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Novel and Highly Efficient Synthesis of Substituted Dibenz[*b*,*g*]1,5-oxazocines. A Direct Comparison of the Solution versus Solid-Phase Approach

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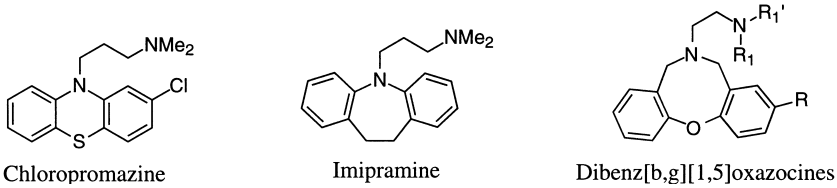
Abstract—We describe a novel and highly efficient synthesis of substituted dibenz[*b*,*g*]1,5-oxazocines. The procedure is based on the S_NAr of fluoride with the phenolic hydroxide of the properly assembled acyclic intermediate. A direct comparison of the solution-phase vs the solid-phase synthesis has been conducted. The speed of the synthesis, the purity of the desired eight-membered heterocycles (>95%), as well as the diversity of the resultant library are definite advantages of the solid-phase procedure. Yields of dibenz[*b*,*g*]1,5-oxazocines synthesized via the solid-phase approach were generally better, while the purity of the products synthesized by both methods were identical.

Application of combinatorial chemistry methods to the drug discovery process considerably shortens the time required for lead development and lead optimization. However, along with the unequivocal advantages offered, especially in the fast assembly of an array of compounds, solid-phase synthesis poses several formidable challenges. For instance, it is generally accepted that the purity, as well as the yields of the products synthesized by a variety of a solid-phase chemistry techniques, are inferior to the analogous reactions conducted in solution phase. Additionally, products synthesized on support contain a linker 'trace'. In many instances, the linker 'trace' is a polar, or metabolically unstable, moiety (for example, carboxylic acid, amide, or phenol), which may have an adverse effect on the biological activity of the product. Solution chemistry, on the other hand, is much more flexible with regard to the experimental techniques and selection of substrates. However, solution chemistry can be very tedious because of the intermediate purification steps. In order to compare the two synthetic methodologies, namely 'traditional' organic synthesis and solid-support synthesis, we attempted the case study synthesis of dibenz[*b, g*][1,5]-oxazocines. Related tricyclic aza-heterocyclic systems are of interest due to their pronounced activity as strong central nervous system supressants and anticancer agents. Some selected examples of these compounds are presented in Scheme 1.

Chloropromazine and imipramine are well-known agents used currently for treatment of arteriosclerosis, Parkinson's disease, and various cancers.[1] Heterocycles of the dibenz[*b*,*g*]1,5-oxazocine series are CNS active, and are used for the treatment of pain and/or inflammation.[2] Two main strategies have been devised to synthesize this heterocyclic core. One approach involves the reaction of the dibromide **A** with primary amines to afford the desired oxazocines **B**.[3] The alternative path proceeds through the bromination of the biphenyl ether **C** followed by its treatment with potassium phthalimide. Hydrazinolysis of the resultant intermediate, and subsequent intramolecular cyclization of the amine affords the targeted eight-membered lactam **D**[3] (Scheme 2).



Scheme 1.

Keywords: supported reagents/reactions; substitution.

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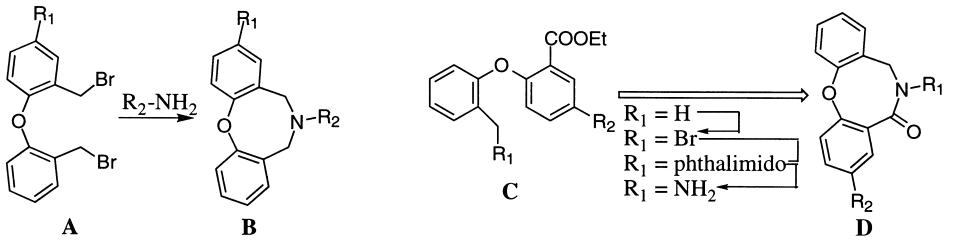
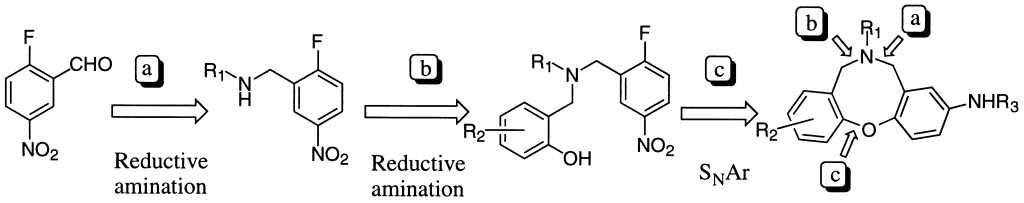


Scheme 2.

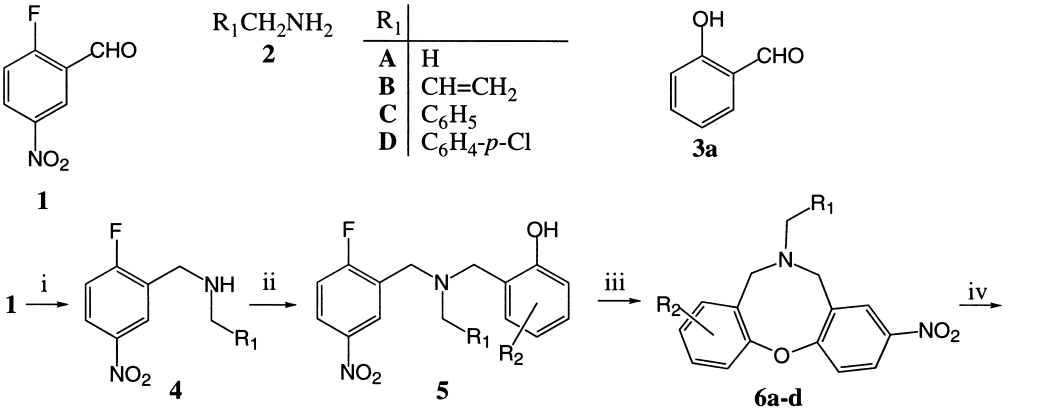


Scheme 3.

