Article

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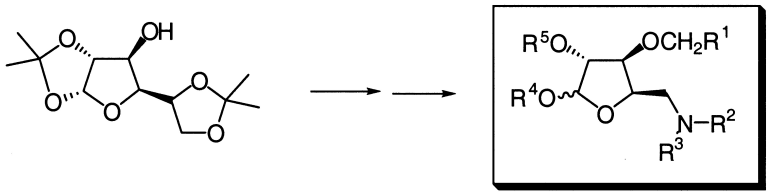

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Solution-Phase Library Synthesis of Furanoses

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The solution-phase synthesis of amido-, urea-, and aminofuranoses was achieved. Alkylated furanose aldehydes were treated with primary amines in the presence of sodium triacetoxyborohydride to give secondary amines. Subsequent acylation with acid chlorides and isocyanates afforded amidofuranoses and ureafuranoses, respectively. Second, reductive amination of furanose aldehydes with secondary amines yielded tertiary amines. The resulting acetonides were treated with alcohols in the presence of acid to yield mixed acetals. In the library syntheses, functionalized scavenger resins were used in the purification of intermediates and products.

Introduction

Library synthesis is an important method for both new chemotype generation and lead optimization of potential drug candidates for the pharmaceutical industry. Since natural products are pharmacologically rich, possess varied structural diversity, and exhibit potent biological activity, they are an attractive source of screening library structures.[1] Several groups have reported the synthesis of "natural product-like" libraries that either possess the structural characteristics of natural products or are derived from natural products.[2] We have developed both solid-phase and solution-phase small-molecule libraries that contain structural motifs of natural products.[3−6] Robust and general synthetic transformations have been developed and applied to the synthesis of these screening libraries.

Carbohydrates are an inexpensive class of molecules that are stereochemically and functionally rich. Hirschmann, Nicolaou, Smith, and co-workers have described the use of monosaccharides as "privileged structures"[7] that modulate receptor and receptor subtype affinities.[8] Sugar sulfamates such as topiramate are also known anticonvulsants.[9] The furanose derivative amiprilose has been reported to provide some effectiveness in the treatment of rheumatoid arthritis.[10] Furthermore, furanoses show promise as filaricides.[11] Despite these reported biological activities and the recent advances in oligosaccharide synthesis,[12] small-molecule libraries derived from sugars have received limited attention.[13] In the context of our ongoing combinatorial chemistry development program, we have found carbohydrates[14] to be useful for the construction of small-molecule libraries. Herein, we describe the library synthesis of furanoses using general, robust methods.

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Results and Discussion

Identification of a Practical Synthetic Route Toward Furanoses. Among several possible pathways for the library synthesis of furanose derivatives, we initially chose to examine solid-phase routes (Scheme 1). Reductive amination of furanose aldehydes **2** onto solid-supported amino acids on Wang derived resin **1a** gave the desired products **6** in <20% yield and in <15% purity (area under the curve at 214 nm). Multiple baseline impurities contributed to the low overall yield and purity. We also explored a library synthesis on PAL resin **1b**. To our disappointment, hemiacetal products **6** obtained using linker **1b** were consistently impure.

We then focused on developing a solution-phase route. The proposed furanose library target structures **7** can be generated from acetonide **8**, which can be derived from aldehyde **9**, readily prepared from diacetone-D-glucose (**10**) (Scheme 2). In the library design, removal of excess reagents and undesired intermediates was a major challenge. For this purpose, we utilized solid-supported scavenger and ion-exchange resins.

Scaffold Synthesis. To begin, the synthesis of aldehydes **9** was well-precedented (Scheme 3).[15,16] While alkylation of diacetone-D-glucose (**10**) with alkyl halides using sodium hydride in DMF gave ethers **11**, the use of potassium *tert*-butoxide in THF facilitated workup of large-scale reactions.[17] However, these conditions did not completely alkylate **10** with alkyl halides such as *n*-ethyl iodide. Powdered potassium hydroxide in DMSO worked well for all types of alkyl halides and was utilized in the syntheses of ethers **11**.

Subsequent chemoselective hydrolysis of the primary isopropylidines of **11** with 70% acetic acid in water gave diols **12**. We found this reaction worked optimally at ≤0.5 M, since at higher concentrations, the hydrolysis did not go to completion. An extractive workup followed by silica gel chromatography gave diols **12** in >95% purity by HPLC−UV analysis (area under the curve at 214 nm). Finally,

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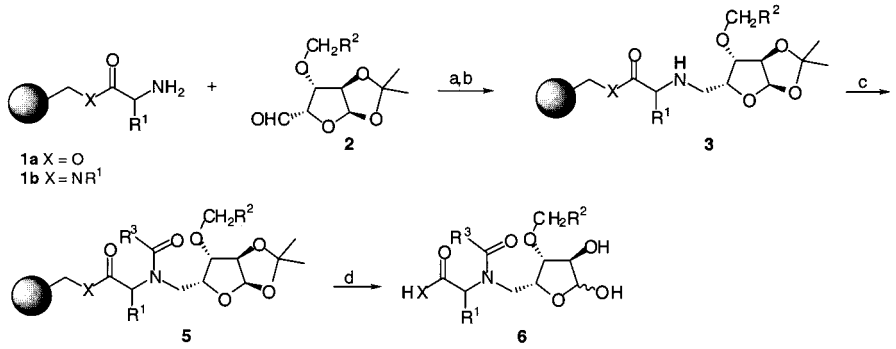
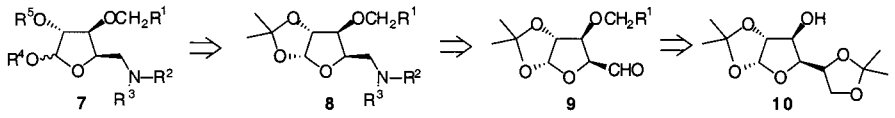
Scheme 1[a]

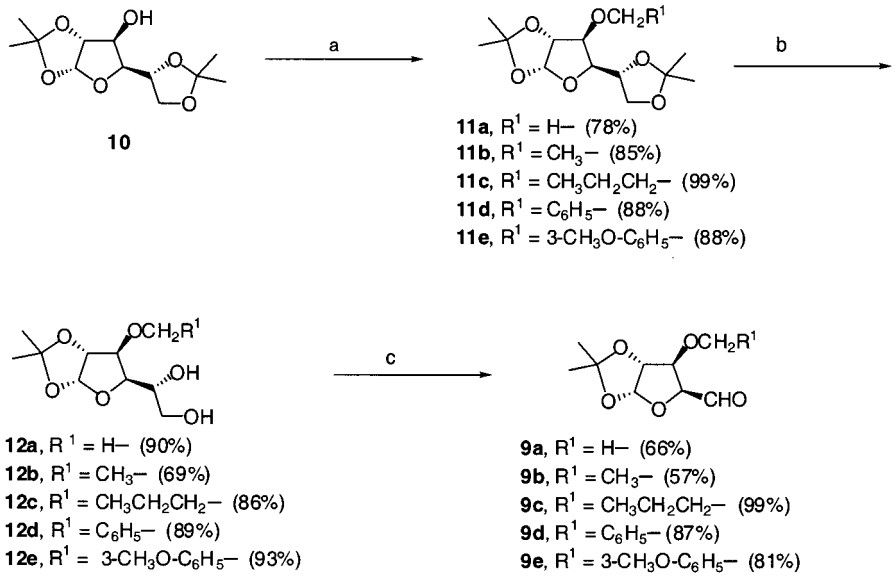


[a] Reagents and conditions: (a) $HC(OMe)_3$, CH_2Cl_2 (1:1); (b) BH_3−pyridine, AcOH, CH_2Cl_2; (c) R^3COCl (**4**), base, solvent; (d) 95% TFA/H_2O.

