and conformational analysis of bispidines have been published.[7]

Depending on the substitution pattern of bispidine derivatives, several synthetic approaches are possible. For instance, synthetic routes based on the Mannich reaction,[8] utilizing pyridine derivatives,[9] or cyclic dicyanoglutarimides[10] as starting materials were reported. However, to the best of our knowledge, combinatorial approaches to these scaffolds have not been reported before.

As part of our research program related to the synthesis of combinatorial libraries based on natural bispidine scaffold, we developed an original synthetic way to novel bispidine derivatives (Figure 1) starting from (−)-cytisine, readily available from natural sources[11] or synthetically.[12] The synthesized structures contain three points of diversity (points around which the structure can be varied) and different combinations of protecting groups. Starting from these compounds, synthesis of a variety of combinatorial libraries containing bispidine moiety is possible. These libraries represent a very useful source of exploratory chemistry for the discovery of novel physiologically active compounds.




**6 a-e**

R1, R2 = H, alkyl, benzyl, BOC, acyl, sulfonyl, etc.
R3 = (**a**): $CO_2H$; (**b**): $CO_2$Alkyl; (**c**): CO(4-morpholyl); (**d**): $CH_2$(4-morpholyl); (**e**): $CH_2OH$

**Figure 1.** Bispidine derivatives synthesized in this work.

## Results and Discussion

**Bispidine Building Blocks.** Initial (−)-cytisine **1** was converted in high yield to decahydro-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one **2** upon catalytic hydrogenation in the presence of $PtO_2$ using a modified published procedure[13] (Scheme 1). Parallel reaction[14] of alkylation with the chlorides **3a**−**e** afforded a library of 3-substituted decahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-ones **4a**−**e** in high yields (88−99%). On the basis of LC/MS data, alkali- or acid-catalyzed hydrolysis of compounds **2** and **4a**−**e** quantitatively led to the corresponding 4-(3,7-diazabicyclo[3.3.1]-non-2-yl)butyric acids **5a**−**g**, a new family of bispidine derivatives. All attempts to separate these acids from the reaction mixture failed because of their spontaneous dehydration into the initial tricyclic compounds **2** and **4a**−**e**. However, the acidic hydrolysis of **2** and **4a**−**e** in the presence of methanol or 2-propanol allowed us to obtain and separate a library of 4-(3,7-diazabicyclo[3.3.1]non-2-yl)butyric acid alkyl esters **7a**−**g** containing one (**7f,g**, $R^1$ = H, $R^2$ = *i*-Pr or Me) or two (**7a**−**e**) different protecting groups. The products **7a**−**g** were isolated using simple procedures, such

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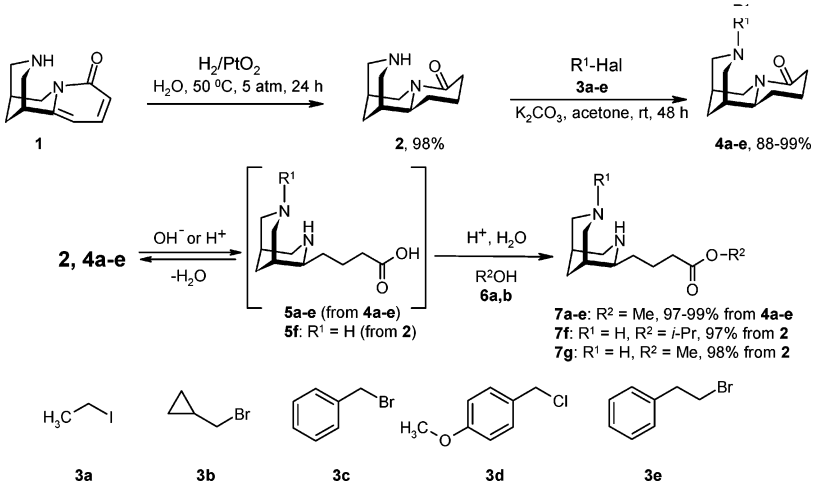
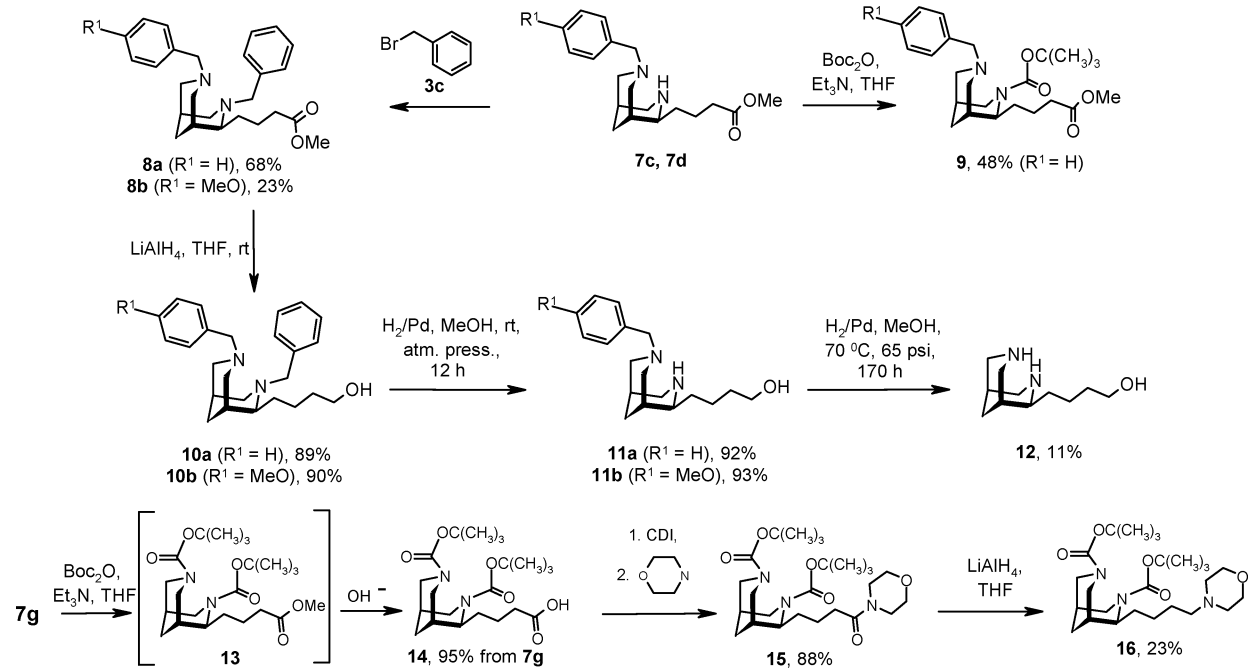
**Scheme 1.** Solution-Phase Parallel Synthesis of Esters **7a**−**g** and Evaluated Building Blocks




**Scheme 2.** Synthesis of Bispidine Building Blocks




as filtration and concentration in vacuo, in excellent yields (98−99%) and purities (>95% as evidenced from LC/MS analysis).