The double disadvantages of the reported procedures are: (i) the fact that both are multistep syntheses; and (ii) the formation of side products. In our group, we were interested in the application of nucleophilic aromatic substitution (S_NAr)[4] toward the assembly of medium- and large-ring heterocycles. Some examples of these procedures in the literature involve the syntheses of vancomycin and the related macrocyclic antibiotics,[5] and parallel synthesis of dibenz[*b,f*]1,5-oxazepines.[6] The retrosynthetic analysis of the desired heterocyclic core suggested that the eight-membered ring could be accessed by the (S_NAr) of fluorine with the phenolic OH function in the properly assembled noncyclic precursor (site **c**). This key intermediate, in its turn, could be prepared by two sequential reductive amination steps involving 2-fluoro-5-nitrobenzaldehyde (**1**, site **a**), a primary amine R_1NH_2 (**2**), and derivatives of salicyclaldehyde (**3**, site **b**) (Scheme 3).

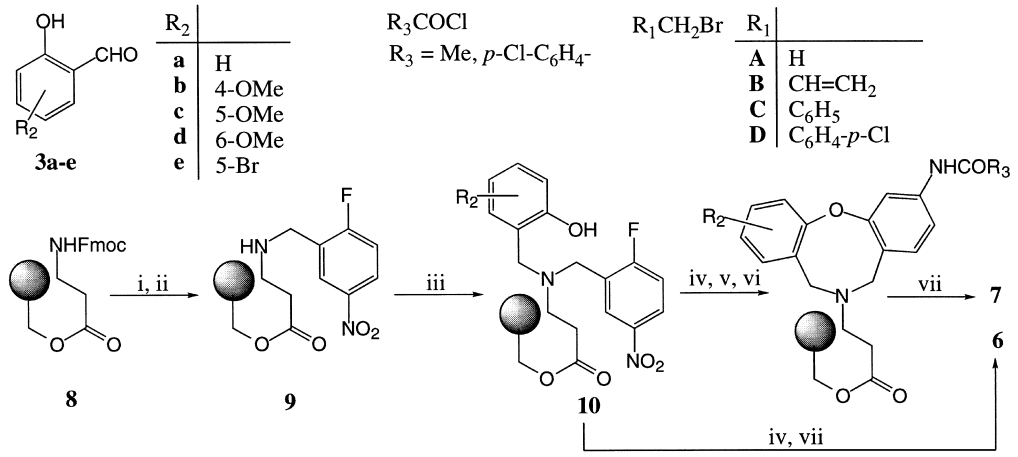
The application of a diverse set of primary amines and salicylaldehydes introduces two elements of diversity into the resulting set of dibenz[1,5-*a*]oxazocines. Subsequent reduction of the NO_2 group, followed by acylation of the resultant aniline, adds yet another dimension into the resulting set of dibenz[*b,g*]1,5-oxazocines.

In the first set of experiments we developed a solution-phase approach to dibenz[*b,g*]1,5-oxazocines. In a typical procedure, the reductive amination reaction of allylamine (**2B**) with 2-fluoro-5-nitrobenzaldehyde (**1**) in toluene, using an excess of $CH(OMe)_3$ and acetic acid (AcOH),



	R_1	R_2	R_3	Overall yield, %
6a	H	H		12
6b	$CH=CH_2$	H		42
6c	C_6H_5	H		59
6d	C_6H_4-*p*-Cl	H		77
7a	H	H	Me	7
7b	H	H	C_6H_4-*p*-Cl	4

Scheme 4. Solution-phase synthesis of dibenz[*b,g*]1,5-oxazocines. Reagents and conditions: (i) **2**, $NaBH(OAc)_3$, AcOH, $CH(OMe)_3$, toluene, 6 h, RT; (ii) **3**, $NaBH(OAc)_3$, AcOH, $CH(OMe)_3$, CH_2Cl_2, 18 h, RT; (iii) DBU, DMF, 6 h, RT; (iv) H_2 10% Pd/C; R_3COCl, Hunig's base, RT, 12 h.



Scheme 5. Solid-phase synthesis of dibenz[1,5-*a*]oxazocines. Reagents and conditions: (i) 20% piperidine, DMF, 30 min, RT; (ii) **1**, $NaBH(OAc)_3$, AcOH, DMF, 8 h, RT; (iii) **3**, $NaBH(OAc)_3$, AcOH, DMF, 8 h, RT; (iv) 5% DBU in DMF, 12 h, RT; (v) $SnCl_2$ H_2O (1 M in DMF), 12 h, RT; (vi) R_3COCl, Hunig's base, CH_2Cl_2, 4 h, RT; (vii) R_1CH_2Br, DMF, 8 h, RT; Hunig's base, CH_2Cl_2, 2 h, RT.

afforded the expected benzylic amine **4** in a 63% yield (Scheme 4). The second reductive amination step was successfully accomplished in CH_2Cl_2 under similar experimental conditions to yield the tertiary amine **5**. The intramolecular cyclization proceeded smoothly upon treatment of **5** with an excess of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in dimethylformamide (DMF) to afford the expected heterocycle **6b** in a 66% yield from **4** (42% overall yield). Similarly, a set of dibenz[*b*,*g*]1,5-oxazocines **6a**, **6c**, and **6d** were prepared in 12–77% overall yields starting from **1**. We attempted to use several other bases to facilitate this cyclization. For example, K_2CO_3,[7] Cs_2CO_3 (suspension in DMF, 5–15 fold excess relative to substrate), KO*t*-Bu or Bu_4NF[8] (0.4 M solutions in THF, 20 fold excess relative to substrate), and CsF[9] were found to afford the desired eight-membered heterocycles, albeit in much lower yields. Reduction of the nitro group in **6** with H_2 over 10% Pd on charcoal, followed by the acylation of the resultant tricyclic anilines with MeCOCl or *p*-Cl–C_6H_4COCl, proceeded smoothly to afford the trisubstituted dibenz[*b*,*g*]1,5-oxazocines **7a**,**b** in 4–7% overall yield from **1** (for the yields of the individual steps, see Table 2 vide infra).

