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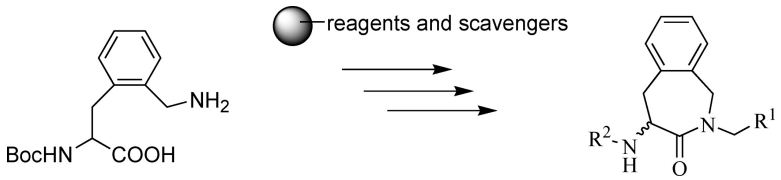


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# *Articles*

## Solid-Supported Solution-Phase Synthesis of 4-Amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones

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Starting from Boc-*o*-aminomethylphenylalanine, a solution-phase parallel synthesis of 2,4-substituted 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones is described. This heterocycle has two nitrogen functions, which are differentiated and can be selectively substituted. The sources of diversity are aldehydes for the $R_1$ position and carboxylic acids, sulfonyl chlorides, or isocyanates for the $R_2$ position. High-throughput synthesis and purification of this multistep synthetic sequence was accomplished using polymer-bound reagents and scavengers and liquid−liquid extraction protocols, and a small library of compounds was prepared. Polymer-bound cyanoborohydride was found to work well for the reductive amination. Scavenging of excess of amine was performed by polymer-bound benzaldehyde, and cyclization was performed in the presence of polymer-bound coupling reagent 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC). After Boc-deprotection, the second nitrogen can be acylated using carboxylic acids, sulfonylated or converted to a urea. The acylation is again performed by polymer-bound EDC. Excellent yields and purities were obtained.

### Introduction

Benzoannelated nitrogen heterocycles are an important class of compounds, displaying a wide variety of biological activities; therefore, these structures have received special attention in combinatorial synthesis.[1,2] Much attention has been paid to the benzodiazepines, -thiazepines, or -oxazepines, for which combinatorial libraries have been reported.[1−4] In comparison, the 2-benzazepine skeleton has received less attention, despite being a common structural feature in a variety of natural products and synthetic bioactive compounds.[5−12]

We recently reported a versatile solution-phase synthesis of the 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-one scaffold.[13] This heterocycle **5** (Scheme 1) has two nitrogen functions that can be differentiated; therefore, a diversity of substituents can be selectively introduced. Since pharmaceutical research increasingly demands efficient methods to generate large numbers of analogues for new lead discovery and for rapid structure−activity relationship development, a method for rapidly synthesising these druglike molecules without tedious and time-consuming purification would be highly useful.

Recently, solid-supported solution-phase chemistry has been receiving increased attention for library generation.[14] Advantages of this technique are that an excess of resin-bound reagent can be used to drive the reaction to completion, side products are bound to the resin (scavenging), and work up merely involves filtration and evaporation of the solvent. This method yields products with very high purity, making those resins very good tools for parallel synthesis and generating libraries, as extensively discussed by S. Ley.[15] We, therefore, developed a synthesis and purification procedure for the substituted 4-amino-2-benzazepines **8** using solid-supported reagents and scavenging resins.

### Results and Discussion

The $N^{\alpha}$-Boc-protected *o*-aminomethylphenylalanine **2** was prepared from Boc-*o*-cyano-phenylalanine **1**[13] and was reductively alkylated using a variety of aldehydes **3**{*a*−*j*}. (Scheme 1) The resulting secondary amines **4**{*a*−*j*} were subsequently cyclized to the 2-benzazepines **5**{*a*−*j*}, which were then Boc-deprotected and further substituted at $N^4$. Polymer-bound cyanoborohydride was found to work well for the reductive alkylation of the aminomethyl compound **2**. This method requires acidic conditions, usually obtained by the addition of a large excess (25 vol %) of acetic acid.[16] However, this acid is not completely removed during workup, which consists of filtration and evaporation. In the subsequent cyclization step to **5**, the remaining acetic acid becomes activated by the polymer-bound carbodiimide and thereby acetylates the secondary amines of **4**{*a*−*j*}. This problem was solved by replacing acetic acid with the sterically

