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Facile and Efficient Synthesis of Carbohybrids as Stereodivergent Druglike Small Molecules

Ram Sagar and Seung Bum Park*

Department of Chemistry, Seoul National University, Seoul 151-747 Korea

sbpark@snu.ac.kr

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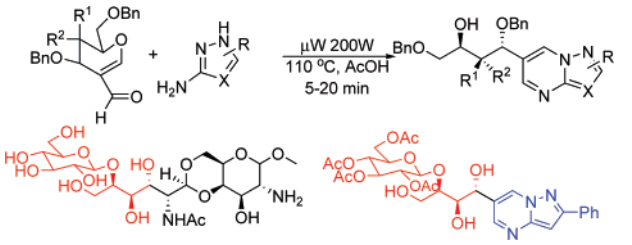

A facile and efficient one-pot synthesis of acyclic polyols fused with pyrazolo[1,5-*a*]pyrimidines and 1,2,4-triazolo[1,5-*a*]pyrimidines as novel carbohybrids with regioselectivity was achieved through the condensation of 2-*C*-formyl glycals with 3-aminopyrazoles and 3-amino-1,2,4-triazoles in excellent yields under the microwave irradiation.

A collection of "natural-product-like" small molecules that specifically perturb the individual functions of gene products are facilitating the exploration of biological pathways.[1] Therefore, the development of an efficient route for the synthesis of druglike small molecules has been the focus of research for medicinal chemists and chemical biologists.[2] Diversity-oriented synthesis (DOS) that aims to populate the chemical space with skeletally and stereochemically diverse small molecules with high appending potentials has been proven to be an essential tool for the discovery of bioactive small molecules.[3] The incorporation of privileged substructural motifs has become an essential element in DOS pathways.[4] Pyrazolo- and 1,2,4-triazolo[1,5-*a*]pyrimidines have been proven as privileged core structures and confirmed in bioactive natural products and in various pharmaceutical agents, as shown in Figure 1 (**I**−**IV**). An exhaustive literature survey reveals that the pyrazolo[1,5-*a*]pyrimidine skeleton has been applied in various therapeutic areas such as antitumor, antidiabetic, benzodiazepine receptor activities, etc.[5] The biological importance of 1,2,4-triazolo[1,5-*a*]pyrimidines, a subtype of purine bioisosteric analogs, is also well documented in diverse biological fields with antihypertensive and antitumor activities, etc.[6]

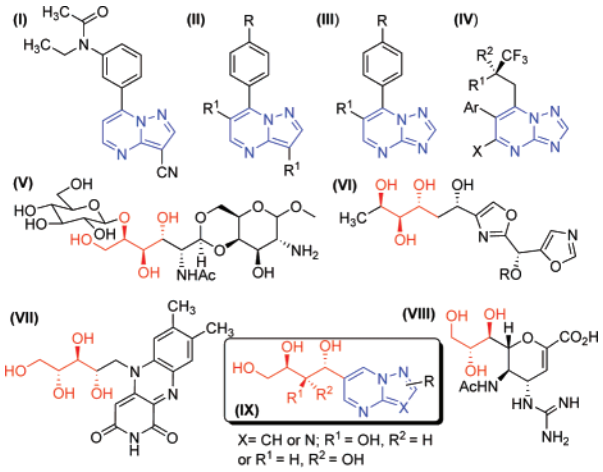

FIGURE 1. Bioactive small molecule with pyrazolo- and triazolo-[1,5-*a*]pyrimidines (**I**−**IV**) and carbohybrids fused with acyclic polyols (**V**−**VIII**). (**I**) Zaleplon, a drug for the treatment of insomnia; (**II**−**III**) selective binders to subtype BZ1 benzodiazepine receptor; (**IV**) an anticancer agent; (**V**) a novel open-chain glycosidic linkage in the lipopolysaccharide (LPS); (**VI**) Bengazoles, an antifungal marine natural product; (**VII**) riboflavin (vitamin B_2); (**VIII**) Relenza, an anti-influenza drug; (**IX**) our novel carbohybrids, hydrophilic acyclic polyols fused with privileged heterocycles.