Scheme 2



Scheme 3[a]



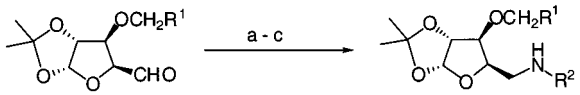
[a] Reagents and conditions: (a) KOH, R^1CH_2Br or R^1CH_2I, DMSO; (b) 70% AcOH/H_2O; (c) $NaIO_4$, SiO_2,CH_2Cl_2, H_2O.

sodium periodate adsorbed on silica gel cleaved diols **12** to provide aldehydes **9** with an average overall yield of 65% (Scheme 3).[16]

Upon scaling the scaffold aldehyde syntheses to 3 mol, we eliminated all silica gel chromatography steps. After hydrolysis to diol **12**, the crude oil was partitioned between hexanes and water. Excess alkylating agent and other nonpolar impurities were exclusively extracted into the organic layer, and the product and a small amount of starting material remained in the aqueous layer. A diethyl ether or methylene chloride extraction transferred the product into the organic layer, from which it was recovered.

Reductive Amination of Tetrahydrofuranocarbaldehydes. The first step of the sequence involved reductive amination with sodium triacetoxyborohydride and aldehydes **9** (Scheme 4).[18] We initially investigated the use of solid-supported borohydride reagents, but the reductive amination slowly proceeded to give only about 50% conversion to

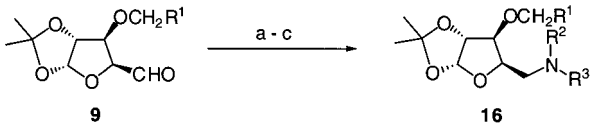
Scheme 4[a]



[a] Reagents and conditions: (a) R^2NH_2 (**13**), $NaBH(OAc)_3$, EtOH; (b) Amberlite IRA-743 resin, EtOH; (c) PS−4-benzyloxybenzaldehyde resin, CH_2Cl_2.

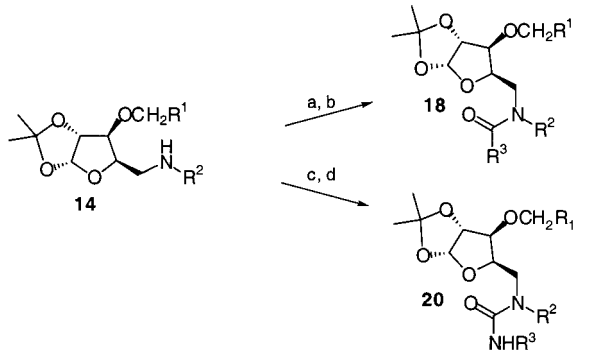
amines **14** after 4 days. In addition to solid-supported borohydride, we examined several other reducing agents including sodium borohydride, borane−pyridine complex, and sodium triacetoxyborohydride. Only sodium triacetoxyborohydride gave the desired products in high conversion and high purity.[19] When only 1 equiv of amine was used, the reductive amination gave 50% of the desired products and also resulted in overalkylation to tertiary amines. The reaction purity was dramatically improved by switching from

Scheme 5[a]



[a] Reagents and conditions: (a) R^2R^2NH (**15**), $NaBH(OAc)_3$, 1,4-dioxane; (b) Amberlite IRA-743 resin, 1,4-dioxane; (c) PS-isocyanate resin, 1,4-dioxane.

Scheme 6[a]



[a] Reagents and conditions: (a) R^3COCl (**17**), *N*-methylmorpholine, 1,4-dioxane; (b) Dowex SBr LC NG OH anion-exchange resin, 1,4-dioxane; (c) R^3NCO (**19**), 1,4-dioxane; (d) tris(2-aminoethyl)amine resin, 1,4-dioxane.

solvents such as methylene chloride or THF to ethanol. Although the overalkylation products were occasionally observed, overalkylation was minimized by using 3 equiv of the reducing amines.

Having found the optimal reductive amination conditions, we removed borates from amines **14** using a boron-chelating ion-exchange resin Amberlite IRA-743.[20] Atomic absorption analysis for boron of samples untreated with the Amberlite IRA-743 resin contained 12% boron by weight. To our delight, samples treated with Amberlite IRA-743 resin for 14−18 h contained less than 1.5% boron by weight. Furthermore, excess amines were removed using the benzaldehyde scavenger resin in dichloromethane.[21] Purities were generally high (>90% area under the curve at 214 nm).

Alternatively, reductive amination of aldehydes **9** with secondary amines **15** was optimized to give the desired tertiary amines products **16** in high purity (Scheme 5). Since overalkylation with secondary amines cannot occur, only an amount of 1.1 equiv of secondary amine in the presence of sodium triacetoxyborohydride was required to provide the tertiary amines **16**. Subsequent removal of borate salts from amines **16** was accomplished by treating the crude reaction mixture with Amberlite IRA-743 resin as described above. Upon treatment with PS-isocyanate resin for 14 h at ambient temperature, excess secondary amine was also removed. After these scavenging steps, acetonide **16** purities were generally very high (>96% area under the curve at 214 nm).

Acylation of Secondary Amines. After purification using scavenger and ion-exchange resins, secondary amines **14** were treated with solutions of acylators in 1,4-dioxane (Scheme 6). Upon completion of the acylation, excess acylator was removed by means of a scavenging step. We chose acid chlorides **17** and isocyanates **19** to furnish the corresponding amides **18** or ureas **20**, respectively. Each type of acylator required a different scavenger resin. Excess acid chlorides were successfully removed from the reaction mixture by hydrolysis with water to the corresponding carboxylic acids followed by treatment with Dowex SBr LC NG OH form anion-exchange resin for 14 h.[22] Excess isocyanates were successfully removed upon treatment with tris(2-aminoethyl)amine scavenger resin for 14 h.[23] We generally found that these acylations were complete in less than 3 h, and scavenging of excess acylators was complete after 14 h. Representative furanoses **18** and **20** prepared by these methods are shown in Table 1.

Hydrolysis of Acetonides to Hemiacetals and Mixed Acetals. To further enhance library diversity, we explored the possibility of hydrolyzing the acetonide moiety. The reaction cleanly proceeded to give the desired hemiacetals, as a mixture of diastereomers, in high purity when treated with a 50% solution of trifluoroacetic acid in water at ambient temperature. We observed significant decomposition of the products over 2 weeks in solutions of TFA. Because of the inherent instability of hemiacetals, acetonides were the final library products.