In the solid-support approach, β-alanine immobilized on Wang resin was selected as a starting point of the synthesis (Scheme 5, **8**). The rationale for the choice of resin was that the final products can be conveniently cleaved off the support using the alkylation-retro-Michael reaction sequence to afford the targeted *N*-alkylated dibenz[*b*,*g*]1,5-oxazocines.[10] In the optimized procedure,[11] reductive amination of β-alanine resin with 2-fluoro-5-nitrobenzaldehyde and $NaBH(OAc)_3$ in DMF, in the presence of 1% TFA, took place smoothly to afford the desired secondary amine (**9**). The second reductive amination with salicylic aldehyde (**3a**) afforded the expected tertiary amine in 83% yield (**10**, as determined by TFA cleavage). The intermediate was treated with 5% DBU in DMF to afford the targeted immobilized 9-nitro-dibenz[*b*,*f*]1,5-oxazocines. The resulting resin was treated with the alkylating agent (R_1CH_2Br) for 8 h at room temperature followed by Hunig's base to result in the expected 9-nitro-dibenzo[*b*,*f*]oxazocines (Table 1, **6a**–**i**, 12–75% yield). Alternatively, cyclization of **10** with DBU was followed by the reduction of the nitro group with 1 M $SnCl_2 \cdot H_2O$ in DMF. Subsequent treatment of the resin with CH_3COCl or *p*-Cl–C_6H_4COCl in DMF, alkylation with R_1CH_2Br, and cleavage with Hunig's base afforded the expected eight-membered heterocycles in 20–78% yield (Table 1, **7a**–**h**).

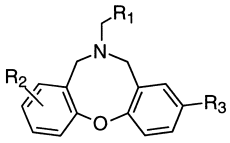
Neither the substitution pattern of the salicyclic aldehyde **3**, nor the nature of the substituents affected the yields of the targeted heterocycles. The notable exception, however, was 2-hydroxy-1-naphthoic aldehyde (Table 1, 12% isolated yield of the corresponding dibenz[*b*,*g*]1,5-oxazocine **6h**). Our attempts to further optimize reaction conditions for this entry were unsuccessful, primarily due to the poor yield of the reductive amination step (Scheme 5 step iii).

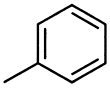
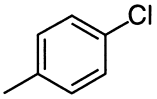
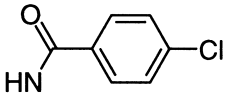
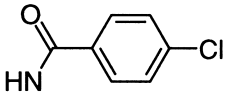
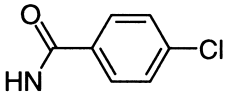
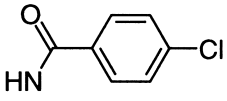
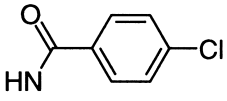
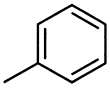
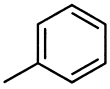
The direct comparison of the isolated yields for the selected 9-nitro-, and 9-*N*-acylated-dibenz[*b*,*g*]1,5-oxazocines synthesized via the two synthetic strategies is summarized in Table 2.

In general, the yields of the targeted dibenz[*b*,*g*]1,5-oxazocines synthesized on solid support are considerably higher (except for the entry **6d**). The solid-support strategy appears to be most beneficial for the sequences involving more than 2–3 steps, given that the chemistry for each step of the sequence is well validated. The syntheses of dibenz[*b*,*g*]1,5-oxazocines **7a** and **7b** are illustrative. Whereas the solid support synthesis resulted in 78 and 45% yield of these heterocycles, respectively, a similar sequence conducted via the 'standard' solution-phase approach afforded only 7 and 4% overall yields. Importantly, the purities of the final products **6** and **7** synthesized by both strategies are virtually identical by LC MS. Both ^1H NMR and combustion analyses data indicate that the purities of the materials cleaved off the solid support were greater than 95%.

In summary, we have described an efficient synthesis of dibenz[*b*,*g*]1,5-oxazocines using either a solution-phase or solid support approach. The procedure is based upon the

Table 1. Yields and purities of dibenz[*b*,*g*]-oxazocines **6**, and **7** synthesized via the solid support strategy



	R_1	R_2	R_3	HPLC purity,[a] (%)	Retention time (min)	Isolated yield (%)
6a	H	H	NO_2	100	1.01	59
6b		H	NO_2	100	1.12	50
6c		H	NO_2	100	1.62	65
6d		H	NO_2	100	1.85	65
6e		6-OMe	NO_2	100	1.25	75
6f		5-OMe	NO_2	98	1.28	55
6g		4-OMe	NO_2	100	1.33	65
6h			NO_2	100	1.57	12
6i		5-Br	NO_2	98	1.48	23
7a	H	H	NHCOMe	100	0.68	78
7b	H	H		100	1.65	45
7c		6-OMe		100	1.65	69
7d		5-OMe		100	1.68	65
7e		4-OMe		100	1.73	20
7f				100	1.28	45
7g		5-Br	NHCOMe	100	1.50	42
7h		6-F	NHCOMe	100	1.30	43

[a] The column employed was YMC Pak ProC18 column, 50×4.6 mm^2. The solvent system was MeCN/H_2O (start: 20:80; finish: 100:0; 3 min runs; 0.1% TFA added), with a flow rate of 3 mL/min.