A series of additional bispidine core building blocks with three points of diversity and different protecting groups were obtained starting from esters **7a**−**g** (Scheme 2). Thus, protection of the free secondary amino-group of **7c** ($R^1$ = H) was achieved by $Boc_2O$ in $Et_3N$ and THF to yield Boc-derivative **9.** This compound represents a valuable combinatorial building block with three differently protected reactive functions. Butanols **10**−**12** represent another interesting series of core building blocks. They were obtained by treatment of esters **7c,d** with benzyl chloride **3c** followed by reduction of carboxyl function to primary alcohol upon the treatment with $LiAlH_4$ in THF. We have found that mild catalytic hydrogenation of **10a,b** in methanol ($H_2$/Pd, rt, 12 h) results in selective 3-*N*-debenzylation which affords 7-monobenzylated butanols **11a,b** in a high yield (92−93%). Fully *N*-deprotected butanol **12** can be obtained in a moderate yield upon prolonged hydrogenation under more severe conditions ($H_2$/Pd, 70 °C, 65 psi, 170 h).

Treatment of compound **12g** with $Boc_2O$ in THF at the presence of $Et_3N$ allowed production of di-Boc derivative **13** (Scheme 3), which was used in the next step without purification. This intermediate underwent mild alkali hydrolysis, and the resulting acid **14** was isolated in a high yield (95% from **12g**) following an acid workup. The acid **14** was treated with carbonyldiimidazole and then with morpholine to smoothly afford morpholide **15**. Reduction of this compound with $LiAlH_4$ in THF led to amine **16** in a moderate yield (23%).

All the described bispidine building blocks were obtained with excellent purities (>95% based on LC/MS data), using only minimal workup of the reaction mixtures. These building blocks are perfectly suited for combinatorial library generation because they have a rigid core with a defined geometry that possesses up to three different sites for the incorporation of diversity.

**Scheme 3.** Solution-Phase Parallel Synthesis of Combinatorial Libraries **19**{*1*−*5*}, **20**{*1*−*20*}, and **21**{*1*−*23*} and Evaluated Building Blocks

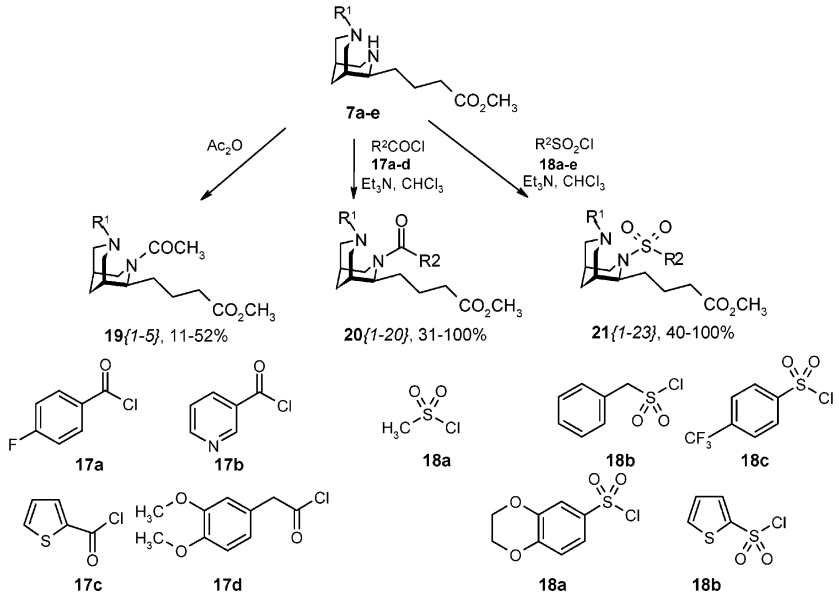



**Table 1.** Analytical Data for Combinatorial Libraries of 3-*N*-Acylated Derivatives **19**{*1-5*} and **20**{*1-20*}

| no. | compd | R1 | R2 | yield, % | purity (LC/MS), % | retention time, min |
|---|---|---|---|---|---|---|
| 1 | **19**{*1*} | Et | Me | 11 | 97 | 2.39 |
| 2 | **19**{*2*} | *c*-Pr$CH_2$ | Me | 12 | 97 | 2.66 |
| 3 | **19**{*3*} | Bn | Me | 52 | 99 | 3.00 |
| 4 | **19**{*4*} | (4-Me$OC_6H_4$)$CH_2$ | Me | 50 | 99 | 3.08 |
| 5 | **19**{*5*} | Ph$CH_2CH_2$ | Me | 52 | 99 | 3.20 |
| 6 | **20**{*1*} | Et | 4-F−$C_6H_4$ | 67 | 99 | 3.05 |
| 7 | **20**{*2*} | *c*-Pr$CH_2$ | 4-F−$C_6H_4$ | 81 | 99 | 3.34 |
| 8 | **20**{*3*} | Bn | 4-F−$C_6H_4$ | 100 | 99 | 3.58 |
| 9 | **20**{*4*} | (4-Me$OC_6H_4$)$CH_2$ | 4-F−$C_6H_4$ | 100 | 99 | 3.56 |
| 10 | **20**{*5*} | Ph$CH_2CH_2$ | 4-F−$C_6H_4$ | 91 | 99 | 3.70 |
| 11 | **20**{*6*} | Et | 3-pyridyl | 31 | 95 | 2.39 |
| 12 | **20**{*7*} | *c*-Pr$CH_2$ | 3-pyridyl | 45 | 99 | 3.59 |
| 13 | **20**{*8*} | Bn | 3-pyridyl | 99 | 92 | 2.95 |
| 14 | **20**{*9*} | (4-Me$OC_6H_4$)$CH_2$ | 3-pyridyl | 99 | 99 | 2.95 |
| 15 | **20**{*10*} | Ph$CH_2CH_2$ | 3-pyridyl | 96 | 99 | 3.06 |
| 16 | **20**{*11*} | Et | 2-thienyl | 61 | 99 | 3.00 |
| 17 | **20**{*12*} | *c*-Pr$CH_2$ | 2-thienyl | 77 | 99 | 3.28 |
| 18 | **20**{*13*} | Bn | 2-thienyl | 99 | 88 | 3.51 |
| 19 | **20**{*14*} | (4-Me$OC_6H_4$)$CH_2$ | 2-thienyl | 99 | 83 | 3.54 |
| 20 | **20**{*15*} | Ph$CH_2CH_2$ | 2-thienyl | 80 | 99 | 3.52 |
| 21 | **20**{*16*} | Et | (3,4-$(MeO)_2C_6H_3$)$CH_2$ | 99 | 99 | 3.57 |
| 22 | **20**{*17*} | *c*-Pr$CH_2$ | (3,4-$(MeO)_2C_6H_3$)$CH_2$ | 99 | 98 | 3.26 |
| 23 | **20**{*18*} | Bn | (3,4-$(MeO)_2C_6H_3$)$CH_2$ | 99 | 99 | 3.40 |
| 24 | **20**{*19*} | (4-Me$OC_6H_4$)$CH_2$ | (3,4-$(MeO)_2C_6H_3$)$CH_2$ | 99 | 98 | 3.44 |
| 25 | **20**{*20*} | Ph$CH_2CH_2$ | (3,4-$(MeO)_2C_6H_3$)$CH_2$ | 99 | 98 | 3.57 |