Acyclic polyols are widely dispersed in the nature, and antibacterial and anticancer macrolides contain polyols as a structural motif.[7] Interestingly, a new type of open-chain glycosidic linkage (**V**) was identified in *Proteus* bacteria as a unique skeleton with an acyclic polyol moiety.[8] Various natural and synthetic acyclo-*C*-nucleosides with acyclic polyols have demonstrated antiviral activities against herpes virus, vaccinia, and simian immunodeficiency virus (SIV).[9] For example, bengazoles (**VI**) are antifungal marine natural products with a unique bisoxazole moiety containing carbohydrate-like acyclic polyols.[10] In terms of molecular skeletons, sialic acid, and relenza (**VIII**) are molecules containing acyclic polyols fused with druglike privileged heterocycles through a carbon linkage.[11]

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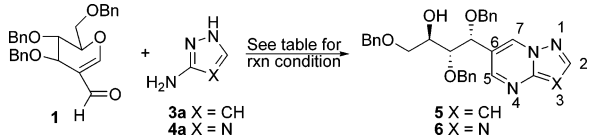
TABLE 1. Synthesis of Pyrazolo- and Triazolo[1,5-*a*]pyrimidines



entry	substrate (enals)	nucleophile	reaction condition	product	yield (%)
1	**1**	**3a**	EtOH, 77 °C, 6 h	**5**	62
2	**1**	**3a**	EtOH:THF (1:1), K_2CO_3, 80 °C, 8 h	**5**	62
3	**1**	**3a**	AcOH, rt, 1 h	**5**	72
4	**1**	**3a**	μW, 250W, 110 °C, toluene, 20 min	**5**	85
5	**1**	**3a**	μW, 200W, 110 °C, toluene:AcOH (10:1) 10 min	**5**	87
6	**1**	**3a**	μW, 200W, 110 °C, AcOH, 5 min	**5**	93
7	**1**	**4a**	EtOH, 77 °C, 6 h	-	no rxn
8	**1**	**4a**	EtOH:THF (1:1), K_2CO_3, 80 °C, 12 h	**6**	65
9	**1**	**4a**	AcOH, rt, 24 h	**6**	23
10	**1**	**4a**	μW, 250W, 110 °C, toluene, 30 min	-	no rxn
11	**1**	**4a**	μW, 200W, 110 °C, AcOH, 20 min	**6**	76

A number of iminoalditols with acyclic polyols chains have been identified as the inhibitors of glycosyltransferases and glycosidase for therapeutic application against cancer, AIDS, and diabetes.[12]

On the basis of their abundancy in literature, we were confident that the carbohybrids[13]—hydrophilic acyclic-polyols fused with privileged heterocycles—would provide the important structural motifs for the discovery of novel bioprobes or therapeutic agents. In continuation of our research on DOS of druglike small molecules,[14] we designed and synthesized acyclic polyols fused with pyrazolo- and 1,2,4-triazolo[1,5-*a*]pyrimidines as novel carbohybrids (**IX**).

For the development of efficient and facile methods for the synthesis of novel carbohybrids, we identified 2-*C*-formyl glycals **1** and **2**,[15a] chiral synthons incorporating an s-*cis* enal system, as the key intermediates[15b] that can be transferred to our designed carbohybrids. The syntheses of molecules containing pyrazole,[16a−c] pyrimidine,[16d] and pyridine/pyridone[16e−f] systems using 2-*C*-formyl glycals were reported in poor to fair yields.

We initiated our synthetic protocol with 2-*C*-formyl glycal (**1**−**2**) obtained from 3,4,6-tri-*O*-benzyl glycal via the Vilsmeier−Haack reaction.[15a] The core of the strategy followed in the present study is depicted in Scheme 1. The condensation reaction of 2-*C*-formyl glucal **1** with 3-aminopyrazole **3a** was performed under several different conditions. Pyrazolo[1,5-*a*]pyrimidine derivative **5** as a carbohybrid was obtained in 62% yield by the treatment of **1** with **3a** in refluxing ethanol for 6 h (Table 1, entry 1). The mechanism of this transformation can be postulated as follows: an amino group of 3-aminopyrazoles **3** attacks an aldehyde moiety of **1** to generate an imine intermediate, followed by the subsequent attack of the nucleophilic nitrogen of **3** on C-1 position to provide **5** through an intramolecular pyran ring opening (see Scheme 1).