Table 2. Selected yields for 9-nitro- and 9-*N*-substituted-dibenz[*b*,*g*]1,5-oxazocines synthesized in solution vs on solid support (yields are reported for isolated, analytically pure compounds)

Compound	Solution synthesis				Solid-phase synthesis overall yield (%)
	Yield of step 1 (%)	Yield of steps 2+3 (%)	Yield of steps 4+5 (%)	Overall yield (%)	
6a	54	22		12	59
6b	63	66		42	50
6c	76	78		59	65
6d	96	80		77	65
7a	54	22	58	7	78
7b	54	22	36	4	45

intramolecular nucleophilic aromatic substitution of fluorine in the derivatives of 2-fluoro-5-nitrobenzaldehyde with the OH function of the immobilized phenols. Direct comparison of solution vs solid-phase synthesis has been conducted. The relative speed of the synthesis, purity of the desired eight-membered heterocycles (>95%), as well as the diversity of the resultant library are definite advantages of the solid-phase procedure. Yields of dibenz[*b*,*g*]1,5-oxazocines synthesized via the solid-phase approach were generally better, while the purity of the products synthesized by both methods were identical.

Experimental Procedure

Materials and methods

All solid-phase reactions were carried out in peptide synthesis vessels and agitated on an orbit shaker at room temperature. Reagents were purchased from Aldrich and used without further purification. The Fmoc-β-Ala-Wang resin (100–200 mesh) purchased from Novabiochem with a loading of 0.80 mmol/g was deprotected with 40% piperidine in DMF, followed by washing with DMF, MeOH, and DCM before use. Concentration of the solutions after workup was performed by reduced pressure rotary evaporation on a Büchi 535 apparatus. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker 400 instrument. MS analyses (ES and CI modes) were performed on a Perkin Elmer API 165 instrument. Melting points were measured with a Büchi 535 melting point apparatus. Elemental analyses were performed by Atlantic Microlab Inc, Norcrosss, GA. HPLC analyses were performed on a Beckman Gold Analytic 126 apparatus with a diode array detector model 168 at the wavelengths of 220 nm and 254 nm. The column employed was a YMC Pak ProC18 column, 50×4.6 mm^2. The solvent system was MeCN/H_2O (start: 20:80; finish: 100:0; 3 min runs; 0.1% TFA added), with a flow rate of 3 mL/min.

Solution phase synthesis of 3-nitro-6-prop-2-enyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6b)

The procedure reported below for the synthesis of **6b** is the typical protocol for the solution-phase synthesis of dibenz[*b*,*g*]1,5-oxazocines **6a**–**6d**.

[(2-Fluoro-5-nitrophenyl)methyl]prop-2-enylamine (4B). To a 1000-mL, round-bottomed flask was added 2-fluoro-5-nitrobenzaldehyde (**1**, 15 g, 88.8 mmol) and allylamine (**2B**, 10.0 mL, 133 mmol) in 300 mL toluene, followed by the addition of acetic acid (25 mL, 88.8 mmol), trimethyl orthoformate (10 mL, 88.0 mmol), and $NaBH(OAc)_3$ (20 g, 94 mmol). The solution was stirred at room temperature for 6 h. 30 mL of MeOH were added, and the solution was stirred for an additional 0.5 h. The reaction solvent was evaporated in vacuo, and the resulting crude material was purified by flash chromatography on silica gel with $MeOH/CH_2Cl_2/NH_4OH$ (5:94:1) as eluant to afford 11.75 g (63%) of **4B** as a brown oil. ^{1}H NMR ($CDCl_3$): δ 3.30 (d, J=6.0 Hz, 2H), 3.92 (s, 2H), 5.10–5.30 (m, 2H), 5.80–6.00 (m, 1H), 8.10–7.40 (m, 2H). MS *m*/*z*: 211 (M+1). Anal. calcd for $C_{10}H_{11}FN_2O_2$.: C, 57.14; H, 5.27; N, 13.33. Found: C, 57.03; H, 5.11; N, 13.26.

2-({[(2-Fluoro-5-nitrophenyl)methyl]prop-2-enylamino}-methyl)phenol (5Ba). To a 25-mL, round-bottomed flask was added **4B** (163 mg, 0.776 mmol) and salicylaldehyde (**3a**, 63 mg, 0.517 mmol) in 8 mL CH_2Cl_2, followed by the addition of acetic acid (310 mg, 5.17 mmol), trimethyl orthoformate (55 mg, 0.517 mmol), and $NaBH(OAc)_3$ (0.55 g, 2.58 mmol). The solution was stirred at room temperature for 18 h. 5 mL of MeOH were added, and the solution was stirred for an additional 0.5 h. The reaction solvent was evaporated in vacuo, and the resulting crude material was purified by flash chromatography on silica gel with EtOAc/Hexane (20:80) as eluant to afford 130 mg (80%) of **5Ba** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.20 (d, J=6.72 Hz, 2H), 3.80 (s, 4H), 5.24–5.33 (m, 2H), 5.90–6.00 (m, 1H), 6.70–8.20 (m, 7H), 10.10 (s, 1H). MS *m*/*z*: 317 (M+1). Anal. calcd for $C_{17}H_{17}FN_2O_3$: C, 64.55; H, 5.42; N, 8.86. Found: C, 64.32; H, 5.33; N, 8.71.

3-Nitro-6-prop-2-enyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6b). To a 10 mL, round-bottomed flask was added 2-fluoro-5-nitro-(*N*-allyl-*N*-2-hydroxybenzyl) benzylamine (**5Ba**, 88 mg, 0.28 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (50 mg, 0.33 mmol) in 3 mL of DMF. The solution was stirred at room temperature for 6 h. The reaction solvent was evaporated in vacuo, and the resulting crude material was purified by flash chromatography on silica gel with EtOAc/Hexane (20:80) as eluant to afford 71 mg (86.5%) of **6b** as a light brown oil.