**Libraries from Libraries.** To illustrate the utility of our synthetic strategy, esters **7a**−**e** were further derivatized, using parallel solution-phase techniques (Scheme 3). Parallel reactions of the core building blocks **7a**−**e** with acetic anhydride, acyl chlorides **17a**−**d** or sulfonyl chlorides **18a**−**e** yielded a series of novel combinatorial libraries containing bispidine moiety, including 25-membered library of 3-*N*-acylated derivatives **19**{*1*−*5*} and **20**{*1*−*20*}, and 23-membered library of 3-*N*-sulfonylated derivatives **21**{*1*−*23*}. The products were obtained in moderate-to-good yields and good purities (Tables 1 and 2) using simple workup procedures.

All new compounds were characterized by LC/MS, $^1$H and $^{13}$C NMR spectroscopy. The individual protons in the bispidine system are largely concealed by other signals, but usually the nonequivalent methylene protons at C-6 and C-8 can be seen as doublets in the range of $\delta$ 3.15−3.60. In many cases, pure crystalline substances could be obtained, thus allowing firm relative and absolute stereochemical assignments to be made to the individual compounds through X-ray crystallography. For instance, the structure of **20**{*5*} was unambiguously established as methyl ester of (1R,2S,5R)−(4-{3-(4-fluorobenzoyl)-7-phenetyl-3,7-diazabicyclo[3.3.1]-non-2-yl}butyric acid by single-crystal X-ray analysis (see Supporting Information).

## Conclusion

In summary, we have developed an efficient synthetic approach to novel (1R,5R)-3,7-diaza-bicyclo[3.3.1]nonane derivatives, which can be used as core building blocks for

**Table 2.** Analytical Data for Combinatorial Library of 3-*N*-Sulfonylated Derivatives **21**{*1-23*}

| no. | compd | R1 | R2 | yield, % | purity (LC/MS), % | retention time, min |
|---|---|---|---|---|---|---|
| | **21**{*1*} | Bn | Me | 60 | 98 | 3.20 |
| | **21**{*2*} | (4-$MeOC_6H_4$)$CH_2$ | Me | 55 | 95 | 3.29 |
| | **21**{*3*} | $PhCH_2CH_2$ | Me | 40 | 90 | 3.42 |
| | **21**{*4*} | Et | Bn | 82 | 86 | 3.44 |
| | **21**{*5*} | *c*-$PrCH_2$ | Bn | 97 | 71 | 3.63 |
| | **21**{*6*} | Bn | Bn | 99 | 90 | 3.76 |
| | **21**{*7*} | (4-$MeOC_6H_4$)$CH_2$ | Bn | 88 | 89 | 3.77 |
| | **21**{*8*} | $PhCH_2CH_2$ | Bn | 67 | 82 | 3.89 |
| | **21**{*9*} | Et | 3-$CF_3$−$C_6H_4$ | 61 | 96 | 3.70 |
| | **21**{*10*} | *c*-$PrCH_2$ | 3-$CF_3$−$C_6H_4$ | 58 | 76 | 3.83 |
| | **21**{*11*} | Bn | 3-$CF_3$−$C_6H_4$ | 99 | 88 | 3.94 |
| | **21**{*12*} | (4-$MeOC_6H_4$)$CH_2$ | 3-$CF_3$−$C_6H_4$ | 99 | 84 | 3.96 |
| | **21**{*13*} | $PhCH_2CH_2$ | 3-$CF_3$−$C_6H_4$ | 99 | 80 | 4.11 |
| | **21**{*14*} | Et | 1,4-benzodioxan-6-yl | 73 | 93 | 3.42 |
| | **21**{*15*} | *c*-$PrCH_2$ | 1,4-benzodioxan-6-yl | 99 | 63 | 3.61 |
| | **21**{*16*} | Bn | 1,4-benzodioxan-6-yl | 99 | 88 | 3.68 |
| | **21**{*17*} | (4-$MeOC_6H_4$)$CH_2$ | 1,4-benzodioxan-6-yl | 99 | 91 | 3.73 |
| | **21**{*18*} | $PhCH_2CH_2$ | 1,4-benzodioxan-6-yl | 99 | 96 | 3.91 |
| | **21**{*19*} | Et | 2-thienyl | 40 | 95 | 3.30 |
| | **21**{*20*} | *c*-$PrCH_2$ | 2-thienyl | 68 | 86 | 3.48 |
| | **21**{*21*} | Bn | 2-thienyl | 99 | 86 | 3.55 |
| | **21**{*22*} | (4-$MeOC_6H_4$)$CH_2$ | 2-thienyl | 99 | 87 | 3.77 |
| | **21**{*23*} | $PhCH_2CH_2$ | 2-thienyl | 99 | 90 | 3.69 |

combinatorial synthesis, as well as for further exploration of chemistry of 3,7-diaza-bicyclo[3.3.1]nonanes. Considering the availability of initial reactants, convenient synthesis and isolation of products, and the overall good chemical yields of these transformations, this route provides a valuable synthetic approach. Access to different bispidine derivatives that are widely found in natural products and related compounds showing interesting biological and pharmaceutical properties is now possible. Biological testing of the obtained compounds and their further exploration as initial syntones for synthesis of novel polycyclic structures are currently under way.