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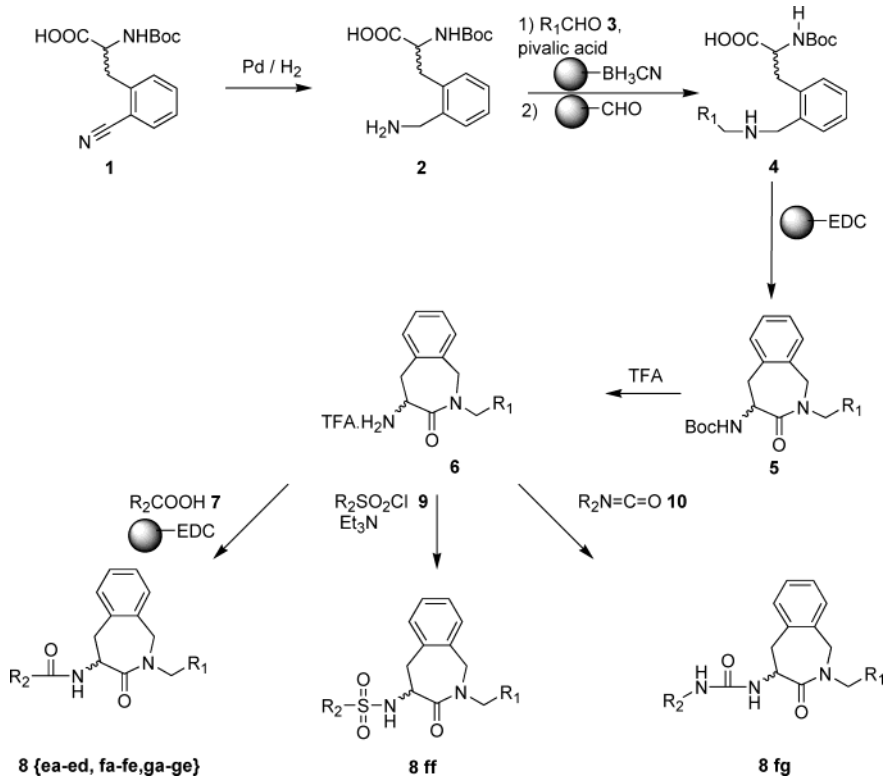
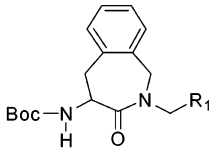
**Scheme 1.** Solution-Phase Synthesis Route toward the 2,4-Disubstituted 4-Amino-1,2,4,5-tetrahydro-2-benzazepin-3-ones Library



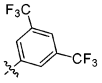
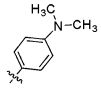
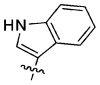

hindered pivalic acid. Although resin-bound reagents are known to be less reactive and more selective than their soluble analogues, overalkylation could not be avoided. Polymer-bound triacetoxyborohydride is reported to give less overalkylation and to work under neutral conditions;[17,18] however, in our hands, this reagent was not successful, since the reaction did not go to completion, even after a prolonged reaction time. To limit the overalkylation, a slight excess (20%) of the amine component **2** was used. This excess was scavenged after the reaction with polymer-bound benzaldehyde. After filtration, the mixture of mono- (and bis-) alkylated product and pivalic acid was evaporated to remove most of the pivalic acid. Redissolving in dichloromethane and cyclization with polymer-bound (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide) EDC, yields pure benzazepinones **5**{*a*−*j*}. The carboxylic acid function of **4**{*a*−*j*} is activated by the polymer-bound EDC and is involved in an intramolecular reaction with the secondary amine. During this reaction, the amide bond is formed, and the product is released from the resin. However, the bisalkylated compound cannot undergo an intramolecular reaction and remains bound to the resin, so the polymer-bound EDC acts as a reagent and as a scavenger at the same time.

After filtration, an extraction with a saturated sodium bicarbonate solution is performed to remove all the pivalic acid, and after separation of the two layers through a phase-separation cartridge, the organic layer is evaporated to give the 2-substituted 4-Boc-amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones **5**{*a*−*j*} in good yield and purity. All products were characterized by $^1$H NMR, LC/MS and HRMS analysis. Yields were calculated on the basis of weight, purities according to area percent in HPLC.