Example of solution phase synthesis of *N*-acylated dibenzo[*b*,*g*]1,5-oxazocines (7)

***N*-[6-Methyl-5*H*, 7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl)acetamide (7a).** To a 150-mL flask was added **6a** (65 mg, 0.24 mmol), 10% Pd/C (6.5 mg) and ethanol (20 mL). The mixture was stirred under a hydrogen balloon for 12 h. The reaction mixture was filtered through Celite and concentrated to afford 55 mg (95%) of a light brown solid. MS *m*/*z*: 241 (M+1). This material (25 mg, 0.104 mmol) was dissolved in 1.5 mL of CH_2Cl_2. Acetyl chloride (16.3 mg, 0.208 mmol) and Hunig's base (27 mg, 0.208 mmol) were added by syringe, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was treated with sat. $NaHCO_3$, and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude oil was purified by flash chromatography on silica gel with MeOH/CH_2Cl_2/NH_4OH(4:95:1) as eluant to afford 18 mg (61%) of an off-white solid. MS *m*/*z*: 283 (M+1).

(4-Chlorophenyl)-*N*-(6-methyl(5*H*, 7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl))carboxamide (7b). The reaction conditions were analogous to the synthesis of **7a**, except 4-chlorobenzoyl chloride (36.4 mg, 0.208 mmol) was used as the acylating agent. The resulting crude oil was purified by flash chromatography on silica gel with EtOAc/hexane (20:80) as eluant to afford 15 mg (38.1%) of an off-white solid. MS *m*/*z*: 379, 381 (M+1).

Solid phase synthesis of dibenzo[*b*,*g*]1,5-oxazocines 6a–6i

The procedure reported below for the synthesis of 3-nitro-6-prop-2-enyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (**6b**) is a representative example of the solid-phase synthesis of dibenzo[*b*,*g*]1,5-oxazocines **6a**–**6i**.

Deprotected β-Ala Wang resin (**8**, 100 g, 0.8 mmol/g loading, available from NovaBiochem) was treated with a mixture of trimethyl orthoformate (480 mL), glacial AcOH (20 mL), and 2-fluoro-5-nitrobenzaldehyde (**1**, 43 g, 250 mmol). The slurry was gently stirred under nitrogen for 3 h. The resin was filtered and washed with anhydrous CH_2Cl_2 followed by DMF. The resulting immobilized imine of 2-fluoro-5-nitrobenzaldehyde (100 g) was treated with a solution of $NaBH(OAc)_3$ (106 g, 500 mmol) and 5 mL of glacial AcOH in 500 mL of anhydrous DMF. The slurry was gently stirred under nitrogen for another 5 h. The resulting resin **9** (100 g) was filtered, washed twice with MeOH, DCM, DMF, dioxane and Et_2O, and treated with a mixture of salicylaldehyde (**3a**, 31 g, 250 mmol), and $NaBH(OAc)_3$ (106 g, 500 mmol) in 500 mL of anhydrous DMF for an additional 8 h. The resin was filtered, washed twice with MeOH, CH_2Cl_2, DMF, dioxane, and Et_2O, and dried in vacuo to afford the precursor **10** for the intramolecular cyclization. 2 g of the resultant resin was shaken with 50 mL of a 5% solution of DBU in DMF at room temperature for 12 h. The resin was filtered and treated with 10% AcOH in DMF to remove excess DBU. The resin was then washed with DMF, MeOH, CH_2Cl_2, and dried in vacuo. The dried resin was treated with a 1 M solution of allyl bromide (25 mL) in DMF for 8 h. The resin containing the quaternized amine on solid support was filtered, washed with MeOH, CH_2Cl_2, and DMF, and treated with a 5% Hunig's base in CH_2Cl_2 (50 mL) for 2 h. The filtrate was collected and washed twice with a saturated $NaHCO_3$ solution. The extract was dried over $MgSO_4$, filtered and co-evaporated twice with MeOH to afford 266 mg of the desired product as a yellow oil (HPLC purity: 100%). The product was further purified by flash chromatography on silica gel with EtOAc/hexane (20:80) as eluent to afford 237 mg (50% yield) of analytically pure **6b** as a light brown oil.

Analytical data

6-Methyl-3-nitro-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6a). Light yellow solid. mp 97–99°C; ^{1}H NMR (CD_2Cl_2) δ 8.14 (s, 1H), 8.00 (s, 1H), 7.33–7.19 (m, 5H), 4.7–2.0 (m, 7H) ^{13}C NMR (CD_2Cl_2) δ 133.2, 130.4, 125.6, 121.0, 6.12, 53.7, 42.8. HRMS (FAB) calcd for $C_{15}H_{14}N_2O_3$: *m*/*z*=271.1083 (MH^+), found: 271.1095. Anal. calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.55; H, 5.11; N, 10.36.

3-Nitro-6-prop-2-enyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6b). Yellow oil. ^{1}H NMR (CD_2Cl_2) δ 8.15 (dd, J_1=8.8 Hz, J_2=2.8 Hz, 1H), 7.98 (d, J=2.8 Hz, 1H), 7.5–7.2 (m, 5H), 5.90 (m, 1H), 5.23 (d, J=6.8 Hz, 2H), 4.65–2.95 (m, 6H); ^{13}C NMR (CD_2Cl_2) δ 136.7, 133.1, 130.4, 129.9, 125.8, 125.6, 120.6, 118.6, 58.1, 51.7, 51.0; HRMS (FAB) calcd for $C_{17}H_{16}N_2O_3$: *m*/*z*=297.1239 (MH^+), found: 297.1251. Anal. calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.70; H, 5.44; N, 9.44.

3-Nitro-6-benzyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6c). Yellow needles. mp 149–152°C; ^{1}H NMR (CD_2Cl_2) δ 8.16 (dd, J_1=8.8 Hz, J_2=2.8 Hz, 1H), 7.9–7.0 (m, 11H), 4.7–3.1 (m, 6H); ^{13}C NMR (CD_2Cl_2) δ 138.9, 132.7, 130.0, 129.1, 128.8, 127.6, 125.2, 120.0, 58.8, 55.8, 51.2; HRMS (FAB) calcd for $C_{21}H_{18}N_2O_3$: *m*/*z*=347.1396 (MH^+), found: 347.1409. Anal. calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.67; H, 5.29; N, 8.12.