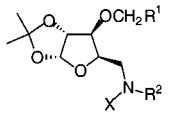
We did, however, explore the possibility of generating the more stable mixed acetals **22** from acetonides **16** as stable library products. A variety of conditions were examined for this transformation using different types of acetonides **16** and alcohols **21** (Table 2). Initially, we considered TFA as the acid source for acetonide removal. However, TFA failed to completely remove acetonides at various stoichiometries and removal of TFA from the final products was difficult. More importantly, TFA generally gave products in low purities (Table 2, entry no. 1). Sulfuric acid also gave many impurities (Table 2, entry no. 2). The best acid for complete acetonide removal was 4 N HCl in 1,4-dioxane (Table 2, entry nos. 3−5). We found that a catalytic amount of HCl failed to completely convert acetonides **16** to mixed acetals **22** (Table 2, entry no. 3). Increasing the amount of HCl (10 equiv) in a 50% solution of alcohol in 1,4-dioxane afforded mixed acetals **22** in greater than 95% purity by HPLC−UV analysis (area under the curve at 214 nm) at 50 °C (Table 2, entry no. 4) or at ambient temperature (Table 2, entry no. 5). We found that fewer equivalents of acid or alcohol did not completely convert acetonides **16** to the desired mixed acetals **22**.

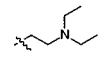
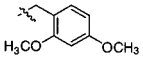
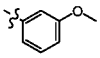
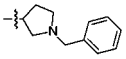
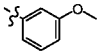
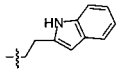
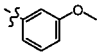
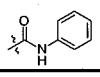
Furthermore, hemiacetal products **23** were formed upon exposure of the acidic solutions to moisture (Figure 1). To remove trace amounts of acid and to ensure long-term stability of acetals **22**, a final treatment with PS-piperidine resin was necessary.[24] Products not treated with the PS-piperidine resin underwent rapid hydrolysis within 1 day to the hemiacetals **23** and other minor, uncharacterized baseline impurities as observed by HPLC−UV analysis. After treatment with PS-piperidine resin and solvent removal, the products were stored below 0 °C in a freezer. Products stored cold (less than −20 °C) did not decompose for 1 month according to HPLC−UV analysis. Representative mixed acetals **22** prepared by these methods are shown in Table 3.

Conclusion

We have developed a solution-phase procedure for the synthesis of furanose libraries. Various scavenger and ion-

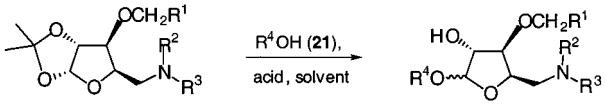
Table 1. Representative Furanoses **18** and **20** Prepared via Solution-Phase Library Syntheses



Entry No.	Compound	R^1	R^2	X	Yield[a] (%)	Purity[b] (%)
1	**18a**				43	83
2	**18b**	H			71	99
3	**18c**				58	99
4	**20a**	H			60	71
5	**20b**				49	82
6	**20c**	H			62	99
7	**20d**				55	99
8	**20e**				67	99

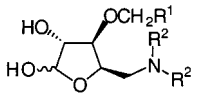
[a] Crude yield. [b] Area under the curve by UV at 214 nm.

Table 2. Optimization of Mixed Acetal Formation



16 **22**

entry no.	R^3OH	acid	solvent	temperature	time, h	observed result
1	50 vol %	TFA (50 vol %)	none	room temp	14	low product purity
2	1 equiv	H_2SO_4 (1 equiv)	CH_2Cl_2	room temp	14	low product purity
3	1 equiv	HCl (0.5 equiv)	1,4-dioxane (0.06 M)	room temp	14	reaction incomplete
4	50 vol %	HCl (10 equiv)	1,4-dioxane (50 vol %)	50 °C	7	>99% conversion
5	50 vol %	HCl (10 equiv)	1,4-dioxane (50 vol %)	room temp	14	>99% conversion



23

Figure 1. Structure of **23**.

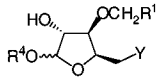
exchange resins were used to purify both intermediates and final products. These methods have been successfully applied to the synthesis of several small-molecule libraries composed of about 5000 compounds each.[25,26]

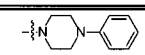
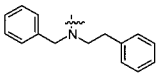
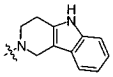
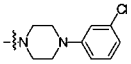
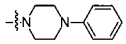
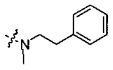
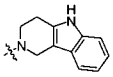
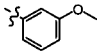
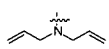
Experimental Section

1. General. All reactions were performed in standard glassware or suitable materials for parallel library synthesis. ^1H NMR and ^{13}C NMR spectra were measured on JEOL 270 and 67.5 MHz spectrometers at 296 K, respectively. Chemical shifts are reported in ppm relative to TMS (δ = 0). EI mass spectra were recorded on a Sciex 150 EX instrument equipped with an HP 1100 HPLC. Elemental analyses were performed by Robertson Microlit Laboratories (Madison, NJ). Flash column chromatography was done on silica gel 230−400 mesh (flash) from EM Science; thin-layer chromatography (TLC) was performed on glass plates coated with silica gel 60 F_{254} from Merck. TLC plates were developed in 1:1 hexanes/EtOAc and stained with anisaldehyde. Reversed-phase HPLC was performed on an HP1100 system (Hewlett-Packard, Palo Alto, CA) equipped with a vacuum degasser, binary pump, autosampler, column compartment, a diode array detector, and a C18 column (3.0 mm × 100 mm, 5 μm, 100 Å) (Phenomenex, Torrance, CA) at 40 °C with a flow rate of 1.0 mL/min. Two mobile phases (mobile phase A, 99% water, 1% acetonitrile, 0.05% TFA; mobile phase B, 1% water, 99% acetonitrile, 0.05% TFA) were employed to run a gradient condition from 0% B to 100% B in 6.0 min and at 100% B for 2.0 min, and they were reequilibrated at 0% B for 2 min. An injection volume of 10 μL was used. All reagents and solvents were reagent grade and were used without further purification.

2. Representative Procedure for the Synthesis of Carbaldehydes (9b). A 1 L three-necked round-bottomed flask

Table 3. Representative Mixed Acetals **22** Prepared via Solution-Phase Library Syntheses



Entry No.	Compound	R^1	Y	R^4	Yield[a] (%)	Purity[b] (%)
1	**22a**	CH_3-			62	85
2	**22b**	CH_3-			56	82
3	**22c**	CH_3-		CH_3-	46	84
4	**22d**	CH_3-			44	83
5	**22e**	H			44	87
6	**22f**				56	92
7	**22g**			CH_3-	41	90
8	**22h**				62	83

[a] Crude yield. [b] Area under the curve by UV at 214 nm.

equipped with a magnetic stir bar was charged with DMSO (545 mL) and finely ground potassium hydroxide (73.4 g, 1.3 mol, 4 equiv). The mixture was stirred until it was homogeneous (~20 min). The suspension was cooled to an internal temperature of 10 °C, and diacetone-D-glucose (85.1 g, 0.327 mol, 1.0 equiv) (**1**) was added in a single portion. The mixture was allowed to stir for 30 min. Iodoethane (52 mL, 0.654 mol, 2.0 equiv) was added over 20 min with an addition funnel, and the internal temperature was kept below 30 °C. Following addition of iodoethane, the reaction was allowed to reach ambient temperature and was stirred overnight (14 h). The opaque brown solution was checked by TLC, and the reaction was judged complete. The reaction was diluted with water (320 mL) and extracted twice with diethyl ether (1 × 300 mL, 1 × 150 mL). The organic layers were combined, washed with saturated aqueous NaCl (200 mL), and dried over anhydrous Na_2SO_4. The organic layers were filtered, concentrated in vacuo, and dried under high vacuum to afford 80.4 g (85%) of acetonide **11b** as a pale-yellow oil. Following analogous procedures, acetonides **11a** (66%), **11c** (99%), **11d** (87%), and **11e** (81%) were obtained.