## Experimental Section

**General.** Unless otherwise noted, all materials were purchased from commercial sources. Analytical thin-layer chromatography was carried out on EM Separations Technology $F_{254}$ silica gel plates. Compounds were visualized with short-wavelength UV light. Silica gel flash chromatography was performed using EM 63 $\mu$m silica gel. $^1$H NMR and $^{13}$C NMR spectra were recorded on Varian Gemini-300 (300 MHz) spectrometer using $CDCl_3$ or DMSO-$d_6$ as solvents and tetramethylsilane as internal standard; $\delta$ values are given in ppm, *J* values in Hz. LC/MS spectra were obtained with PE SCIEX API 150EX liquid chromatograph equipped with a UV (215 and 254 nm) and ELS detectors and using a $C_{18}$ column (100 × 4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. Melting point are uncorrected.

All the described parallel solution-phase reactions were performed using laboratory synthesizers "CombiSyn-012−3000",[14] which provide some advanced opportunities for high-throughput solution-phase combinatorial synthesis. All the workup, isolation, purification and analytic procedures were carried out using a proprietary technology platform, which includes all the equipment required for parallel synthesis of large combinatorial libraries.[15]

**(1*S*,5*S*)-Decahydro-1,5-methanopyrido[1,2-a][1,5]-diazocin-8-one (2).** A mixture of (−)-cytisine **1** (20 g, 104 mmol) and $PtO_2$ (0.5 g) in distilled water (100 mL) was prepared. Hydrogen was introduced, and the mixture was stirred for 24 h at a temperature of 50 °C and a pressure of 5 atm. Then the reaction mixture was filtered and concentrated in vacuo to give **2** (20 g, 98%). mp 99−102 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.64 (dt, $J$ = 13.8 Hz, 1.9 Hz, 1H), 3.45−3.56 (m, 1H), 3.31 (d, $J$ = 14.2 Hz, 1H), 3.06 (d, $J$ = 13.5 Hz, 1H), 2.70−3.00 (m, 3H), 2.15−2.52 (m, 3H), 1.54−2.05 (m, 7H), 1.49 (br. s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 169.9, 59.9, 51.9, 46.9, 46.8, 33.5, 33.1, 33.0, 28.5, 28.2, 20.2; LC/MS *m*/*z* 285 ($M^+$ + 1).

**General Procedure for the Synthesis of 3-Substituted Decahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-ones (4a−e).** Parallel solution-phase reactions were performed using a laboratory synthesizer "CombiSyn-012-3000". In each of five individual reaction units, amine **2** (1.94 g, 10 mmol), chloride **3a**−**e** (10.5 mmol), anhydrous $K_2CO_3$ (3.93 g, 28.5 mmol), and dry acetone (20 mL) were loaded and then stirred at room temperature for 48 h. The reaction mixtures were filtered, and the solvent was removed in vacuo to give individual compounds **4a**−**e** in high yields. **(1*S*,5*S*)-3-Ethyldecahydro-1,5-methanopyrido[1,2-a][1,5]-diazocin-8-one (4a).** Yield 100%, yellow oil; $^1$H NMR (DMSO-$d_6$) $\delta$ 4.75 (d, $J$ = 13.3 Hz, 1H), 3.41−3.48 (m, 1H), 3.12 (d, $J$ = 11.4 Hz, 1H), 2.79 (d, $J$ = 10.9 Hz, 1H), 2.66 (d, $J$ = 13.2 Hz, 1H), 1.95−2.22 (m 5H), 1.80−1.90 (m, 2H), 1.50−1.80 (m, 7H), 0.90 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 167.7, 59.3, 58.3, 53.6, 52.5, 46.1, 33.6, 33.4, 33.3, 29.1, 27.8, 20.0, 12.8; LC/MS *m*/*z* 223 ($M^+$ + 1). **(1*S*,5*S*)-3-Cyclopropylmethyldecahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (4b).** Yield 88%, yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 4.67 (d, $J$ = 13.2 Hz, 1H), 3.40−3.52 (m, 1H), 3.32 (d, $J$ = 11.4 Hz, 1H), 2.77 (d, $J$ = 14.7 Hz, 1H), 1.50−2.50 (m, 14H), 0.67−0.80 (m, 1H), 0.30−0.50 (m, 2H), −0.05 to 0.07 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$