6-[(4-Chlorophenyl)methyl]-3-nitro-5*H*, 7*H*-dibenzo[*b*,*g*]-1,5-oxazocine (6d). Light orange powder. mp 165–168°C; ^{1}H NMR (CD_2Cl_2) δ 8.16 (dd, J_1=8.8 Hz, J_2=2.8 Hz, 1H), 7.9–6.9 (m, 10H), 4.7–3.1 (m, 6H); ^{13}C NMR (CD_2Cl_2) δ 133.0, 130.9, 130.5, 129.3, 125.7, 120.4; HRMS (FAB) calcd for $C_{21}H_{17}ClN_2O_3$: *m*/*z*=381.1006 (MH^+), found: 381.0995. Anal. calcd for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36: Cl, 9.31. Found: C, 66.25; H, 4.57; N, 7.31; Cl, 9.37.

1-Methoxy-9-nitro-6-prop-2-enyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6e). Light yellow solid. mp 121–123°C; ^{1}H NMR (CD_2Cl_2) δ 8.12 (dd, J_1=8.8 Hz, J_2=2.8 Hz, 1H), 7.91 (d, J=2.8 Hz, 1H), 7.35 (dd, J_1=6.8 Hz, J_2=2.8 Hz, 1H), 7.2–7.0 (m, 3H), 5.79 (m, 1H), 5.14 (d, J=8.8 Hz, 2H), 4.5–2.7 (m, 6H); ^{13}C NMR (CD_2Cl_2) δ 138.1, 131.3, 129.2, 127.7, 126.8, 125.6, 122.8, 121.8, 119.7, 114.8, 59.7, 58.1, 53.7, 52.8; HRMS (FAB) calcd for $C_{18}H_{18}N_2O_4$: *m*/*z*=327.1345 (MH^+), found: 327.1349. Anal. calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.17; H, 5.59; N, 8.51.

2-Methoxy-9-nitro-6-prop-2-enyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6f). Light yellow solid. mp 119–122°C; ^{1}H NMR (CD_2Cl_2) δ 8.13 (dd, J_1=8.8 Hz, J_2=2.8 Hz, 1H), 7.96 (d, J=2.8 Hz, 1H), 7.32 (s, 1H), 7.10 (s, 1H), 6.96 (d, J=8.0 Hz, 1H), 6.78 (s, 1H), 5.89 (m, 1H), 5.18 (d, J=9.2 Hz, 2H), 4.5–2.8 (m, 6H), 3.91 (s, 3H); ^{13}C NMR (CD_2Cl_2) δ 161.4, 136.8, 133.7, 129.9, 125.6, 121.0, 118.6, 117.2, 111.3, 105.9, 58.1, 56.3, 51.1; HRMS (FAB) calcd for $C_{18}H_{18}N_2O_4$: m/z=327.1345 (MH^+), found: 327.1342. Anal. calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.10; H, 5.55; N, 8.50.

9-Methoxy-3-nitro-6-prop-2-enyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6g). Yellow thick oil. ^{1}H NMR (CD_2Cl_2) δ 8.11 (dd, J_1=8.8 Hz, J_2=2.8 Hz, 1H), 7.97 (d, J=2.8 Hz, 1H), 7.5–6.7 (m, 4H), 5.90 (m, 1H), 5.22 (d, J=6.8 Hz, 2H), 4.58–2.79 (m, 6H), 3.78 (s, 3H); ^{13}C NMR (CD_2Cl_2) δ 155.9, 135.0, 128.5, 126.3, 123.8, 122.7, 119.8, 119.2, 118.6, 115.8, 114.7, 113.5, 56.5, 54.6, 50.4, 49.6; HRMS (FAB) calcd for $C_{18}H_{18}N_2O_4$: m/z=327.1345 (MH^+), found: 327.1340. Anal. calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.00; H, 5.56; N, 8.54.

11-Nitro-8-prop-2-enyl-7*H*, 9*H*-benzo[*g*]naphtho[2,1-*b*]1,5-oxazocine (6h). Light yellow solid. mp 146–148°C; ^{1}H NMR (CD_2Cl_2) δ 8.07 (dd, J_1=9.0 Hz, J_2=2.8 Hz, 1H), 8.01 (d, J=9.0 Hz, 1H), 7.85 (d, J=2.8 Hz, 1H), 7.78 (d, J=9.0 Hz, 2H), 7.50 (t, J=7.6 Hz, 1H), 7.41 (t, J=7.6 Hz, 1H), 7.25 (t, J=8.0 Hz, 2H), 5.92 (m, 1H), 5.20 (t, J=7.6 Hz, 2H), 3.99 (s, 2H), 3.59 (s, 2H), 3.03 (s, 2H); ^{13}C NMR (CD_2Cl_2) δ 136.6, 133.6, 132.5, 130.9, 130.3, 129.2, 127.8, 126.2, 125.6, 124.7, 121.2, 120.7, 120.4, 118.9, 58.7, 52.0, 47.4; HRMS (FAB) calcd for $C_{21}H_{18}N_2O_3$: m/z=347.1396 (MH^+), found: 347.1393. Anal. calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.54; H, 5.28; N, 7.98.

9-Bromo-3-nitro-6-prop-2-enyl-5*H*, 7*H*-dibenzo[*b*,*g*]1,5-oxazocine (6i). Yellow solid. mp 123–126°C; ^{1}H NMR (CD_2Cl_2) δ 8.06 (dd, J_1=9.0 Hz, J_2=2.8 Hz, 1H), 7.91 (d, J=2.8 Hz, 1H), 7.35 (dd, J_1=6.8 Hz, J_2=2.8 Hz, 1H), 7.2–7.0 (m, 3H), 5.79 (m, 1H), 5.14 (d, J=8.6 Hz, 2H), 4.5–2.7 (m, 6H); ^{13}C NMR (CD_2Cl_2) δ 136.4, 135.6, 133.2, 129.9, 125.7, 124.5, 122.6, 121.1, 120.4, 118.8, 58.1, 51.2; HRMS (FAB) calcd for $C_{17}H_{15}BrN_2O_3$: m/z=375.0345 (MH^+), found: 375.0355. Anal. calcd for $C_{17}H_{15}BrN_2O_3$: C, 54.42; H, 4.03; N, 7.47. Found: C, 54.27; H, 4.12; N, 7.41.