To optimize the synthetic reaction conditions for **5**, we tested a mild inorganic base (K_2CO_3) and various organic bases (*n*-BuLi, NaH, NaOMe, and *t*-BuOK) with no improvement observed in the yields and reaction time. Conversely, strong organic bases led to a deterioration in the yields (10∼20%) of the desired **5**, due to the instability of 2-*C*-formyl glucal **1** against strong bases in a polar solvent. As shown in entry 3 (Table 1), acetic acid as a solvent can successfully complete this transformation within 1 h with an improved yield (72%) through the activation of enals on 2-*C*-formyl glycal (**1**−**2**). Next, we focused on the application of microwave for this transformation.[17] Without much difficulty, the desired **5** from 2-*C*-formyl glucal **1** with 3-aminopyrazole **3a** was successfully obtained in fairly good yields (85%) by the microwave irradiation in toluene (entry 4, Table 1). Considerable attempts were made in order to optimize the reaction condition under the microwave irradiation by changing solvents, temperatures, and microwave energy.

As shown in Table 1, the optimized microwave reaction condition (200 W, 110 °C, 5 min) in glacial acetic acid provides the desired **5** in excellent yields (93%). In the case of the condensation of 2-*C*-formyl glucal **1** with 3-amino-1,2,4-triazole **4a**, a slightly different reaction pattern was observed. In our initial attempts, the condensation of **1** with 3-aminotriazole **4a** in refluxing ethanol over 12 h (entry 7, Table 1) did not yield the desired product **6**. Comparing entries 1 and 7 in Table 1, it was concluded that 3-aminopyrazole **3a** is a better nucleophile than 3-amino-1,2,4-triazole **4a**. After an extensive survey of the reaction condition, the regioselective synthesis of the desired 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives **6** was achieved in good yields (entry 11, Table 1). Due to the equilibrium of

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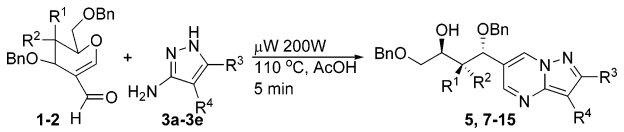
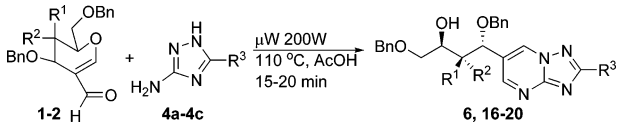
TABLE 2. Synthesis of Carbohybrids Fused with Pyrazolo[1,5-*a*]pyrimidines Skeleton



entry	enals	amino-pyrazole	product	R^1	R^2	R^3	R^4	yield (%)
1	**1**	**3a**	**5**	H	OBn	H	H	93
2	**1**	**3b**	**7**	H	OBn	Ph	H	94
3	**1**	**3c**	**8**	H	OBn	H	Ph	84
4	**1**	**3d**	**9**	H	OBn	H	2-pyridinyl	89
5	**1**	**3e**	**10**	H	OBn	H	2-thiophenyl	90
6	**2**	**3a**	**11**	OBn	H	H	H	88
7	**2**	**3b**	**12**	OBn	H	Ph	H	98
8	**2**	**3c**	**13**	OBn	H	H	Ph	97
9	**2**	**3d**	**14**	OBn	H	H	2-pyridinyl	98
10	**2**	**3e**	**15**	OBn	H	H	2-thiophenyl	96

TABLE 3. Synthesis of Carbohydrids with 1,2,4-Triazolo[1,5-*a*]pyrimidine Skeleton



entry	enals	amino-triazole	product[a]	R^1	R^2	R^3	time (min)	yield (%)
1	**1**	**4a**	**6**	H	OBn	H	20	76
2	**1**	**4b**	**16**	H	OBn	SMe	15	85
3	**1**	**4c**	**17**	H	OBn	COOMe	20	80
4	**2**	**4a**	**18**	OBn	H	H	15	82
5	**2**	**4b**	**19**	OBn	H	SMe	15	90
6	**2**	**4c**	**20**	OBn	H	COOMe	20	86

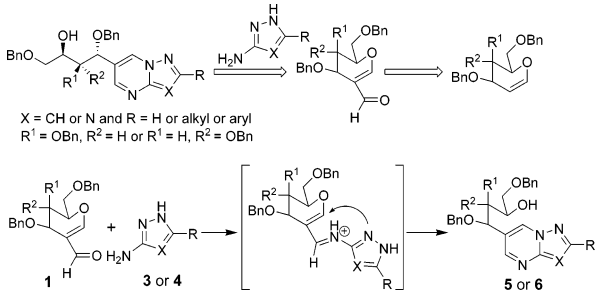
[a] The regioselectivity was >99%. See the Supporting Information for crude ^{1}H NMR and crude LC/MS data to support regioselectivity

tautomers in 3-amino-1,2,4-triazole **4a**, the formation of two regioisomers is possible, but the single regioisomer **6** was isolated under the optimized reaction condition.[18] The molecular structure of regioisomer **6** was confirmed by various spectroscopic tools (see Supporting Information). In particular, 1-D ^{1}H NOE spectra provided a definitive clue on the structural determination: the absence of an NOE cross-peak between H-2/H-5 and H-2/H-7 confirms the molecular skeleton of the obtained regioisomer **6**.[19]