**Table 1.** Synthesis of Benzazepinones **5**{*a*−*j*} from a Set of Aldehydes



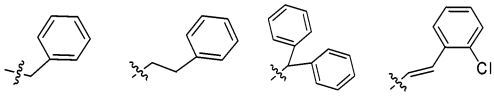
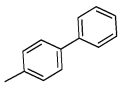
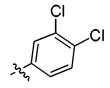

**5**

| Entry | $R_1$CH=O $R_1$ = | | Entry | $R_1$CH=O $R_1$ = | |
|---|---|---|---|---|---|
| 1 |  | **5a** y = 60 % 90 % pure | 6 |  | **5f** y = 64 % 88 % pure |
| 2 |  | **5b** y = 67 % 90 % pure | 7 |  | **5g** y = 78 % 98 % pure |
| 3 |  | **5c** y = 60% 80 % pure | 8 |  | **5h** y = 73 % 91 % pure |
| 4 |  | **5d** y = 32 % 70 % pure | 9 |  | **5i** y = 78 % 95 % pure |
| 5 |  | **5e** y = 63 % 93 % pure | 10 |  | **5j** y =72 % 90 % pure |

y = yield from **2**, calculated over two reaction steps.

This procedure was optimized using a set of five aldehydes (Table 1, entries 1−5) in glass vessels equipped with a frit, which were rocked gently. Reaction monitoring by HPLC revealed that most reductive aminations were complete after overnight reaction; however, the indole-3-carboxaldehyde

**Table 2.** Transformation of **5**{*e*−*g*} into Amides **8**{*ea*−*ed*,*fa*−*fe*,*ga*−*ge*}, Sulfonamide **8ff**, and Urea **8fg**

| starting compound \ $R_2$ | **6** $R_2$ = H | **8{ea-ed,fa-fe,ga-ge}** $R_2$ =  | | | | | **8ff** $R_2$ =  | **8fg** $R_2$ =  |
|---|---|---|---|---|---|---|---|---|
| | **6e** | **8ea** | **8eb** | **8ec** | **8ed** | | | |
| **5e** | y = 100 %<br>94 % pure | y = 94 %<br>95 % pure | y = 91 %<br>90 % pure | y = 82 %<br>85 % pure | y = 91 %<br>95% pure | | | |
| | **6f** | **8fa** | **8fb** | **8fc** | **8fd** | **8fe** | **8ff** | **8fg** |
| **5f** | y = 100 %<br>100% pure | y = 90 %<br>96 % pure | y = 85 %<br>90% pure | y = 100 %<br>95 % pure | y = 90 %<br>85 % pure | y = 85 %<br>100 % pure | y = 92 %<br>96 % pure | y = 93 %<br>96 % pure |
| | **6g** | **8ga** | **8gb** | **8gc** | **8gd** | **8ge** | | |
| **5g** | y = 100 %<br>100% pure | y = 92 %<br>92 % pure | y = 98 %<br>100% pure | y =89%<br>95 % pure | y = 93 %<br>95 % pure | y = 90 %<br>100 % pure | | |

(entry 4) reacted much slower, and the reaction required 5 days. A similar observation was made for the cyclization reaction. The procedure was then transferred to a parallel synthesizer. To ensure that the reactions were complete with each aldehyde, the longest reaction time that was observed in the previous experiments (5 days) was used. The overall yields and purities were slightly better (Table 1, entries 6−10).

Boc deprotection was performed by stirring in trifluoroacetic acid (TFA). This reaction was quantitative and yielded pure products **6**{*e*−*g*}. Direct acylation of the TFA salts **6** required long reaction times and resulted in unsatisfactory purities. Therefore, the free amines were obtained after stirring in $CH_2Cl_2$ and sodium bicarbonate solution, after which the organic layer was separated from the aqueous layer through a phase-separation cartridge. Derivatizations of the 4-amino position were then carried out with polymer-bound EDC and different carboxylic acids **7**{*a*−*e*} and were complete after overnight reaction. An excess (1.8 equiv) of carboxylic acid was used to drive the reaction to completion. This excess was scavenged by the polymer-bound EDC (2 equiv). After filtration and evaporation, products **8**{*ea*−*ee*,*fa*−*fe*,*ga*−*ge*} (Table 2) were obtained in excellent yields and purities. Derivatizations at $N^4$ can also be performed by reaction with sulfonyl chlorides **9** or isocyanates **10**. Equimolar amounts were used, and purification was performed by polymer-bound tris(2-aminoethyl)amine.