Solid phase synthesis of dibenzo[*b*,*g*]1,5-oxazocines 7a–7h

The procedure reported below is typical for the solid-phase synthesis of dibenzo[*b*,*g*]1,5-oxazocines **7a**–**7h**.

The resin resulting from the DBU cyclization of **10** (2 g) was treated with 25 mL of a 1 M solution of $SnCl_2 \cdot H_2O$ in DMF for 12 h at room temperature. After filtration, the resin was washed with MeOH, CH_2Cl_2, DMF, and treated with a mixture of acylating agent and Hunig's base (0.2 M solution for each component, 25 mL overall volume) in CH_2Cl_2 for 4 h. The resin was filtered, washed with MeOH, CH_2Cl_2, DMF, and treated with a 1 M solution of allyl bromide (50 mL) in DMF for 8 h. The resultant quaternized amine on solid support was filtered, washed with MeOH, CH_2Cl_2, and DMF, and treated with 5% Hunig's base in CH_2Cl_2 (100 mL) for 2 h. The filtrate was collected and washed twice with a saturated $NaHCO_3$ solution. The extract was dried over $MgSO_4$, filtered, and co-evaporated twice with MeOH to afford the desired products as solids (HPLC purity: 100%). The compounds were further purified by flash chromatography on silica gel with EtOAc/hexane (20:80) as eluent to afford the analytically pure **7a**–**7h** in 20–78% yields.

Analytical data

***N*-(6-Methyl-5*H*, 7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl)acetamide (7a).** Pale yellow solid. mp 71–73°C; ^{1}H NMR (CD_2Cl_2) δ 8.03 (s, 1H), 7.43 (dd, J_1=8.6 Hz, J_2=2.5 Hz, 1H), 7.3–7.0 (m, 6H), 4.7–1.9 (m, 7H), 2.08 (s, 3H); ^{13}C NMR (CD_2Cl_2) δ 171.3, 162.4, 158.5, 137.7, 134.8, 132.1, 127.5, 126.1, 125.2, 123.6, 122.2, 62.2, 44.7, 39.5, 26.8; HRMS (FAB) calcd for $C_{17}H_{18}N_2O_2$: m/z=283.1447 (MH^+), found: 283.1446. Anal. calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.21; H, 6.32; N, 9.69.

(4-Chlorophenyl)-*N*-(6-methyl(5*H*,7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl))carboxamide (7b). Pale solid. mp 189–191°C; ^{1}H NMR (CD_2Cl_2) δ 7.69 (d, J=8.6 Hz, 3H), 7.44 (dd, J_1=8.6 Hz, J_2=2.5 Hz, 1H), 7.36 (d, J=8.6 Hz, 2H), 7.27 (s, 2H), 7.17 (t, J=6.8 Hz, 2H), 6.98 (m, 2H), 4.58–3.51 (m, 4H), 2.14–1.88 (m, 3H). ^{13}C NMR (d_6-DMSO) δ 162.4, 157.8, 153.7, 134.6, 133.7, 131.7, 130.2, 127.8, 127.5, 126.6, 125.9, 123.0, 122.0, 120.9, 119.5, 117.3, 58.0, 50.9, 35.0. HRMS (FAB) calcd for $C_{22}H_{19}ClN_2O_2$: m/z=283.1447379.1213 (MH^+), found: 379.1222. Anal. calcd for $C_{22}H_{19}ClN_2O_2$: C, 69.75; H, 5.05; N, 7.39. Found: C, 69.57; H, 5.02; N, 7.34.

(4-Chlorophenyl)-*N*-(11-methoxy-6-prop-2-enyl(5*H*,7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl))carboxamide (7c). Pale solid. mp 149–152°C; ^{1}H NMR (CD_2Cl_2) δ 8.15 (s, 1H), 7.80 (d, J=8.6 Hz, 2H), 7.54 (dd, J_1=8.6 Hz, J_2=2.8 Hz, 1H), 7.44 (d, J=8.6 Hz, 2H), 7.36 (s, 1H), 7.05 (t, J=7.6 Hz, 1H), 6.96 (d, J=8.6 Hz, 1H), 6.74 (d, J=6.8 Hz, 1H), 5.90 (m, 1H), 5.16 (d, J=6.8 Hz, 2H), 3.96 (s, 6H), 4.58–2.28 (m, 3H); ^{13}C NMR (CD_2Cl_2) δ 165.4, 138.6, 137.1, 134.2, 129.6, 129.4, 125.4, 124.6, 121.7, 117.9, 113.2, 58.6, 56.6, 53.2; HRMS (FAB) calcd for $C_{25}H_{23}ClN_2O_3$: m/z=435.1475 (MH^+), found: 435.1495. Anal. calcd for $C_{25}H_{23}ClN_2O_3$: C, 69.04; H, 5.33; N, 6.44. Found: C, 69.00; H, 5.35; N, 6.52.