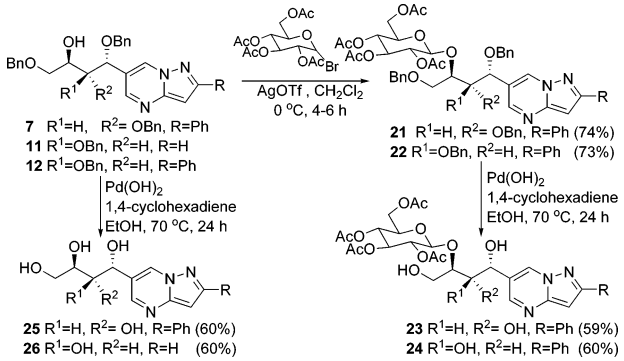
Having obtained the optimized condition, we probed the scope of this transformation with respect to both 2-*C*-formyl glycals (**1**−**2**) and 3-aminopyrazoles (**3a**−**e**). As shown in Table 2, both 2-*C*-formyl glucal **1** and 2-*C*-formyl galactal **2** were successfully coupled with 3-amiopyrazoles (**3a**−**e**) to produce the respective pyrazolo[1,5-*a*]pyrimidines **5, 7**−**15** under the optimized condition in excellent yields. The substituents at the R^3 and R^4 positions do not significantly influence the yields and reaction rates.

Subsequently, the generality in the transformation of 2-*C*-formylglycals (**1**−**2**) with substituted 3-amino-1,2,4-triazoles (**4a**−**c**) for the synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidines **6, 16**−**20** was successfully demonstrated with good to excellent yields (Table 3). There was no significant difference between

SCHEME 1. Retrosynthetic Analysis and Plausible Mechanism



SCHEME 2. Further Modification of Carbohybrids through Glycosidation and Debenzylation



the isolated yields of 3-aminotriazole **4a** and substituted 3-aminotriazoles **4b** and **4c** having an electron donating and an electron withdrawing group, respectively, at the R^3 position. Therefore, we accomplished the practical and efficient synthetic protocol for the transformation of 2-*C*-formyl glucal **1** and 2-*C*-formyl galactal **2** into novel carbohybrids with orthogonally substituted pyrazolo[1,5-*a*]pyrimidines (**5, 7**−**15**) and 1,2,4-triazolo[1,5-*a*]-pyrimidines (**6**, **16**−**20**) in excellent yields and regioselectivity.

For a further diversification, these carbohybrids were pursued through a glycosidation reaction on a free hydroxyl group at C-3′ on carbohybrid **7** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (Scheme 2). After a survey of the glycosidation reactions using different halophiles, it was observed that the use of AgOTf in CH_2Cl_2 at 0 °C for 4 h provides the desired glycosidic product **21** in good yields. The resulting **21** was identified as a single *β*-glycosidated carbohybrid stereoisomer due to the neighboring group participation, which was confirmed by ^{1}H and ^{13}C NMR spectra. 2-*C*-formylgalactal-derived carbohybrid **12** was also glycosidated under the identical reaction protocol to provide *β*-glycosidated product **22** in good yields. The debenzylation of these carbohybrids was then pursued. Surprisingly, a catalytic hydrogenation with Pd−C/H_2 or Pd-$(OH)_2$/H_2 was not successful because of the incomplete deprotection even under an extended reaction time, elevated pressure, and temperature. In contrast, a catalytic hydrogen transfer using $Pd(OH)_2$/1,4-cyclohexadiene[21] at 70 °C in ethanol was found superior to the catalytic hydrogenation. The debenzylation of compounds **21** and **22** was performed under the optimized catalytic transfer hydrogenation to provide fully debenzylated acyclic-polyols **23** and **24** in acceptable yields (Scheme 2).