168.9 (C═O), 63.7 ($CH_2$), 59.3 ($CH_2$), 58.8 (CH), 53.9 ($CH_2$), 46.4 ($CH_2$), 34.1 (CH), 33.6 ($CH_2$), 33.1 ($CH_2$), 29.3 (CH), 28.0 ($CH_2$), 20.1 ($CH_2$), 8.8 (CH), 4.3 ($CH_2$), 3.2 ($CH_2$); LC/MS *m*/*z* 249 ($M^+ + 1$). **(1*S*,5*S*)-3-Benzyldecahydro-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one (4c).** Yield 89%, mp 90−95 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.15−7.40 (m, 5H), 4.77 (d, $J$ = 13.6 Hz, 1H), 3.48 (d, $J$ = 13.0 Hz, 1H), 3.36−3.47 (m, 1H), 3.07 (d, $J$ = 13.0 Hz, 1H), 3.00−3.07 (m, 1H), 2.90−3.00 (m, 1H), 2.77−2.88 (m, 1H), 2.23−2.52 (m, 3H), 1.90−2.03 (m, 2H), 1.68−1.80 (m, 3H), 1.49−1.65 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.8, 139.1, 128.9, 128.1, 126.9, 63.4, 59.9, 59.1, 53.5, 46.2, 34.0, 33.5, 33.2, 29.4, 27.9, 20.1; LC/MS *m*/*z* 285 ($M^+ + 1$). **(1*S*,5*S*)-3-(4-Methoxybenzyl)-decahydro-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one (4d).** Yield 98%, mp 91−93 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.17 (d, $J$ = 8.5 Hz, 2H), 6.83 (d, $J$ = 8.5 Hz), 4.75 (d, $J$ = 13.6 Hz, 1H), 3.79 (s, 3H), 3.40 (d, $J$ = 12.7 Hz, 1H), 3.38−3.49 (m, 1H), 3.02 (d, $J$ = 12.7 Hz, 1H), 2.90−3.06 (m, 2H), 2.77−2.88 (m, 1H), 2.40−2.52 (m, 1H), 2.22−2.35 (m, 2H), 1.90−2.00 (m, 2H), 1.70−1.80 (m, 3H), 1.50−1.67 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.8, 158.5, 131.2, 129.9, 113.4, 62.7, 59.8, 59.1, 55.2, 53.5, 46.2, 34.0, 33.6, 33.2, 29.4, 27.9, 20.1; LC/MS *m*/*z* 315 ($M^+ + 1$). **(1*S*,5*S*)-3-Phenetyldecahydro-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one (4e).** Yield 100%, yellow oil, $^1$H NMR ($CDCl_3$) $\delta$ 4.67 (d, $J$ = 13.6 Hz, 1H), 3.40−3.50 (m, 1H), 3.12−3.26 (m, 1H), 2.95−3.08 (m, 1H), 2.83 (d, $J$ = 13.6 Hz, 1H), 2.62−2.77 (m, 2H), 2.00−2.55 (m, 6H), 1.95 (br.s, 1H), 1.50−1.85 (m, 7H); $^{13}$C NMR ($CDCl_3$) $\delta$ 169.1, 140.5, 128.6, 128.2, 125.7, 60.4, 59.2, 58.8, 54.0, 46.4, 33.9, 33.2, 33.2, 32.9, 29.1, 28.0, 20.1; LC/MS *m*/*z* 299 ($M^+ + 1$).

**4-((1*S*,5*S*)-3,7-Diazabicyclo[3.3.1]non-2-yl)butyric Acid Isopropyl Ester (7f).** A suspension of **2** (1.48 g, 7.6 mmol) in 4 N HCl (7 mL) and *i*-$C_3H_7OH$ (43 mL) was heated at reflux for 48 h. An excessive amount of dry sodium bicarbonate was added after cooling. The reaction mixture was filtered and concentrated in vacuo to yield **7f** (2 g, 97%) as an oil (LC/MS purity >95%); LC/MS *m*/*z* 255 ($M^+ + 1$).

**4-((1*S*,5*S*)-3,7-Diazabicyclo[3.3.1]non-2-yl)butyric Acid Methyl Ester (7g)** was prepared by a similar procedure, except methanol was used instead of *i*-$C_3H_7OH$ (yield 98%, LC/MS purity >95%); LC/MS *m*/*z* 227 ($M^+ + 1$).

**General procedure for the synthesis of 4-[(1*S*,5*S*)-7-Substituted 3,7-Diazabicyclo[3.3.1]non-2-yl]Butyric Acid Methyl Esters (7a−e).** Parallel solution-phase reactions were performed using a laboratory synthesizer, CombiSyn-012−3000. In each of five individual reaction units, **4a**−**e** (10 mmol), methanol (25 mL) and concentrated HCl (5 mL) were loaded. The mixtures were heated at reflux for 24 h. An excessive amount of dry sodium bicarbonate was added to each reaction mixture. The mixtures were filtered and concentrated in vacuo to give **7a**−**e**. Purities of all these products were >95% (as measured by LC/MS).

**4-[(1*S*,5*S*)-7-Ethyl-3,7-diazabicyclo[3.3.1]non-2-yl]butyric Acid Methyl Ester (7a).** Yield 100%, yellow oil, $^1$H NMR ($CDCl_3$) $\delta$ 3.62 (s, 3H), 3.54 (d, $J$ = 12.9 Hz, 1H), 3.20−3.40 (m, 3H), 3.05−3.15 (m, 2H), 1.6−2.45 (m, 12H), 1.32−1.40 (m, 1H), 1.06 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.3 (C═O), 59.3 (CH), 58.2 ($CH_2$), 52.8 ($CH_2$), 52.1 ($CH_2$), 51.5 ($CH_3$), 49.9 ($CH_2$), 33.0 ($CH_2$), 31.9 ($CH_2$), 30.2 ($CH_2$), 28.8 (CH), 26.8 (CH), 20.1 ($CH_2$), 11.7 ($CH_3$). LC/MS *m*/*z* 225 ($M^+ + 1$). **4-[(1*S*,5*S*)-7-Cyclopropylmethyl-3,7-diazabicyclo[3.3.1]non-2-yl]butyric Acid Methyl Ester (7b).** Yield 100%, mp 117−120 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.61 (s, 3H), 3.52 (d, $J$ = 13.1 Hz, 1H), 3.25−3.45 (m, 3H), 3.15 (d, $J$ = 11.6 Hz, 1H), 3.02−3.12 (m, 1H), 1.50−2.50 (m, 13H), 1.30−1.40 (m, 1H), 0.80−0.90 (m, 1H), 0.40−0.60 (m, 2H), 0−0.20 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.2 (C═O), 63.0 ($CH_2$), 59.3(CH), 58.5 ($CH_2$), 53.2 ($CH_2$), 51.5 ($CH_3$), 49.9 ($CH_2$), 33.0 ($CH_2$), 31.9 ($CH_2$), 30.2 ($CH_2$), 28.8 (CH), 26.8 (CH), 20.1 ($CH_2$), 8.0 (CH), 4.2 ($CH_2$), 3.4 ($CH_2$); LC/MS *m*/*z* 281 ($M^+ + 1$).