(4-Chlorophenyl)-*N*-(10-methoxy-6-prop-2-enyl(5*H*,7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl))carboxamide (7d). Pale solid. mp 147–150°C; ^{1}H NMR (CD_2Cl_2) δ 8.23 (s, 1H), 7.81 (d, J=8.0 Hz, 2H), 7.60 (dd, J_1=8.6 Hz, J_2=2.2 Hz, 1H), 7.44 (d, J=8.6 Hz, 4H), 7.02 (d, J=8.0 Hz, 1H), 6.65 (dd, J_1=8.6 Hz, J_2=2.8 Hz, 1H), 5.90 (m, 1H), 5.18 (d, J=6.8 Hz, 2H), 3.96 (s, 4H), 4.58 (s, 1H), 3.65 (s, 2H), 2.56 (m, 2H); ^{13}C NMR (CD_2Cl_2) δ 165.4, 138.6, 137.1, 134.2, 129.6, 129.4, 125.4, 124.6, 121.7, 117.9, 113.2, 58.6, 56.6, 53.2; HRMS (FAB) calcd for

$C_{25}H_{23}ClN_2O_3$: *m*/*z*=435.1475 (MH^+), found: 435.1487. Anal. calcd for $C_{25}H_{23}ClN_2O_3$: C, 69.04; H, 5.33; N, 6.44. Found: C, 69.0; H, 5.35; N, 6.38.

(4-Chlorophenyl)-*N*-(9-methoxy-6-prop-2-enyl(5*H*,7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl))carboxamide (7e). Light yellow solid. mp 127–130°C; ^{1}H NMR (CD_2Cl_2) δ 7.75 (s, 1H), 7.68 (d, *J*=8.6 Hz, 2H), 7.43 (d, *J*=8.6 Hz, 1H), 7.36 (d, *J*=8.6 Hz, 2H), 7.23 (b, 2H), 6.69 (d, *J*=7.6 Hz, 1H), 6.54 (s, 1H), 5.78 (m, 1H), 5.05 (d, *J*=9.6 Hz, 2H), 4.5–2.6 (m, 6H), 3.64 (s, 3H); ^{13}C NMR (CD_2Cl_2) δ 163.5, 155.2, 136.9, 135.4, 133.4, 132.4, 127.9, 127.6, 123.1, 121.9, 120.2, 118.7, 116.2, 112.7, 56.8, 54.5, 521.0, 51.5; HRMS (FAB) calcd for $C_{25}H_{23}ClN_2O_3$: *m*/*z*=435.1475 (MH^+), found: 435.1487. Anal. calcd for $C_{25}H_{23}ClN_2O_3$: C, 69.04; H, 5.33; N, 6.44. Found: C, 69.06; H, 5.47; N, 6.37.

***N*-(8-Prop-2-enyl-7*H*,9*H*-benzo[3,4-*g*]naphtho[2,1-*b*]1,5-oxazocin-11-yl)acetamide (7f).** White solid. mp 227–230°C; ^{1}H NMR (d_6-DMSO) δ 9.88 (s, 1H), 8.14 (s, 1H), 7.90 (d, *J*=8.6 Hz, 2H), 7.57–7.44 (m, 4H), 7.29 (d, *J*=2.4 Hz, 2H), 5.89 (m, 1H), 5.18 (d, *J*=7.6 Hz, 2H), 4.03–2.98 (m, 6H), 2.01 (s, 3H); ^{13}C NMR (d_6-DMSO) δ 168.3, 136.4, 133.2, 131.0, 130.1, 128.7, 127.0, 125.1, 124.0, 120.2, 118.1, 24.2; HRMS (FAB) calcd for $C_{23}H_{22}N_2O_2$: *m*/*z*=359.1759 (MH^+), found: 359.1746. Anal. calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 77.09; H, 6.13; N, 7.75.

***N*-(9-Bromo-6-benzyl-5*H*,7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl)acetamide (7g).** White solid. mp 192–195°C; ^{1}H NMR (d_6-DMSO) δ 9.89 (s, 1H), 7.51–7.46 (m, 3H), 7.36–7.12 (m, 8H), 7.36–7.24 (m, 7H), 4.54–3.15 (m, 6H), 1.99 (s, 3H); ^{13}C NMR (d_6-DMSO) δ 166.6, 137.0, 134.6, 133.5, 132.7, 130.5, 126.8, 126.7, 125.4, 121.0, 120.8, 118.3, 117.6, 55.0, 51.3, 22.3; HRMS (FAB) calcd for $C_{23}H_{21}BrN_2O_2$: *m*/*z*=437.0865 (MH^+), found: 437.0862. Anal. calcd for $C_{23}H_{21}BrN_2O_2$: C, 63.17; H, 4.84; N, 6.41. Found: C, 63.17; H, 4.86; N, 6.46.

***N*-(11-Fluoro-6-benzyl-5*H*,7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocin-3-yl)acetamide (7h).** White solid. mp 185–187°C ^{1}H NMR (d_6-DMSO) δ 9.93 (s, 1H), 7.52 (d, *J*=7.6 Hz, 1H), 7.44 (s, 1H), 7.36–7.24 (m, 7H), 7.08 (dd J_1=7.6 , J_2=5.2 Hz, 1H), 6.77 (s, 1H), 4.58–3.25 (m, 6H), 2.03 (s, 3H); ^{13}C NMR (d_6-DMSO) δ 168.5, 139.0, 136.6, 135.9, 132.4, 128.7, 128.6, 127.8, 127.3, 125.8, 122.9, 120.2, 116.9, 116.8, 57.3, 53.2, 52.6, 24.2; HRMS (FAB) calcd for $C_{23}H_{21}FN_2O_2$: *m*/*z*=377.1665 (MH^+), found: 371.1669. Anal. calcd for $C_{23}H_{21}FN_2O_2$: C, 73.39; H, 5.62; N, 7.44. Found: C, 73.33; H, 5.58; N, 7.45.

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11. Initially, we attempted the reductive amination reaction of

salicylaldehyde **3a** (instead of **1**), and immobilized β-alanine **8** in DMF in the presence of 1% of AcOH. However, treatment of the resulting resin with 20% TFA in CH_2Cl_2 afforded the expected amino acid in only a 7% yield. Additionally, attempts to conduct the second reductive amination reaction with 2-fluoro-5-nitrobenzaldehyde (**1**) were unsuccessful under a variety of experimental conditions. However, changing the reductive amination sequence proved to be beneficial.