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Similarly, compounds **7** and **11** were debenzylated as per our optimized reaction condition to give compound **25** and **26** respectively in 60% yield. The left-half of the carbohybrid with glycosylated polyols **24** was found to be superimposable with the left-half of the novel open-chain glycosidic linkage (**V**) presented in the core part of lipopolysaccharide (LPS) in the cell wall of Gram-negative *Proteus* bacteria (see Figure 1).[8]

In summary, we have developed a efficient synthetic protocol for the synthesis of novel carbohybrids—acyclic polyols fused with pyrazolo- and 1,2,4-triazolo[1,5-*a*]pyrimidines—from 2-*C*-formyl glycals under microwave irradiation in one step. These carbohybrids were designed through the recombination of acyclic chiral polyols found in abundance in bioactive natural products with druglike privileged heterocycles through a carbon linkage that is stable under a chemical and enzymatic hydrolysis. Subsequently, we successfully demonstrated a further diversification of C-3′−OH on the carbohybrids via glycosylation, followed by global debenzylation; this opens new avenue for a further diversification on these novel carbohybrids. The complete library realization of these novel carbohybrids using DOS and associated biological evaluations will be reported in due course.

Experimental Section

General Procedure for the Synthesis of 5 and 6 under Microwave Irradiation in Glacial AcOH. A mixture of 2-C-formyl glucal **1** (110 mg, 0.250 mmol) and 3-aminopyrazole **3a** (31.1 mg, 0.375 mmol, 1.5 equiv) dissolved in glacial AcOH (1.5 mL) was heated in capped microwave vessel under microwave irradiation (200 W, 110 °C) for 5 min. Controlled air cooling was applied to maintain the temperature. Resulting product mixture was diluted with EtOAc (15 mL) and neutralized by saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude product was concentrated in vacuo and purified by flash column chromatography to yield desired compound **5** (118 mg) in 93% yield. All other compounds **7**−**15** were synthesized by the condensation of 2-*C*-formyl glycals **1**−**2** with respective 3-aminopyrazole **3b**−**e** under same reaction procedure.

A similar reaction protocol was applied when 2-*C*-formyl glycals **1**−**2** were reacted with 3-amino-1,2,4-triazoles **4a**−**c**. The desired products **6**, **16**−**20** were obtained in good isolable yield (76−90%) after 15−20 min of microwave irradiation (200 W, 110 °C). We observed greater than 99% regioselectivity in all the cases for the synthesis of triazolo[1,5-*a*]pyrimidines from their crude ^{1}H NMR spectra and LC/MS of crude product.

Compound 5. Amorphous solid (118 mg, 93%). $[\alpha]^{D}_{28}$ −37.73 (*c* 0.343, $CHCl_3$). TLC: R_f = 0.27 (1:1, EtOAc:hexane, v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, J = 2.0 Hz, 1H), 8.42 (d, J = 2.5 Hz, 1H), 8.11 (d, J = 2.5 Hz, 1H), 7.34−7.25 (m, 10H), 7.06−7.05 (m, 3H), 6.95 (dd, J = 7.5, 2.0 Hz, 2H), 6.69 (d, J = 2.0 Hz, 1H), 4.77 (d, J = 2.5 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 4.53 (brs, 2H), 4.42 (d, J = 11.0 Hz, 1H), 4.32 (d, J = 11.5 Hz, 1H), 4.14 (d, J = 11.0 Hz, 1H), 4.06 (m, 1H), 3.68−3.67 (m, 2H), 3.62 (dd, J = 8.0, 2.5 Hz, 1H), 2.62 (brd, J = 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 148.3, 145.2, 137.6, 137.0, 136.8, 134.0, 128.8, 128.7, 128.5, 128.3, 128.2, 119.5, 97.0, 80.9, 76.0, 74.5, 73.7, 72.0, 70.7, 70.0. FAB HRMS *m*/*z*: calcd for $C_{31}H_{31}N_3O_4$ $[M + H]^+$, 510.2393; found, 510.2393.

Compound 6. Amorphous solid (96.5 mg, 76%). $[\alpha]_D^{28}$ −50.56 (*c* 0.396, $CHCl_3$). TLC: R_f = 0.33 (4:1, EtOAc:hexane, v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 2.0 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.46 (s, 1H), 7.35−7.24 (m, 10H), 7.01−6.98 (m, 3H), 6.88 (dd, J = 7.5, 1.0 Hz, 2H), 4.88 (d, J = 2.5 Hz, 1H), 4.57−4.54 (m, 3H), 4.47 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.09 (d, J = 11.5 Hz, 1H), 4.06 (m, 1H), 3.74−3.72 (m, 2H), 3.63 (dd, J = 8.5, 2.5 Hz, 1H), 2.64 (brd, J = 7.0 Hz, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 155.0, 137.6, 136.7, 136.5, 134.9, 128.9, 128.8, 128.6, 128.5, 128.37, 128.3, 128.1, 122.9, 104.9, 80.6, 75.8, 74.4, 73.8, 72.5, 70.6, 70.0. FAB HRMS *m*/*z*: calcd for $C_{30}H_{30}N_4O_4$ $[M + H]^+$, 511.2345; found, 511.2350.