**4-[(1*S*,5*S*)-7-Benzyl-3,7-diazabicyclo[3.3.1]non-2-yl]butyric Acid Methyl Ester (7c).** Yield 100%, mp 107−110 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.20−7.32 (m, 5H), 3.62 (d, $J$ = 12.5 Hz, 1H), 3.58 (s, 3H), 3.27−3.35 (m, 2H), 3.24 (d, $J$ = 12.5 Hz, 1H), 3.17 (d, $J$ = 11.2 Hz, 1H), 3.03 (d, $J$ = 11.2 Hz, 1H), 2.47 (dt, $J$ = 3.0, 11.3 Hz, 1H), 2.25−3.37 (m, 1H), 2.06−2.20 (m, 3H), 1.86−2.02 (m, 3H), 1.76−1.84 (m, 3H), 1.48−1.64 (m, 2H), 1.24−1.40 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.1 (C═O), 136.1 (C), 129.4 (CH), 128.5 (CH), 127.7 (CH), 63.0 ($CH_2$), 59.1 (CH), 58.6 ($CH_2$), 52.8 ($CH_2$), 51.5 ($CH_3$), 49.8 ($CH_2$), 33.0 ($CH_2$), 31.8 ($CH_2$), 30.1 ($CH_2$), 28.8 ($CH_3$), 26.9 ($CH_3$), 20.0 ($CH_2$); LC/MS *m*/*z* 317 ($M^+ + 1$).

**4-[(1*S*,5*S*)-7-Methoxybenzyl-3,7-diazabicyclo[3.3.1]non-2-yl]butyric Acid Methyl Ester (7d).** Yield 98%, mp 79−82 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.18 (d, $J$ = 8.5 Hz, 2H), 6.83 (d, $J$ = 8.5 Hz, 2H), 3.76 (s, 3H), 3.57 (s, 3H), 3.55 (d, $J$ = 12.4 Hz, 1H), 3.25−3.34 (m, 2H), 3.17 (d, $J$ = 12.4 Hz, 1H), 3.10−3.16 (m, 1H), 3.00−3.07 (m, 1H), 1.30−2.50 (m, 14H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.1 (C═O), 159.1 (C), 130.5 (CH), 128.1 (C), 113.8 (CH), 62.3 ($CH_2$), 59.1 (CH), 58.4 ($CH_2$), 55.1 ($CH_3$), 52.6 ($CH_2$), 51.4 ($CH_3$), 49.8 ($CH_2$), 32.9 ($CH_2$), 31.8 ($CH_2$), 30.0 ($CH_2$), 28.8 (CH), 26.9 (CH), 20.0 ($CH_2$); LC/MS *m*/*z* 347 ($M^+ + 1$).

**4-[(1*S*,5*S*)-7-Phenetyl-3,7-diazabicyclo[3.3.1]non-2-yl]-butyric Acid Methyl Ester (7e).** Yield 100%, mp 71−75 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.14−7.38 (m, 5H), 3.64 (s, 3H), 3.05−3.30 (m, 4H), 2.81 (t, $J$ = 7.7 Hz, 2H), 2.50−2.68 (m, 2H), 2.19−2.45 (m, 4H), 2.02−2.10 (m, 1H), 1.90−1.97 (m, 1H), 1.20−1.85 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.4 (C═O), 139.4 (C), 129.0 (CH), 128.2 (CH), 127.0 (CH), 58.9 (CH), 58.7 ($CH_2$), 57.7 ($CH_2$), 53.9 ($CH_2$), 51.5 ($CH_3$), 49.8 ($CH_2$), 32.9 ($CH_2$), 32.8 ($CH_2$), 31.7 ($CH_2$), 30.0 ($CH_2$), 29.0 (CH), 26.8 (CH), 20.0 ($CH_2$); LC/MS *m*/*z* 331 ($M^+ + 1$).

**7-Benzyl-2-(3-methoxycarbonyl-propyl)-3,7-diazabicyclo-[3.3.1]nonane-3-carboxylic Acid *tert*-Butyl Ester (9).** A soluton of **7c** (2.22 g, 7.03 mmol) and $Et_3N$ (1.08 mL, 7.7 mmol) in THF (5 mL) was stirred at room temperature. A solution of $Boc_2O$ (1.69 g, 7.7 mmol) in THF (10 mL) was slowly added, and the reaction mixture was stirred for 6 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate (15 mL) and water (15 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting viscous oil was subjected to flash chromatography

(hexanes−ethyl acetate, 4:1) to give **9** as a clear oil. Yield 1.4 g (48%), $^1$H NMR ($CDCl_3$) $\delta$ 7.22−733 (m, 5H), 4.00−4.25 (br.s, 2H), 3.64 (s, 3H), 3.46 (d, $J$ = 12.8 Hz, 1H), 3.38 (d, $J$ = 12.8 Hz, 1H), 3.10 (dd, $J$ = 2.9, 13.2 Hz, 1H), 2.84 (d, $J$ = 11.7 Hz, 1H), 2.56 (d, $J$ = 10.3 Hz, 1H), 1.90−2.30 (m, 6H), 1.70−1.80 (m, 1H), 1.50−1.65 (m, 4H), 1.46 (s, 9H), 1.24−1.33 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.1, 156.1, 138.6, 129.2, 128.1, 127.0, 79.0, 63.0, 58.6, 54.5, 54.3, 54.2, 51.4, 33.9, 29.6, 29.5, 28.5, 27.9, 27.6, 22.3. LC/MS $m/z$ 417 ($M^+ + 1$).

**General Procedure for the Synthesis of 4-(3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]non-2-yl)butyric Acid Methyl Esters (8a,b).** Benzyl bromide (1.71 g, 10 mmol) and anhydrous $K_2CO_3$ (3.93 g, 28.5 mmol) were added to a solution of amine **7c**,**d** (10 mmol) in acetone (20 mL). The mixture was stirred at room temperature for 48 h. The reaction mixture was then filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, 0−50% THF/dichloromethane) afforded **8a**,**b** as a colorless oil.

**4-(3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]non-2-yl)butyric Acid Methyl Ester 8a.** Yield 2.81 g (68%); $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (d, $J$ = 7,0 Hz, 4H), 7.18−7.38 (m, 6H), 4.22 (d, $J$ = 14.3 Hz, 1H), 3.63 (s, 3H), 3.50 (d, $J$ = 13.3 Hz, 1H), 3.40 (d, $J$ = 13.3 Hz, 1H), 2.72−3.13 (m, 4H), 2.09−2.49 (m, 6H), 1.43−1.90 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.6, 141.4, 140.1, 129.5, 129.1, 128.6, 128.6, 127.2, 126.9, 64.4, 64.2, 60.1, 59.1, 58.6, 54.5, 52.0, 34.9, 34.0, 32.9, 31.6, 30.9, 22.3; LC/MS $m/z$ 407 ($M^+ + 1$).