A 1 L round-bottomed flask equipped with a magnetic stir bar was charged with acetonide **11b** (80.4 g, 279 mmol) dissolved in aqueous acetic acid (560 mL, 70%, v/v, 0.5 M). After the mixture was stirred at ambient temperature for 14 h, the reaction was judged complete by TLC. The solvent was removed in vacuo (<35 °C), followed by azeotroping in a rotary evaporator with toluene (2 × 200 mL) to afford a crude yellow oil. The crude oil was dissolved in water (250 mL), and the aqueous layer was washed with hexane (2 × 200 mL). The aqueous layer was extracted with dichloromethane (3 × 200 mL) and dried over anhydrous $MgSO_4$. The organic layers were filtered and concentrated in vacuo to yield 47.7 g (69%) of diol **12b** as a clear, colorless oil. Following analogous procedures, diols **12a** (90%), **12c** (86%), **12d** (89%), and **12e** (93%) were obtained.

A 2 L Erlenmeyer flask equipped with a magnetic stir bar was charged with silica gel (80.6 g, EM Science, catalog no. 9385-9) and dichloromethane (806 mL). An aqueous solution of sodium periodate (80.6 mL, 52.3 mmol, 0.65 M) was added dropwise over 5 min, and a white precipitate formed. A solution of diol **12b** (10.0 g, 40.3 mmol, 0.5 M) in dichloromethane (80.6 mL) was added in one portion to the Erlenmeyer flask. After the mixture was stirred at ambient temperature for 1.5 h, the reaction was judged complete by TLC. The reaction was diluted with water (275 mL), and the suspension was transferred to a 2 L separatory funnel. The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 75 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to yield a colorless oil that was dried under high vacuum for 12 h to afford 6.4 g (57%) of aldehyde **9b**. Following analogous procedures, aldehydes **9a** (66%), **9c** (99%), **9d** (87%), and **9e** (81%) were obtained. The aldehydes can be stored for 3−5 days under high vacuum prior to use in the reductive amination step.

9a: 66%; clear, colorless oil; $[\alpha]^{25}_D$ −59.8° (*c* 1.03, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.62 (d, J = 1.5 Hz, 1H), 6.07 (d, J = 3.7 Hz, 1H), 4.61 (d, J = 3.7 Hz, 1H), 4.53 (dd, J = 3.7, 1.7 Hz, 1H), 4.10 (d, J = 3.7 Hz, 1H), 3.33 (s, 3H), 1.46 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 199.5, 112.3, 105.9, 85.9, 84.3, 81.3, 57.9, 26.7, 26.1; MS (ESI) *m*/*z* 203.1 [(M + H)$^+$].

9b: 57%; clear, colorless oil; $[\alpha]^{25}_D$ −53.4° (*c* 1.04, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.66 (d, J = 1.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 4.60 (d, J = 3.3 Hz, 1H), 4.54 (dd, J = 2.0, 2.0 Hz, 1H), 4.22 (d, J = 3.8 Hz, 1H),

3.67−3.56 (m, 1H), 3.51−3.39 (m, 1H), 1.48 (s, 3H), 1.34 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 200.1, 112.4, 106.1, 84.5, 84.3, 82.3, 66.2, 26.9, 26.3, 14.9; MS (ESI) m/z 217.1 [$(M + H)^+$].

9c: 99%; clear, colorless oil; $[\alpha]^{25}_D$ −46.5° (c 1.05, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.65 (d, J = 1.7 Hz, 1H), 6.10 (d, J = 3.5 Hz, 1H), 4.60 (d, J = 3.5 Hz, 1H), 4.54 (dd, J = 3.8, 1.8 Hz, 1H), 4.19 (d, J = 3.9 Hz, 1H), 3.56 (ddd, J = 9.3, 6.5, 6.5 Hz, 1H), 3.39 (dd, J = 9.3, 6.5, 6.5 Hz, 1H), 1.48 (s, 3H), 1.47 (dddd, J = 7.3, 1.5, 1.5 Hz, 2H), 1.34 (s, 3H), 1.31 (dddd, J = 15.1, 5.8, 5.8 Hz, 2H), 0.88 (t, J =7.4 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 199.9, 112.4, 106.1, 84.5, 82.1, 70.5, 31.6, 26.9, 26.3, 18.9, 13.6; MS (ESI) m/z 245.1 [$(M + H)^+$].

9d: 87%; colorless oil; $[\alpha]^{25}_D$ −34.5° (c 1.02, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.62 (d, J = 1.4 Hz, 1H), 7.31−7.17 (m, 5H), 6.07 (d, J = 3.4 Hz, 1H), 4.59 (d, J = 3.4 Hz, 2H), 4.52 (dd, J = 3.7, 1.5 Hz, 1H), 4.45 (s, 1H), 4.40 (s, 1H), 4.29 (d, J = 3.7 Hz, 1H), 1.41 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 199.7, 136.5, 128.4, 128.0, 127.6, 112.4, 106.1, 84.5, 83.6, 82.0, 72.2, 26.9, 26.2; MS (EI) m/z 279 [$(M + H)^+$].

9e: 81%; colorless oil; $[\alpha]^{25}_D$ −63.3° (c 1.05, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.68 (d, J = 1.7 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 6.89−6.75 (m, 3H), 6.13 (d, J = 3.4 Hz, 1H), 4.65−4.56 (m, 3H), 4.47 (s, 1H), 4.32 (d, J = 3.7 Hz, 1H), 3.80 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 199.8, 159.7, 1137, 112.8, 112.4, 106.1, 84.5, 83.5, 82.0, 71.9, 55.1, 26.9, 26.3; MS (EI) m/z 308 [M^+].

3. General Procedure for the Preparation of Library Compounds. 3.1. Reductive Amination with Primary Amines and Purification (14). To a 125 mL Nalgene bottle was added the appropriate 0.25 M solution of aldehyde scaffold (30 mL, 7.5 mmol, 1 equiv) in absolute ethanol. The bottle was then treated with neat reducing amine (23 mmol, 3 equiv). No more than 6 mL of absolute ethanol was used to rinse the vessel containing the amine. Sodium triacetoxyborohydride (2.07 g, 9.75 mmol, 1.3 equiv) was quickly added to each bottle. The bottle was then loosely capped and shaken upright at ambient temperature (22−27 °C) between 5 and 7 h.

Amberlite IRA-743 resin (150 g, Aldrich) followed by absolute ethanol (100 mL) was added to a 250 mL coarse-sintered-glass funnel. The resin slurry was stirred, and the ethanol was removed by applying house vacuum for 5 min. This process was repeated twice, and the resin was dried under vacuum. After drying for 10 min, 15 g of the resin was transferred into each Nalgene bottle containing the ethanolic scaffold solution. The bottle was capped and shaken at ambient temperature (22−27 °C). After 14 h, the contents of the Nalgene bottle were filtered into a 500 mL round-bottomed flask, and the resin was washed with absolute ethanol (2 × 30 mL). The contents of the flasks were concentrated to dryness.

The concentrated material was diluted with dichloromethane (260 mL) and transferred to a 500 mL Nalgene bottle containing 4-benzyloxybenzaldehyde polymer supported scavenger resin (14 g/bottle, unwashed, Midwest Biotech, catalog no. 20815, 1 g/mmol). The Nalgene bottle was capped and shaken at ambient temperature (22−27 °C). After 14 h, the contents of the Nalgene bottle were filtered through a 600 mL coarse-sintered-glass funnel into a tared 500 mL round-bottomed flask, and the resin was washed with dichloromethane (2 × 50 mL). The contents of the round-bottomed flask were concentrated to dryness and stored under nitrogen.