## Conclusions

In conclusion, we have developed a protocol for solution-phase organic synthesis of 2,4-substituted 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones using polymer-supported reagents and scavengers, resulting in a library of compounds with excellent overall yields and purities.

## Experimental Section

**General.** All commercially available chemicals were used without further purification. Dichloromethane, p.a. >99.9%, obtained from Fluka was used without further drying or purification. Polystyrylmethyl-$BH_3CN$ (capacity 4.2 mmol/g, bead size of 300−850 $\mu$m), and tris(2-aminoethyl)amine polystyrene (capacity 3.4 mmol/g, bead size of 45−106 $\mu$m) were purchased from Novabiochem. PL-CHO (capacity 3.0 mmol/g, bead size of 150−300 $\mu$m) and PL-EDC (capacity 1.45 mmol/g, bead size of 150−300 $\mu$m) were obtained from Polymer Laboratories. Different batches of these three polymer-bound reagents were used, and no difference was noticed among them. MP-Triacetoxyborohydride (capacity 2.14 mmol/g, Lot No. 200-91, bead size of 350−1250 $\mu$m) was purchased from Argonaut Technologies. Phase-separation columns (70 mL) were obtained from IST (International Sorbent Technology). Parallel syntheses were performed on a Quest 210 (Argonaut) in 5-mL reaction vessels.

RP-HPLC was performed using a RP C-18 column (Vydac 218TP54, i.d. = 0.46 cm, $L$ = 25 cm, particle size = 5 $\mu$m) on a Waters system with a gradient: $t$ = 0 min, 100% A; $t$ = 30 min, 20% A, 80% B; $t$ = 40 min, 100% B with A, 100% $H_2O$ + 0.1% TFA and B; 100% acetonitrile (ACN) + 0.1% TFA. Flow rate, 1.0 mL $min^{-1}$. $\lambda$ = 215 nm. LC/MS was performed on a Kontron HPLC (same column and gradient as described above), coupled to a VG Quattro II mass spectrometer using electrospray ionization (positive ion mode). All $^1$HNMR spectra were recorded on an AC 250 Bruker spectrometer at 250 MHz in $CDCl_3$. Chemical shifts are expressed in parts-per-million downfield from internal tetramethylsilane. All coupling constants are reported in hertz. References used for HRMS were poly(ethylene glycol) 300, poly(ethylene glycol) 400, poly(ethylene glycol) 600, poly(propylene glycol) 725, all purchased from Aldrich.

**Reductive Amination and Cyclization with Polymer-Bound Reagents.** Aldehyde **3**{a−j}(1 equiv, 0.5 mmol) and Boc-(*R*,*S*)-*o*-Amp **2** (aminomethylphenylalanine) (1.2 equiv, 0.6 mmol, 170 mg) were dissolved in $CH_2Cl_2$ (5 mL). Pivalic acid (10 equiv, 5 mmol) was added as well as polymer-bound cyanoborohydride (2.5 equiv, 1.25 mmol, 0.538 g, loading = 2.32 mmol/g). The reaction mixture was shaken for 5 days. Polymer-bound benzaldehyde (0.5 equiv, 0.25 mmol, 83.3 mg, loading = 3.0 mmol/g) was added to scavenge the excess of primary amine. The mixture was shaken overnight. After filtration, the resin was washed frequently, and the filtrate was evaporated until almost all of the pivalic acid was removed and members **4**{*a*−*j*} remained. These members were redissolved in $CH_2Cl_2$ (5 mL), and polymer-bound EDC (2 equiv, 1 mmol, 0.714 g, loading = 1.4 mmol/g) was

added. The mixture was shaken for 4 days and filtered, and the resin was washed with $CH_2Cl_2$. The filtrate was diluted to 40 mL and extracted with saturated $NaHCO_3$ (40 mL). The dichloromethane layer was isolated through a phase-separation cartidge and evaporated to yield products **5**{*a*−*j*}.