**4-(3-Benzyl-7-(4-methoxybenzyl)-3,7-diazabicyclo[3.3.1]-non-2-yl)butyric Acid Methyl Ester 8b.** Yield 1.03 g (23%); $^1$H NMR ($CDCl_3$) $\delta$ 7.46 (d, $J$ = 7,2 Hz, 2H), 7.19−7.40 (m, 5H), 6.81−6.89 (m, 2H), 4.20 (d, $J$ = 15.0 Hz, 1H), 3.82 (s, 3H), 3.63 (s, 3H), 3.42 (d, $J$ = 11.5 Hz, 1H), 3.33 (d, $J$ = 11.5 Hz, 1H), 2.71−3.07 (m, 4H), 2.08−2.45 (m, 6H), 1.45−2.00 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.6, 158.9, 141.5, 132.2, 130.5, 129.1, 128.6, 126.9, 114.0, 64.4, 63.5, 60.1, 59.2, 58.5, 55.8, 54.4, 52.0, 34.9, 34.0, 32.9, 31.6, 30.9, 22.3; LC/MS $m/z$ 437 ($M^+ + 1$).

**General Procedure for the Synthesis of 4-(3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]non-2-yl)butanols (10a,b).** $LiAlH_4$ (0.436 g, 11.45 mmol) was added to a solution of ester **8a**,**b** (2.29 mmol) in dry THF (15 mL). The mixture was stirred at room temperature for 2 h and then treated with a mixture of water (1 mL) and THF (5 mL). The mixture was washed with brine (10 mL), and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to give **10a**,**b** as a clear oil.

**4-(3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]non-2-yl)butanol 10a.** Yield 89%; $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.53 (m, 4H), 7.19−7.39 (m, 6H), 4.25 (d, $J$ = 14.3 Hz, 1H), 3.49−3.63 (m, 2H), 3.45 (br.s, 2H), 2.72−3.10 (m, 4H), 2.03−2.55 (m, 4H), 1.61−1.94 (m, 4H), 1.10−1.61 (m, 7H); $^{13}$C NMR ($CDCl_3$) $\delta$ 141.6, 140.2, 129.5, 129.1, 128.6, 128.6, 127.2, 126.9, 64.7, 64.2, 63.2, 60.1, 59.2, 58.8, 54.4, 34.0, 33.5, 32.7, 31.7, 30.9, 22.9; LC/MS $m/z$ 379 ($M^+ + 1$).

**4-(3-Benzyl-7-(4-methoxybenzyl)-3,7-diazabicyclo[3.3.1]-non-2-yl)butanol 10b.** Yield 90%; $^1$H NMR ($CDCl_3$) $\delta$ 7.46 (d, $J$ = 7.3 Hz, 2H), 7.18−7.41 (m, 5H), 6.80−6.85 (m, 2H), 4.23 (d, $J$ = 15.0 Hz, 1H), 3.81 (s, 3H), 3.50−3.62 (m, 2H), 3.40 (br.s, 2H), 2.72−3.16 (m, 4H), 1.98−2.60 (m, 4H), 1.61−1.98 (m, 4H), 1.11−1.61 (m, 7H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.1, 141.5, 130.6, 129.1, 128.6, 128.6, 126.9, 114.0, 64.7, 63.4, 63.1, 59.9, 59.2, 58.6, 55.8, 54.3, 34.0, 33.5, 32.6, 31.6, 30.8, 22.9; LC/MS $m/z$ 409 ($M^+ + 1$).

**General Procedure for the Synthesis of 4-(7-Benzyl-3,7-diazabicyclo[3.3.1]non-2-yl)butanols (11a,b).** A solution of **10a** (**10b**) (2.06 mmol) in methanol (10 mL) containing 10% palladium on carbon (0.1 g) was stirred in an atmosphere of hydrogen at room temperature for 24 h. The reaction mixture was filtered, and the solvent was removed in vacuo to give **11a** (**11b**) as a clear oil.

**4-(7-Benzyl-3,7-diazabicyclo[3.3.1]non-2-yl)butanol 11a.** Yield 92%; $^1$H NMR ($CDCl_3$) $\delta$ 7.21−7.54 (m, 5H), 4.63 (br.s, 2H), 2.76−3.78 (m, 9H), 2.39−2.56 (m, 1H), 2.08−2.27 (m, 1H), 1.19−2.06 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 137.5, 129.2, 128.4, 127.4, 63.7, 61.5, 59.3, 59.3, 53.8, 50.9, 33.2, 32.3, 32.0, 31.1, 28.3, 21.8; LC/MS $m/z$ 289 ($M^+ + 1$).

**4-(7-(4-Methoxybenzyl)-3,7-diazabicyclo[3.3.1]non-2-yl)butanol 11b.** Yield 93%; $^1$H NMR ($CDCl_3$) $\delta$ 7.23−7.35 (m, 2H), 6.89 (d, $J$ = 8.1 Hz, 2H), 3.81 (s, 3H), 3.49−3.72 (m, 4H), 3.46 (br.s, 2H), 3.31−3.44 (m, 2H), 3.11−3.31 (m, 2H), 2.94−3.11 (m, 1H), 2.38−2.61 (m, 1H), 2.05−2.25 (m, 2H), 1.73−2.00 (m, 3H), 1.18−1.71 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.2, 130.8, 128.3, 114.0, 62.3, 61.1, 59.4, 58.7, 55.4, 52.8, 50.5, 31.9, 31.6, 30.7, 29.9, 27.0, 21.2; LC/MS $m/z$ 319 ($M^+ + 1$).

**4-(3,7-Diazabicyclo[3.3.1]non-2-yl)butanol (12).** A solution of **11a** (2.06 mmol) in methanol (10 mL) containing 10% palladium on carbon (0.3 g) was stirred in an atmosphere of hydrogen at 70 °C and 65 psi for 170 h. The reaction mixture was filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, 0−50% methanol/THF) afforded **12** as a yellowish oil. Yield 11%; $^1$H NMR (**12**, dihydrochloride salt) (DMSO-$d_6$) $\delta$ 9.83 (d, $J$ = 53.5 Hz, 2H), 9.55 (d, $J$ = 71.4 Hz, 2H), 3.48−3.76 (m, 11H), 3.40 (t, $J$ = 6.3 Hz, 2H), 3.05−3.35 (m, 2H), 2.21 (d, $J$ = 20.2 Hz, 1H), 1.73−1.98 (m, 2H), 1.27−1.50 (m, 2H); $^{13}$C NMR (**12**, dihydrochloride salt) (DMSO-$d_6$) $\delta$ 94.1, 60.4, 55.8, 45.4, 44.7, 32.0, 30.0, 26.9, 26.5, 23.7, 21.2; LC/MS $m/z$ 199 ($M^+ + 1$).