3.2. Reductive Amination with Secondary Amines and Purification (16). The 0.25 M stock solutions of scaffold aldehyde were prepared by diluting each scaffold (450 mmol) to a total volume of 1.8 L with 1,4-dioxane. Each reducing amine (6.32 mmol, 1.1 equiv) was weighed and treated with the appropriate scaffold aldehyde solution (23 mL, 5.75 mmol, 1.0 equiv). The resulting solutions were used within 3 h.

Sodium triacetoxyborohydride (70−80 mg/well, 0.30 mmol, 1.5 equiv) was added to a deep-well plate. The appropriate amine/aldehyde solution (0.80 mL/well) was added to the appropriate well of the deep-well plate. The plates were capped and agitated on an orbital shaker for 7−14 h at ambient temperature (22−27 °C).

A deep-well filter plate was filled with 400−500 mg/well with the washed Amberlite IRA-743 resin. The contents of the deep-well reaction plate were diluted with anhydrous, inhibitor-free THF (Aldrich, 500 μL/well). The plates were recapped and placed back on the orbital shaker for an additional 30 min. The contents of the wells were transferred to the corresponding wells of the clamped deep-well plates packed with washed Amberlite resin. The deep-well plates were rinsed with 1,4-dioxane (2 × 0.25 mL/well), and the rinse was transferred to the appropriate wells of the deep-well filter plates. Upon complete transfer, the deep-well filter plates were each clamped and shaken for at least 14 h and no longer than 72 h.

To another deep-well filter plate was added 200−225 mg/well of PS-isocyanate resin (Argonaut Technologies, catalog no. 800262, loading 1.49 mmol/g). The deep-well filter plate containing the Amberlite resin was frozen in dry ice for 15 min, quickly unclamped, transferred to the top of the second set of clamped deep-well filter plates prepacked with PS-isocyanate resin (200 mg/well), and allowed to drain for at least 45−60 min. The resins in the top deep-well filter plate containing Amberlite resin were washed with 1,4-dioxane (2 × 0.25 mL/well, 5 min between washes), allowing the washes to be collected into the bottom deep-well filter plate. After complete drainage, the bottom deep-well filter plates were clamped and shaken.

After 14 h, the deep-well plate was frozen in dry ice for 15 min, quickly unclamped, transferred to the top of the tared deep-well plate, and allowed to drain for at least 45−60 min. The resins in the deep-well filter plate were washed with 1,4-dioxane (2 × 0.25 mL/well, 5 min between washes), and the washes were collected into the deep-well plate. The plates were frozen for at least 1 h at −80 °C and lyophilized for at least 18 h.

3.3. Acylation of Secondary Amines with Acid Chlorides and Purification (18). The contents of the round-bottomed flasks containing amines **14** were diluted with 1,4-dioxane to a final concentration of 0.50 M and stored under

nitrogen. The 0.60 M solutions of each acid chloride in 0.75 M *N*-methylmorpholine in 1,4-dioxane were prepared and used within 1 h. Each appropriate well of a deep-well plate was treated with a 0.50 M solution of the appropriate secondary amine **14** (0.20 mL/well, 0.10 mmol, 1 equiv). Each appropriate well of the deep-well plate was then treated with a 0.6 M solution of the appropriate acid chloride (0.20 mL, 0.12 mmol, 1.2 equiv) in 0.75 M solution of *N*-methylmorpholine in 1,4-dioxane. The plates were capped and agitated on an orbital shaker at ambient temperature (22−27 °C). After at least 3 h, the contents of the wells were treated with water (0.02 mL/well, 1.11 mmol, 11 equiv). The deep-well plates were then recapped and agitated for an additional hour on an orbital shaker.

To a deep-well filter plate was added 100 mg/well of Dowex anion-exchange resin (SBr LC NG OH form, Supelco, no. 14036-U). The resin was then washed with MeOH (2 × 1.0 mL/well). After the 1 h reaction time, the contents of the deep-well filter plate were then diluted with 1,4-dioxane (0.25 mL/well) and the contents were transferred into the clamped deep-well filter plate prepacked with the washed Dowex anion-exchange resin. The deep-well plate was rinsed with 1,4-dioxane (2 × 0.25 mL/well), and the solutions were transferred to the appropriate wells of the clamped deep-well filter plate. The clamped plate was agitated at ambient temperature (22−27 °C). After 14 h, the plates were frozen in dry ice for 10−15 min, unclamped, quickly transferred onto a new, tared deep-well plate, and allowed to drain for 45 min. The contents of the deep-well filter plate were rinsed with 1,4-dioxane, 0.5 mL/well (2 × 0.25 mL), and collected in the tared deep-well plates. The deep-well plates were then frozen at −80 °C for 1 h. After 1 h at −80 °C, the deep-well plates were lyophilized for at least 14 h. Representative compounds below were purified by reversed-phase preparative HPLC, normal-phase preparative HPLC, or normal-phase flash chromatography.

3.4. Acylation of Secondary Amines with Isocyanates and Purification (20). The contents of the round-bottomed flasks containing amines **14** were diluted with 1,4-dioxane to a final concentration of 0.50 M and stored under nitrogen. The 0.60 M solutions of each isocyanate in 1,4-dioxane were prepared and used within 1 h. Each well of a deep-well plate was treated with the 0.50 M solution of the appropriate secondary amine (0.20 mL/well, 0.10 mmol, 1 equiv). Each well of the deep-well plate was then treated with the 0.60 M solution of the appropriate isocyanate (0.20 mL, 0.12 mmol, 1.2 equiv) in 1,4-dioxane. The deep-well plates were capped and agitated for at least 3 h at ambient temperature on an orbital shaker.

During the 3 h reaction time, a deep-well filter plate was prepacked with tris(2-aminoethyl)amine scavenger resin (75 mg/well, Midwest Biotech, catalog no. 20920, 1 mmol/g). After the 3 h reaction time, the contents of the deep-well plate were then diluted with 1,4-dioxane (0.25 mL/well), and the contents were transferred to the clamped deep-well filter plate prepacked with scavenger resin. The deep-well plate was then rinsed with 0.50 mL/well 1,4-dioxane (2 × 0.25 mL), and the solutions were transferred to the appropriate wells of the clamped deep-well filter plate. The capped, clamped plate was agitated at ambient temperature (22−27 °C). After 14 h, the plates were frozen in dry ice for 10−15 min, unclamped, quickly transferred onto a new tared deep-well plate, and allowed to drain for 45 min. The contents of the deep-well filter plates were rinsed with 1,4-dioxane (0.50 mL/well, 2 × 0.25 mL) and collected in tared deep-well plates. The deep-well plates were then frozen at −80 °C for 1 h. After 1 h at −80 °C, the deep-well plates were lyophilized for at least 14 h. Representative compounds below were purified by reversed-phase preparative HPLC, normal-phase preparative HPLC, or normal-phase flash chromatography.