**Boc Deprotection and Coupling with Polymer-Bound EDC.** Products **5**{*e*−*g*} were dissolved in a minimal amount TFA/$H_2O$ 95/5, and the solution was stirred for 1 h. After evaporation, the pure TFA salts **6**{*e*−*g*} were obtained in a quantitative yield. The free amines were obtained after an extraction with $CH_2Cl_2$ (20 mL) and a saturated $NaHCO_3$ (1 × 10 mL) solution. The dichloromethane layer was separated through a phase-separation cartridge, and after evaporation, the free amines were obtained in a quantitative yield. The free amines of **6**{*e*−*g*} (1 equiv, 0.2 mmol) were dissolved in $CH_2Cl_2$ (5 mL), and carboxylic acids {*a*−*e*} (1.8 equiv, 0.36 mmol) were added as well as polymer-bound EDC (2 equiv, 0.4 mmol, 0.286 g, loading = 1.4 mmol/g). The mixture was shaken overnight at room temperature, and after filtration and evaporation, pure compounds **8** {*ea*−*ed*, *fa*−*fg*, *ga*−*ge*} were obtained in excellent yield and purity.

**Sulfonylation.** The free amine **6f** (1 equiv, 0.15 mmol, 40 mg), obtained as described above, was dissolved in $CH_2Cl_2$ (5 mL), and biphenylsulfonyl chloride **9** (1 equiv, 0.15 mmol, 37.8 mg) and $Et_3N$ (1equiv, 0.15 mmol, 15.2 mg) were added. The reaction mixture was stirred 24 h at room temperature. Polymer-bound tris(2-aminoethyl)amine (1equiv, 0.15 mmol, 44 mg, loading = 3.4 mmol/g) was added, and the vessel was shaken overnight at room temperature. After filtration and evaporation under reduced pressure, the sulfonamide **8ff** was obtained in excellent yield and purity.

**Ureum Formation.** The free amine **6f** (1 equiv, 0.15 mmol, 40 mg), obtained as described above, was dissolved in $CH_2Cl_2$ (5 mL), and 3,4-dichlorophenylisocyanate **10** (1 equiv, 0.15 mmol, 28.0 mg) was added. The reaction mixture was stirred 24 h at room temperature. Polymer-bound tris-(2-aminoethyl)amine (1 equiv, 0.15 mmol, 44 mg, loading = 3.4 mmol/g) was added, and the vessel was shaken overnight at room temperature. After filtration and evaporation under reduced pressure, the ureum **8fg** was obtained in excellent yield and purity.

**Compound 5a.** $^1$H NMR ($CDCl_3$): $\delta$ 1.47 (s, 9H), 3.00 (m, 1H), 3.49 (dd, $^3J$ = 4.6 Hz, $^2J$ = 17.2 Hz, 1H), 3.80−3.89 (m, 4H), 4.19 (d, $^2J$ = 14.7 Hz, 1H), 4.93−5.00 (m, 2H), 5.19 (m, 1H), 5.97 (d, $^3J$ = 6.0 Hz, 1H), 6.79−7.25 (m, 8H). HPLC: $t_{ret}$ = 26.2 min. MS: *m*/*z* = 396. HRMS: calcd, 396.2127; found, 396.2116.

**Compound 5b.** $^1$H NMR ($CDCl_3$): $\delta$ 1.48 (s, 9H), 2.99 (dd, $^3J$ = 12.9 Hz, $^2J$ = 17.0 Hz, 1H), 3.46 (m, 1H), 3.68 (s, 3H), 3.82 (m, 1H), 4.33 (m, 1H), 4.91−5.06 (m, 2H), 5.26 (m, 1H), 5.97 (d, $^3J$ = 6.3 Hz, 1H), 6.42−7.25 (m, 8H). HPLC: $t_{ret}$ = 26.4 min. MS: *m*/*z* = 396. HRMS: calcd, 396.2127; found, 396.2131.

**Compound 5c.** $^1$H NMR ($CDCl_3$): $\delta$ 1.47 (s, 9H), 2.96 (m, 1H), 3.10 (s, 6H), 3.50 (dd, $^3J$ = 4.2 Hz, $^2J$ = 17.0 Hz, 1H), 3.79 (d, $^2J$ = 16.7 Hz, 1H), 4.48 (d, $^2J$ = 15.0 Hz, 1H), 4.86 (d, $^2J$ = 15.0 Hz, 1H), 5.11 (d, $^2J$ = 16.5 Hz, 1H), 5.25 (m, 1H), 5.87 (d, $^3J$ = 6.4 Hz, 1H), 6.69−7.72 (m, 8H). HPLC: $t_{ret}$ = 18.9 min. MS: *m*/*z* = 409. HRMS: calcd, 409.2443; found, 409.2447.