Glycosidation. Synthesis of 21 and 22. 2,3,4,6-Tetra-*O*-acetyl-glucopyranosyl bromide (158 mg, 0.384 mmol) and glycosyl acceptor **7** (150 mg, 0.256 mmol) were placed in a aluminum foil covered RB flask in CH_2Cl_2 (3 mL) along with 100 mg of 4 Å molecular sieves under nitrogen atmosphere and cooled to 0 °C. AgOTf (98.6 mg, 0.384 mmol) in dry toluene (1.5 mL) was added dropwise within 10 min. After 4 h of stirring at 0 °C, the reaction was quenched by the addition of iPr_2NEt (1 mL) and stirred for additional 10 min. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude mixture was chromatographed to obtain β-glycosidated product **21** (173 mg) in 74% yield. Similarly, β-glycosidated product **22** was obtained from **12** in 73% yield.

Compound 21. Amorphous solid (173 mg, 74%). $[\alpha]_D^{28}$ −28.60 (*c* 0.363, $CHCl_3$). TLC: R_f = 0.54 (1:1, EtOAc:hexane, v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 7.7, 1.5 Hz, 2H), 7.48 (t, J = 8.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.35−7.25 (m, 10H), 7.10−7.05 (m, 5H), 6.96 (s, 1H), 5.19 (t, J = 9.5 Hz, 1H), 5.07 (t, J = 10.0 Hz, 1H), 4.99 (dd, J = 9.5, 8.0 Hz, 1H), 4.76 (d, J = 8.5 Hz, 1H), 4.71 (d, J = 4.0 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.52 (d, J = 11.5 Hz, 1H), 4.50−4.47 (m, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.32 (d, J = 11.5 Hz, 1H), 4.22 (m, 1H), 4.16 (dd, J = 12.5, 4.5 Hz, 1H), 3.99 (dd, J = 12.5, 2.0 Hz, 1H), 3.88 (m, 1H), 3.86 (dd, J = 11.5, 3.0 Hz, 1H), 3.63 (dd, J = 11.0, 5.5 Hz, 1H), 3.55 (ddd, J = 10.0, 4.5, 2.5 Hz, 1H), 2.01, 2.00, 1.97, 1.96 (4s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.4, 169.4, 169.5, 156.6, 149.8, 149.6, 137.9, 137.4, 133.9, 133.0, 129.2, 129.0, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 119.8, 99.6, 93.7, 81.9, 77.8, 77.1, 75.0, 73.7, 72.9, 72.1, 71.8, 71.7, 69.3, 68.4, 61.7, 20.9, 20.81, 20.80. FAB HRMS *m*/*z*: calcd for $C_{51}H_{53}N_3O_{13}$ $[M + H]^+$, 916.3657; found, 916.3657.

Debenzylation. Compounds **7** and **11** were debenzylated as per optimized reaction condition to yield compound **25** and **26** respectively in 60% yield. Compound **25**: Amorphous solid, TLC: R_f = 0.52 (1:4, MeOH:CH_2Cl_2,v/v). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.09 (brs, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.24 (brd, J = 7.0 Hz, 2H), 6.70 (t, J = 7.7 Hz, 2H), 6.63 (t, J = 8.0 Hz, 1H), 6.39 (s, 1H), 4.62 (d, J = 6.5 Hz, 1H), 4.23 (d, J = 5.0 Hz, 1H), 3.97 (d, J = 8.5 Hz, 1H), 3.91 (d, J = 5.5 Hz, 1H), 3.62 (t, J = 5.5 Hz, 1H), 2.86−2.80 (m, 2H), 2.69−2.65 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 155.3, 150.9, 149.2, 133.3, 129.5, 126.7, 125.8, 93.2, 74.7, 72.1, 68.5, 64.1. FAB HRMS *m*/*z*: calcd for $C_{16}H_{17}N_3O_4$ $[M + H]^+$, 316.1297; found, 316.1293.

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Supporting Information Available: Text giving experimental procedures, structures of the compounds, and figures showing complete spectroscopic data and NOE experiments along with the copies of ^{1}H and ^{13}C NMR spectra of all compounds **5**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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