3.5. Acetonide Hydrolysis, Mixed Acetal Formation, and Purification (22). Freshly prepared solutions of primary alcohol/4 N HCl in dioxane (1:1, v/v) were prepared. Amines **16** lyophilized in deep-well plates were treated with the appropriate alcohol/4 N HCl in 1,4-dioxane solutions (1.5 mL/well). Once all wells were treated, the plates were capped and placed on an orbital shaker at ambient temperature (22−27 °C). After 14 h, the deep-well plates were placed under vacuum for least 3−5 h to remove the HCl. The contents of the deep-well plate were dissolved in a 5:1 solution of 1,4-dioxane/anhydrous inhibitor-free THF (1.5 mL/well) and transferred into a deep-well clamped filter plate containing PS-piperidine resin (200 mg/well, Polymer Labs, PL-PIP catalog no. 3410-4679, loading 3.1 mmol/g). The deep-well clamped filter plates were placed on a reciprocal shaker at ambient temperature (22−27 °C). After 14 h, the deep-well filter plates were frozen in dry ice for 15 min, quickly unclamped, and transferred onto the tops of tared deep-well plates. The deep-well filter plates were allowed to drain over 45−60 min. The resins in the plates were washed with 1,4-dioxane (2 × 0.50 mL/well). The deep-well plates were immediately frozen at −80 °C for at least 1 h and lyophilized for 14 h. Representative compounds below were purified by reversed-phase preparative HPLC, normal-phase preparative HPLC, or normal-phase flash chromatography.

18a: pale-yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.86 (t, 1H), 4.70−4.40 (m, 3H), 4.29−4.09 (m, 2H), 3.89 (d, J = 3.2 Hz, 1H, major rotamer), 3.82 (d, J = 3.2 Hz, 1H, minor rotamer), 3.71 (d, J = 7.4 Hz, 1H, minor rotamer), 3.65 (d, J = 7.7 Hz, 1H, major rotamer), 3.57−3.20 (m, 3H), 3.05 (dd, J = 14.3, 8.2 Hz, 1H), 2.60−2.37 (m, 7H), 1.80−1.45 (m, 6H), 1.40 (s, 3H, minor rotamer), 1.37 (s, 3H, major rotamer), 1.25 (s, 3H, minor rotamer), 1.23 (s, 3H, major rotamer), 1.19−1.02 (m, 2H), 0.96 (m, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.6, 176.4, 137.2, 136.9, 128.2, 127.4, 127.3, 111.4, 111.3, 104.9, 104.6, 81.7, 79.9, 71.8, 71.3, 51.9, 47.4, 47.3, 47.2. 46.2, 40.4, 40.2, 29.3, 25.7, 25.6, 25.5, 11.8, 11.6; MS (ESI) *m/z* 489.3 [$(M + H)^+$]. Anal. Calcd for $C_{28}H_{44}N_2O_5$ (488.7): C, 68.82; H, 9.08; N, 5.73. Found: C, 68.80; H, 8.83; N, 5.63.

18b: white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.32−7.11 (m, 10H), 7.04 (d, J = 8.9 Hz, 1H), 6.47 (s, 1H, major rotamer), 6.44 (s, 1H, minor rotamer), 6.41−6.36 (m, 1H), 5.95 (d, J = 4.0 Hz, 1H, minor rotamer), 5.86 (d, J = 4.0 Hz, 1H, major rotamer), 5.63 (s, 1H, minor rotamer), 5.00 (s, 1H, major rotamer), 4.82−4.40 (m, 3H), 4.29 (ddd, J = 7.2, 3.7, 3.7 Hz, 1H), 4.14 (dd, J = 14.3, 2.6 Hz, 1H), 3.76

(s, 3H), 3.74 (s, 3H), 3.46 (d, $J = 3.2$ Hz, 1H), 3.28 (s, 3H), 3.19 (dd, $J = 14.3$, 8.5 Hz, 1H), 1.51 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.5, 172.2, 160.2, 160.0, 158.2, 157.9, 140.3, 139.9, 139.1, 130.5, 129.1, 128.8, 128.4, 128.3, 127.9, 127.8, 126.8, 126.6, 126.5, 126.3, 117.7, 117.4, 111.3, 111.2, 104.8, 104.5, 103.9, 103.7, 98.4, 98.0, 84.6, 84.0, 81.0, 80.9, 79.2, 78.3, 57.4, 57.2, 55.1, 55.0, 54.9, 53.9, 53.6, 47.7, 45.9, 45.4, 43.4, 34.4, 31.3, 26.6, 26.4, 26.2, 22.4; MS (ESI) *m/z* 548.5 [$(M + H)^+$]. Anal. Calcd for $C_{32}H_{37}NO_7$ (547.6): C, 70.18; H, 6.81; N, 2.56. Found: C, 69.92; H, 6.67; N, 2.48.

18c: yellow solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35 (d, $J = 1.9$ Hz, 2H), 7.31−7.19 (m, 7H), 6.93 (bs, 3H), 6.84 (dd, $J = 8.2$, 1.9 Hz, 2H), 5.96 (d, $J = 3.2$ Hz, 1H, minor rotamer), 5.77 (d, $J = 3.7$ Hz, 1H, major rotamer), 4.73−4.39 (m, 4H), 4.14−4.03 (m, 3H), 3.76 (d, $J = 1.9$ Hz, 3H), 3.65 (d, J =13.0 Hz, 1H), 3.39 (t, $J = 13.2$ Hz, 1H), 3.22 (d, $J = 7.2$ Hz, 1H), 2.87−2.04 (m, 5H), 1.44 (s, 3H), 1.29 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.1, 172.0, 159.6, 139.1, 138.7, 138.6, 136.9, 136.7, 128.3, 127.9, 126.7, 119.6, 119.5, 113.1, 113.0, 112.9, 111.3, 104.6, 104.5, 82.7, 82.2, 78.4, 78.0, 71.6, 60.1, 60.0, 59.9, 57.9, 57.1, 54.9, 53.5, 53.3, 42.5, 30.5, 29.3, 26.7, 26.6, 26.2, 26.1; MS (ESI) *m/z* 574.7 [$(M + H)^+$]. Anal. Calcd for $C_{34}H_{40}N_2O_6$ (572.7): C, 71.31; H, 7.04; N, 4.89. Found: C, 71.04; H, 7.08; N, 4.74.

20a: pale-yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 5.87 (d, $J = 3.7$ Hz, 1H), 5.32 (bs, 1H), 4.60−4.57 (s, 2H), 4.55 (s, 1H), 4.17 (ddd, $J = 7.2$, 3.9, 3.9 Hz, 1H), 3.61−3.52 (m, 2H), 3.44 (d, $J = 7.2$ Hz, 1H), 3.35 (s, 3H), 3.31−3.19 (m, 2H), 1.41 (s, 3H), 1.30 (s, 3H), 1.10 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 158.6, 138.2, 128.3, 127.1, 126.9, 111.4, 104.4, 83.9, 80.6, 79.1, 57.0, 50.8, 46.1, 35.4, 26.3, 25.9, 15.2; MS (ESI) *m/z* 365.1 [$(M + H)^+$]. Anal. Calcd for $C_{19}H_{28}N_2O_5$ (364.4): C, 62.62; H, 7.74; N, 7.69. Found: C, 62.39; H, 7.58; N, 7.95.