**Compound 5d.** $^1$H NMR ($CDCl_3$): $\delta$ 1.26 (s, 9H), 2.97 (m, 1H), 3.45 (m, 1H), 3.92 (d, $^2J$ = 16.7 Hz, 1H), 4.42 (d, $^2J$ = 14.7 Hz, 1H), 4.83 (d, $^2J$ = 16.8 Hz, 1H), 5.17 (d, $^2J$ = 14.6 Hz, 1H), 6.07 (m, 1H), 6.76−7.60 (m, 9H), 8.45 (m, 1H). HPLC: $t_{ret}$ = 25.6 min. MS: *m*/*z* = 405. HRMS: calcd, 405.2130; found, 405.2149.

**Compound 5e.** $^1$H NMR ($CDCl_3$): $\delta$ 0.85 (d, 3H, $^3J$ = 6.6 Hz), 0.96 (d, 3H, $^3J$ = 6.6 Hz), 1.58 (s, 9H), 1.97 (m, 1H), 3.05 (dd, $^3J$ = 12.8 Hz, $^2J$ = 17.1 Hz, 1H), 3.33−3.50 (m, 2H), 3.58 (dd, $^3J$ = 4.2 Hz, $^2J$ = 17.2 Hz, 1H), 3.94 (d, $^2J$ = 16.7 Hz, 1H), 5.23−5.30 (m, 2H), 6.05 (d, $^3J$ = 5.9 Hz, 1H), 7.13−7.38 (m, 4H). HPLC: $t_{ret}$ = 27.6 min. MS: *m*/*z* = 332. HRMS: calcd, 332.2178; found, 332.2180

**Compound 5f.** $^1$H NMR ($CDCl_3$): $\delta$ 1.46 (s, 9H), 2.96 (dd, $^3J$ = 12.7 Hz, $^2J$ = 17.1 Hz, 1H), 3.48 (dd, $^3J$ = 4.4 Hz, $^2J$ = 16.7 Hz, 1H), 3.79 (d, $^2J$ = 16.7 Hz, 1H), 4.25 (d, $^2J$ = 14.9 Hz, 1H), 4.97−5.03 (m, 2H), 5.21 (dd, $^2J$ = 12.4 Hz, $^3J$ = 4.3 Hz, 1H), 5.94 (d, $^3J$ = 5.9 Hz, 1H), 6.81−7.51 (m, 9H). HPLC: $t_{ret}$ = 28.6 min. MS: *m*/*z* = 366. HRMS: calcd, 366.2021; found, 366.2025.

**Compound 5g.** $^1$H NMR ($CDCl_3$): $\delta$ 1.46 (s, 9H), 2.95 (dd, $^3J$ = 12.9 Hz, $^2J$ = 17.2 Hz, 1H), 3.51 (dd, $^3J$ = 5.6 Hz, $^2J$ = 17.7 Hz, 1H), 3.77 (d, $^2J$ = 16.9 Hz, 1H), 4.68−4.85 (m, 2H), 5.16−5.31 (m, 2H), 5.84 (d, $^3J$ = 6.3 Hz, 1H), 6.74−7.69(m, 7H). HPLC: $t_{ret}$ = 30.7 min. MS: *m*/*z* = 502. HRMS: calcd, 502.1769; found, 502.1758.

**Compound 5h.** $^1$H NMR ($CDCl_3$): $\delta$ 1.47 (s, 9H), 2.99 (dd, $^3J$ = 12.8 Hz, $^2J$ = 17.0 Hz, 1H), 3.51(dd, $^3J$ = 4.4 Hz, $^2J$ = 17.1 Hz, 1H), 3.83 (d, $^2J$ = 16.8 Hz, 1H), 4.31 (d, $^2J$ = 14.9 Hz, 1H), 5.00−5.06 (m, 2H), 5.24 (m, 1H), 5.98 (d, $^3J$ = 6.3 Hz, 1H), 6.83−7.55 (m, 13H). HPLC: $t_{ret}$ = 30.3 min. MS: *m*/*z* = 442. HRMS: calcd, 442.2334; found, 442.2361.