**2-(3-Carboxypropyl)-3,7-diazabicyclo[3.3.1]nonane-3,7-dicarboxylic Acid di-*tert*-Butyl Ester (14).** $Boc_2O$ (0.457 g, 2.1 mmol) in THF (1.5 mL) was added to a solution of **7g** (0.227 g, 1 mmol) and $Et_3N$ (0.15 mL, 1.1 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then concentrated in vacuo and partitioned between ethyl acetate (15 mL) and water (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to give 2-(3-methoxycarboxypropyl)-3,7-diazabicyclo[3.3.1]-nonane-3,7-dicarboxylic acid di-*tert*-butyl ester **13**. LC/MS $m/z$ 427 ($M^+ + 1$). The residue was dissolved in dioxane (1 mL), and 3 N NaOH (1 mL) was slowly added under stirring. A Small additional portion of dioxane was added until a

homogeneous solution was obtained. The mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was acidified with diluted $H_2SO_4$ until pH 3 and then extracted with ethyl acetate (2 × 3 mL). The combined organic layer was washed with water (2 × 3 mL), dried over magnesium sulfate, and concentrated in vacuo to give **14** (0.391 g, 95%). Mp 131−133 °C, LC/MS *m*/*z* 413 ($M^+ + 1$).

**2-(4-Morpholin-4-yl-4-oxobutyl)-3,7-diazabicyclo[3.3.1]-nonane-3,7-dicarboxylic Acid di-*tert*-Butyl Ester (15).** A mixture of **14** (0.412 g, 1 mmol) and *N*,*N*′-carbonyldiimidazole (0.178 g, 1.1 mmol) in dichloromethane (20 mL) was stirred at room temperature for 1 h. Morpholine (175 μL, 2 mmol) was added, and the reaction mixture was stirred for 36 h. The mixture was washed with water (2 × 5 mL), and the organic phase was concentrated in vacuo to give **15** (0.423 g, 88%) as a clear viscous oil. $^1$H NMR ($CDCl_3$) δ 4.00−4.30 (m, 3H), 3.30−3.90 (m, 11H), 1.90−2.80 (m, 7H), 1.20−1.70 (m, 4H), 1.40 (s, 18H); $^{13}$C NMR ($CDCl_3$) δ 171.5 (C═O), 156.0 (C═O), 155.2 (C═O), 79.6 (C), 79.4 (C), 66.9 ($CH_2$), 66.7 ($CH_2$), 66.4 ($CH_2$), 54.1 (CH), 46.7 ($CH_2$), 45.9 ($CH_2$), 41.9 ($CH_2$), 41.2 ($CH_2$), 32.9 ($CH_2$), 29.5 (CH), 29.2 ($CH_2$), 28.4 ($CH_3$), 28.4 ($CH_3$), 27.6 ($CH_2$), 27.0 (CH), 22.4 ($CH_2$); LC/MS *m*/*z* 482 ($M^+ + 1$).

**2-(4-Morpholin-4-yl-butyl)-3,7-diazabicyclo[3.3.1]nonane-3,7-dicarboxylic Acid di-*tert*-Butyl Ester (16).** $LiAlH_4$ (0.014 g, 0.37 mmol) was added to a solution of **15** (0.089 g, 0.185 mmol) in dry THF (10 mL). The mixture was stirred at room temperature for 12 h and then treated with a mixture of water (1 mL) and THF (5 mL). Water (10 mL) and $Boc_2O$ (0.121 g, 0.555 mmol) were then added, and the mixture was stirred for 1 h. $K_2CO_3$ (1 g) was added, and the organic phase was separated and dried over $K_2CO_3$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 15−100% THF−$CHCl_3$) to give **16** (0,020 mg, 23%) as a viscous yellowish oil. H$^1$ NMR ($CDCl_3$) δ 4.00−4.35 (m, 3H), 3.60−3.80 (m, 4H), 2.65−2.85(m, 3H), 2.40−2.50 (m, 4H), 2.30−2.40 (t, $J$ = 7.4 Hz, 2H), 1.80−2.30 (m, 3H), 1.43 (s, 18H), 1.15−1.75 (m, 8H); LC/MS *m*/*z* 468 ($M^+ + 1$).

**Library of 4-(3-Acetyl-7-alkyl-3,7-diazabicyclo[3.3.1]-non-2-yl)butyric Acid Methyl Esters (19{*1*−*5*}).** Parallel solution-phase reactions were performed using a laboratory synthesizer, CombiSyn-012-3000. In each of five individual reaction units, **7a**−**e** (1 g) and acetic anhydride (10 mL) were loaded. The mixtures were stirred at room temperature for 12 h and then concentrated to dryness in a vacuum centrifuge to give **19**{*1*−*5*}. Purities of all these products were >96% (as measured by LC/MS), and the reaction yields varied between 11 and 52%.

**Libraries of 4-(3-Acyl-7-alkyl-3,7-diazabicyclo[3.3.1]-non-2-yl)butyric Acid Methyl Esters (20{*1*−*20*}) and 4-(7-alkyl-3-sulfonyl-3,7-diazabicyclo[3.3.1]non-2-yl)butyric Acid Methyl Esters (21{*1*−*23*}).** Parallel solution-phase reactions were performed using four laboratory synthesizers, Combi-Syn-012-3000. In each of individual reaction units, **7a**−**e** (1 g), $Et_3N$ (660 μL, ∼1.2 equiv), and $CHCl_3$ (10 mL) were mixed and stirred at room temperature. Acyl chloride **17a**−**d** or sulfonyl chloride **18a**−**e** was added (∼1.2 equiv), and the reaction mixtures were stirred at room temperature for 12 h. Water (10 mL) was added to each reactor. The organic layers were separated and concentrated in vacuo to give **20**{*1*−*20*} and **21**{*1*−*23*}**.** Purities of all these products were generally >85% (as measured by LC/MS), and the reaction yields ranged from 50 to 100%.

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**Supporting Information Available.** $^1$H NMR and LC/MS spectra of synthesized compounds and crystallographic data for **20**{*5*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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