20b: pale-yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36−7.30 (m, 1H), 6.97−6.89 (m, 3H), 5.89 (d, $J = 3.9$ Hz, 1H), 5.09 (d, $J = 6.7$ Hz, 1H), 4.64 (d, $J = 12.1$ Hz, 1H), 4.58 (d, $J = 3.9$ Hz, 1H), 4.41 (d, $J = 12.1$ Hz, 1H), 4.30 (ddd, $J = 6.7$, 3.2, 3.2 Hz, 1H), 3.92−3.75 (m, 1H), 3.75 (s, 3H), 3.59−3.48 (m, 2H), 3.45 (d, $J = 6.9$ Hz, 1H), 3.40 (d, $J = 6.9$ Hz, 1H), 3.23 (dd, $J = 14.8$, 6.4 Hz, 1H), 3.02 (dd, $J = 14.6$, 6.7 Hz, 1H), 1.41 (s, 3H), 1.26 (s, 3H), 0.97 (d, $J = 6.4$ Hz, 6H), 0.42−0.39 (m, 2H), 0.12−0.08 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.3, 159.6, 158.0, 138.5, 129.4, 119.7, 113.2, 111.5, 104.7, 82.1, 81.6, 80.4, 71.3, 65.6, 54.9, 51.8, 46.9, 42.3, 26.5, 25.9, 23.3, 22.9, 20.7, 15.0, 9.9, 3.6, 3.3; MS (ESI) *m/z* 449.2 [$(M + H)^+$]. Anal. Calcd for $C_{24}H_{36}N_2O_6$ (448.6): C, 64.26; H, 8.09; N, 6.25. Found: C, 64.08; H, 8.07; N, 6.30.

20c: pale-yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.32−7.15 (m, 5H), 5.88 (d, $J = 3.9$ Hz, 1H), 5.02 (s, 1H), 4.58 (d, $J = 3.9$ Hz, 1H), 4.26−4.21 (m, 1H), 3.61 (d, $J = 3.2$ Hz, 1H), 3.56−3.43 (m, 3H), 3.38 (s, 3H), 3.27 (dd, $J = 10.7$, 6.9 Hz, 1H), 3.21−3.12 (m, 2H), 2.87 (t, $J = 7.4$ Hz, 2H), 1.46 (s, 3H), 1.33 (s, 3H), 1.06 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 158.1, 139.2, 128.5, 128.2, 125.9, 111.3, 104.4, 83.8, 80.6, 79.2, 57.0, 49.9, 46.2, 35.2, 34.3, 26.3, 25.8, 15.1; MS (ESI) *m/z* 379.1 [$(M + H)^+$]. Anal. Calcd for $C_{20}H_{30}N_2O_5$ (378.5): C, 63.47; H, 7.99; N, 7.40. Found: C, 63.22; H, 8.03; N, 7.32.

20d: yellow solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.58 (d, $J = 7.6$ Hz, 1H), 7.37−7.22 (m, 6H), 7.16−7.03 (m, 2H), 6.92 (d, $J = 1.9$ Hz, 1H), 5.93 (d, $J = 3.7$ Hz, 1H), 4.79 (bs, 1H), 4.59 (d, $J = 7.4$ Hz, 1H), 4.56 (s, 1H), 4.34 (d, $J = 11.8$ Hz, 2H), 3.77 (d, $J = 3.2$ Hz, 1H), 3.71−3.60 (m, 2H), 3.44 (m, 2H), 3.14−2.90 (m, 4H), 1.42 (s, 3H), 1.28 (s, 3H), 0.82 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 158.7, 136.9, 136.3, 128.3, 127.9, 127.5, 126.9, 122.5, 121.5, 118.9, 118.2, 112.3, 111.5, 111.3, 104.7, 82.2, 81.6, 80.1, 71.5, 60.2, 48.9, 47.1, 35.3, 26.5, 25.9, 24.1, 14.8; MS (ESI) *m/z* 495.0 [$(M + H)^+$]. Anal. Calcd for $C_{28}H_{35}N_3O_5$ (493.6): C, 68.13; H, 7.15; N, 8.51. Found: C, 68.05; H, 6.91; N, 8.39.

20e: clear, colorless yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.49 (bs, 1H), 7.33−7.20 (m, 5H), 6.97 (ddd, $J = 10.2$, 2.7, 1.5 Hz, 1H), 6.89−6.83 (m, 3H), 6.03 (d, $J = 3.9$ Hz, 1H), 5.95−5.81 (m, 1H), 5.22 (d, $J = 1.0$ Hz, 1H), 5.17 (dd, $J = 5.2$, 1.2 Hz, 1H), 4.68 (d, $J = 12.3$ Hz, 1H), 4.65 (s, 1H), 4.44 (d, $J = 12.1$ Hz, 2H), 4.08 (dd, $J = 16.3$, 5.4 Hz, 1H), 3.94 (d, $J = 3.2$ Hz, 1H), 3.87 (d, $J = 5.7$ Hz, 1H), 3.78 (s, 3H), 3.66−3.51 (m, 2H), 1.48 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 159.6, 156.0, 139.4, 138.4, 134.2, 129.5, 128.6, 122.3, 119.8, 119.4, 116.9, 113.4, 113.2, 111.9, 104.9, 82.0, 81.8, 80.1, 81.5, 55.0, 50.7, 47.3, 26.6, 26.1; MS (ESI) *m/z* 470.1 [$(M + H)^+$]. Anal. Calcd for $C_{26}H_{32}N_2O_6$ (468.5): C, 66.65; H, 6.88; N, 5.98. Found: C, 66.48; H, 6.69; N, 5.95.

22a: orange oil; ^{1}H NMR (270 MHz, CD_3OD) δ 7.26−7.18 (m, 2H), 6.96 (dd, $J = 8.7$, 0.9 Hz, 2H), 6.83 (t, $J = 7.1$ Hz, 1H), 5.08 (d, $J = 4.5$ Hz, 1H), 4.43 (ddd, $J = 8.7$, 5.9, 3.2 Hz, 1H), 4.01 (t, $J = 4.2$ Hz, 1H), 3.95 (t, $J = 6.2$ Hz, 1H), 3.90−3.85 (m, 1H), 3.77−3.66 (m, 1H), 3.58−3.47 (m, 1H), 3.18 (t, $J = 5.2$ Hz, 4H), 2.82−2.63 (m, 5H), 2.55 (dd, $J = 13.6$, 8.2 Hz, 1H), 1.25−1.17 (m, 9H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 146.9, 124.3, 115.4, 111.7, 95.3, 80.0, 72.2, 70.7, 66.0, 61.1, 53.4, 49.0, 44.5, 18.1, 16.4, 9.9; MS (ESI) *m/z* 365.7 [$(M + H)^+$]. Anal. Calcd for $C_{20}H_{32}N_2O_4$: C, 65.91; H, 8.85; N, 7.69. Found: C, 65.88; H, 8.73; N, 7.62.

22b: yellow oil; ^{1}H NMR (270 MHz, CD_3OD) δ 7.34−7.19 (m, 7H), 7.15−7.10 (m, 3H), 4.99 (d, $J = 4.5$ Hz, 1H), 4.39−4.34 (m, 1H), 4.03 (dd, $J = 4.2$, 3.9 Hz, 1H), 3.87−3.75 (m, 3H), 3.68−3.47 (m 6H), 3.35 (s, 3H), 3.31 (s, 1H), 3.01−2.62 (m, 6H), 1.13−1.06 (m, 3H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 141.9, 140.5, 130.3, 129.8, 129.3, 129.2, 128.0, 126.9, 110.3, 102.7, 85.7, 81.1, 79.8, 78.1, 72.9, 68.5, 68.1, 66.7, 60.0, 59.1, 57.4, 54.0, 34.0, 15.6; MS (ESI) *m/z* 430.5 [$(M + H)^+$]. Anal. Calcd for $C_{25}H_{35}NO_5$: C, 69.90; H, 8.21; N, 3.26. Found: C, 69.73; H, 8.23; N, 3.21.