**Compound 5i.** $^1$H NMR ($CDCl_3$): $\delta$ 1.47 (s, 9H), 2.95 (m, 1H), 3.47 (dd, $^3J$ = 4.4 Hz, $^2J$ = 17.1 Hz, 1H), 3.68 (s, 3H), 3.91 (d, $^2J$ = 16.7 Hz, 1H), 4.68 (s, 2H), 5.00 (d, $^2J$ = 16.6 Hz, 1H), 5.20 (m, 1H), 6.03 (d, $^3J$ = 6.31 Hz, 1H), 6.70−7.25 (m, 8H). HPLC: $t_{ret}$ = 28.2 min. MS: *m*/*z* = 396. HRMS: calcd, 396.2127; found, 396.2115.

**Compound 5j.** $^1$H NMR ($CDCl_3$): $\delta$ 0.87−1.71 (m, 10H), 1.46 (s, 9H), 2.93 (m, 1H), 3.21−3.86 (m, 2H), 3.45 (dd, $^3J$ = 4.6 Hz, $^2J$ = 17.3 Hz, 1H), 3.83 (d, $^2J$ = 16.7 Hz, 1H), 5.12−5.23 (m, 2H), 6.00 (d, $^3J$ = 6.4 Hz, 1H), 7.02−7.27 (m, 4H). HPLC: $t_{ret}$ = 31.8 min. MS: *m*/*z* = 372. HRMS: calcd, 372.2491; found, 372.2471.

**Compound 6e.** $^1$H NMR ($CDCl_3$): $\delta$ 0.62 (d, $^3J$ = 6.5 Hz, 3H), 0.75 (d, $^3J$ = 6.6 Hz, 3H), 1.78 (m, 1H), 3.07−3.61 (m, 4H), 3.85 (d, $^2J$ = 16.9 Hz, 1H), 5.07−5.14 (m, 2H), 7.02−7.25 (m, 4H), 8.5 (bs, 2H). HPLC: $t_{ret}$ = 15.5 min. MS: *m*/*z* = 232. HRMS: calcd, 232.1654; found, 232.1656.

**Compound 6f.** $^1$H NMR ($CDCl_3$): $\delta$ 3.24 (m, 1H), 3.47 (m, 1H), 3.68 (d, $^2J$ = 16.8 Hz, 1H), 4.25 (d, $^2J$ = 15.1 Hz, 1H), 4.64 (d, $^2J$ = 15.2 Hz, 1H), 4.81 (d, $^2J$ = 16.6 Hz, 1H), 5.06 (m, 1H), 6.65−7.21 (m, 9H). HPLC: $t_{ret}$ = 15.5 min. MS: *m*/*z* = 266. HRMS: calcd, 266.1497; found, 266.1523.

**Compound 6g.** $^1$H NMR ($CDCl_3$): $\delta$ 3.28 (m, 1H), 3.56−3.45 (m, 2H), 4.47 (d, $^2J$ = 15.6 Hz, 1H), 4.76 (d, $^2J$ = 15.6 Hz, 1H), 5.05−5.23 (m, 2H), 6.59−7.63 (m, 7H), 8.44 (s, 1H). HPLC: $t_{ret}$ = 22.1 min. MS: $m/z$ = 402. HRMS: calcd, 402.1245; found, 402.1249.

**Compound 8ea.** $^1$H NMR ($CDCl_3$): $\delta$ 0.70 (d, $^3J$ = 6.6 Hz, 3H), 0.82 (d, $^3J$ = 6.6 Hz, 3H), 1.81 (m, 1H), 2.48 (m, 1H), 3.17 (dd, $^3J$ = 6.4 Hz, $^2J$ = 14.4 Hz, 1H), 3.37 (dd, $^3J$ = 8.5 Hz, $^2J$ = 13.4 Hz, 1H), 3.48 (dd, $^3J$ = 4.5 Hz, $^2J$ = 17.0 Hz, 1H), 3.62 (s, 2H), 3.82 (d, $^2J$ = 16.7 Hz, 1H), 5.15 (d, $^2J$ = 16.6 Hz, 1H), 5.38 (m, 1H), 7.01−7.40 (m, 10H). HPLC: $t_{ret}$ = 24.1 min. MS: $m/z$ = 350. HRMS: calcd, 350.2072; found, 350.2042.