22c: white solid; ^{1}H NMR (270 MHz, CD_2Cl_2) δ 7.89 (bs, 1H), 7.42 (dd, $J = 6.7$, 0.7 Hz, 1H), 7.35 (dt, $J = 8.4$, 0.7 Hz, 1H), 7.11−7.00 (m, 2H), 4.95 (d, $J = 4.7$ Hz, 1H), 4.38 (ddd, $J = 7.4$, 4.7, 4.7 Hz, 1H), 4.10 (dd, $J = 1.5$, 3.0 Hz, 1H), 3.83−3.62 (m, 4H), 3.54−3.45 (m, 4H), 2.96−2.85 (m, 3H), 2.78−2.69 (m, 3H), 1.18 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 136.4, 132.7, 127.6, 121.4,

119.5, 118.1, 111.0, 108.5, 102.4, 85.3, 77.5, 76.8, 65.9, 57.0, 56.0, 52.0, 51.1, 21.7, 15.5; MS (ESI) *m/z* 347.4 [(M + H)$^+$]. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.63; H, 7.39; N, 7.90.

22d: clear, colorless oil; ^{1}H NMR (270 MHz, CD_3OD) δ 7.17 (t, J = 8.4 Hz, 1H), 6.93−6.84 (m, 2H), 6.79−6.76 (m, 1H), 4.88 (m, 1H), 4.42 (ddd, J = 8.4, 5.7, 3.2 Hz, 1H), 4.05 (dd, J = 4.5, 2.7 Hz, 1H), 3.75 (q, J = 2.7 Hz, 1H), 3.70−3.61 (m, 2H), 3.59−3.47 (m, 2H), 3.20 (t, J = 5.2 Hz, 4H), 2.86−2.58 (m, 6H), 1.19 (t, J = 6.9 Hz, 3H), 1.08−1.02 (m, 1H), 0.54−0.49 (m, 2H), 0.24−0.19 (m, 2H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 154.0, 135.9, 131.2, 120.2, 116.7, 115.2, 109.8, 86.0, 80.2, 80.0, 73.7, 66.7, 59.5, 54.8, 15.6, 11.3, 3.8, 3.2; MS (ESI) *m/z* 411.8 [(M + H)$^+$]. Anal. Calcd for $C_{21}H_{31}ClN_2O_4$: C, 61.38; H, 7.60; N, 6.82. Found: C, 61.35; H, 7.63; N, 6.78.

22e: white solid; ^{1}H NMR (270 MHz, CD_2Cl_2) δ 7.25−7.18 (m, 2H), 6.92−6.83 (m, 2H), 6.83−6.77 (m, 1H), 4.82 (d, J = 2.0 Hz, 1H), 4.39 (dddd, J = 7.6, 5.7, 3.7 Hz, 1H), 4.11 (dd, J = 2.7, 2.0 Hz, 1H), 3.70−3.61 (m, 2H), 3.41−3.31 (m, 4H), 3.16 (t, J = 4.9 Hz, 4H), 2.79−2.52 (m, 6H), 2.24 (bs, 1H), 1.63−1.51 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 147.3, 124.7, 115.0, 111.5, 104.4, 82.1, 74.8, 74.7, 65.8, 53.83, 53.77, 50.0, 44.8, 18.6, 6.1; MS (ESI) *m/z* 351.8 [(M + H)$^+$]. Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 64.99; H, 8.54; N, 7.88.

22f: clear, colorless oil; ^{1}H NMR (270 MHz, CD_2Cl_2) δ 7.29−7.12 (m, 5H), 5.06 (d, J = 4.7 Hz, 0.67H), 4.94 (d, J = 4.2 Hz, 0.33H), 4.29−3.35 (m, 10H), 3.32 (s, 3H), 2.81−2.49 (m, 6H), 2.42 (s, 1H), 2.34 (d, J = 1.8 Hz, 1H), 2.32 (s, 1H), 1.54−1.45 (m, 2H), 1.42−1.25 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 141.3, 129.1, 128.8, 128.6, 126.4, 126.1, 110.6, 101.7, 88.2, 85.6, 85.4, 77.5, 76.9, 76.7, 72.1, 72.0, 70.2, 67.9, 67.1, 62.0, 60.3, 59.7, 59.0, 56.6, 45.0, 42.8, 34.0, 32.3, 32.2, 19.7, 19.7, 14.0; MS (ESI) *m/z* 382.8 [(M + H)$^+$]. Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25; N, 3.67. Found: C, 66.00; H, 9.12; N, 3.62.

22g: white solid; ^{1}H NMR (270 MHz, CD_2Cl_2) δ 7.95 (bs, 1H), 7.42 (dd, J = 7.7, 1.0 Hz, 1H), 7.31−7.27 (m, 1H), 7.09−7.02 (m, 2H), 4.96 (d, J = 4.7 Hz, 1H), 4.44−4.38 (m, 0.5H), 4.26−4.23 (m, 0.5H), 4.11−3.98 (m, 1H), 3.92 (s, 2H), 3.84−3.47 (m, 2H), 3.47 (s, 2H), 3.44−3.38 (m, 1H), 3.32 (s, 3H), 3.20−3.11 (m, 1H), 2.99−2.68 (m, 4H), 1.57−1.48 (m, 2H), 1.41−1.31 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 131.4, 127.4, 126.6, 122.6, 116.8, 116.5, 114.6, 114.5, 113.2, 113.1, 106.8, 106.0, 103.4, 103.3, 97.4, 83.4, 80.9, 80.5, 72.4, 71.7, 71.5, 65.4, 65.2, 53.8, 51.9, 51.0, 50.2, 47.7, 46.9, 46.0, 27.3, 27.2, 16.6, 16.0, 14.7, 14.6, 9.0; MS (ESI) *m/z* 375.5 [(M + H)$^+$]. Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.07; N, 7.48. Found: C, 67.09; H, 7.89; N, 7.40.

22h: clear, colorless oil; ^{1}H NMR (270 MHz, CD_2Cl_2) δ 7.26−7.19 (m, 1H), 6.90−6.78 (m, 3H), 5.89−5.71 (m, 1H), 5.19−5.03 (m, 3H), 4.89 (s, 1H), 4.67−4.42 (m, 1H), 4.30−4.11 (m, 2H), 4.01 (s, 1H), 3.85−3.82 (m, 1H), 3.77 (s, 3H), 3.66−3.52 (m, 1H), 3.40−2.56 (m, 9H), 1.93−1.82 (m, 1H), 0.90 (d, J = 5.7 Hz, 6H), 0.86 (d, J = 2.0 Hz, 1H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 156.3, 136.5, 136.4, 132.31, 132.25, 131.0, 125.8, 116.5, 116.3, 115.3, 113.9, 113.7, 109.6, 106.6, 97.3, 83.4, 81.3, 73.5, 71.6, 70.7, 67.9, 55.4, 54.0, 53.6, 51.7, 48.9, 25.0, 15.6; MS (ESI) *m/z* 406.5 [(M + H)$^+$]. Anal. Calcd for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45. Found: C, 67.97; H, 8.57; N, 3.46.

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