**Compound 8eb.** $^1$H NMR ($CDCl_3$): $\delta$ 0.74 (d, $^3J$ = 6.6 Hz, 3H), 0.85 (d, $^3J$ = 6.6 Hz, 3H), 1.85 (m, 1H), 2.51−3.49 (m, 5H), 3.83 (d, $^2J$ = 16.7 Hz, 1H), 5.16 (d, $^2J$ = 16.5 Hz, 1H), 5.38 (m, 1H), 6.90−7.33 (m, 10H). HPLC: $t_{ret}$ = 25.1 min. MS: $m/z$ = 364. HRMS: calcd, 364.2229; found, 364.2184.

**Compound 8ec.** $^1$H NMR ($CDCl_3$): $\delta$ 0.69 (d, $^3J$ = 6.6 Hz, 3H), 0.82 (d, $^3J$ = 6.6 Hz, 3H), 1.82 (m, 1H), 2.86 (m, 1H), 3.15 (dd, $^3J$ = 6.4 Hz, $^2J$ = 13.4 Hz, 1H), 3.40 (dd, $^3J$ = 8.5 Hz, $^2J$ = 13.4 Hz, 1H), 3.55 (dd, $^3J$ = 4.3 Hz, $^2J$ = 16.9 Hz, 1H), 3.82 (d, $^2J$ = 16.7 Hz, 1H), 4.97 (s, 1H), 5.15 (d, $^2J$ = 16.5 Hz, 1H), 5.43 (m, 1H), 7.00−7.38 (m, 15H). HPLC: $t_{ret}$ = 28.3 min. MS: $m/z$ = 426. HRMS: calcd, 426.2385; found, 426.2368.

**Compound 8ed.** $^1$H NMR ($CDCl_3$): $\delta$ 0.77 (d, $^3J$ = 6.6 Hz, 3H), 0.87 (d, $^3J$ = 6.6 Hz, 3H), 1.89 (m, 1H), 2.95 (m, 1H), 3.25−3.43 (m, 2H), 3.65 (dd, $^3J$ = 4.5 Hz, $^2J$ = 17.0 Hz, 1H), 3.88 (d, $^2J$ = 16.7 Hz, 1H), 5.22 (d, $^2J$ = 16.5 Hz, 1H), 5.54 (m, 1H), 6.52 (d, $^3J$ = 15.6 Hz, 1H), 7.04−7.61 (m, 9H), 8.03 (d, $^3J$ = 15.7 Hz, 1H). HPLC: $t_{ret}$ = 26.9 min. MS: $m/z$ = 396. HRMS: calcd, 396.1683; found, 396.1698.

**Compound 8fa.** $^1$H NMR ($CDCl_3$): $\delta$ 2.91 (m, 2H), 3.61−3.65 (m, 2H), 3.79 (m, 1H), 4.31 (m, 1H), 4.89−4.96 (m, 2H), 5.47 (m, 1H), 6.82−7.38 (m, 14H), 8.02 (s, 1H). HPLC: $t_{ret}$ = 24.6 min. MS: $m/z$ = 384. HRMS: calcd, 384.1916; found, 384.1930.

**Compound 8fb.** $^1$H NMR ($CDCl_3$): $\delta$ 2.56−3.04 (m, 5H), 3.45 (dd, $^3J$ = 4.7 Hz, $^2J$ = 17.1 Hz, 1H), 3.80 (d, $^2J$ = 16.7 Hz, 1H), 4.26 (d, $^2J$ = 14.9 Hz, 1H), 4.97−5.06 (m, 2H), 5.49 (m, 1H), 6.82−7.33 (m, 15H). HPLC: $t_{ret}$ = 25.7 min. MS: $m/z$ = 398. HRMS: calcd, 398.2072; found, 398.2078.

**Compound 8fc.** $^1$H NMR ($CDCl_3$): $\delta$ 2.89 (m, 1H), 3.58 (dd, $^3J$ = 4.6 Hz, $^2J$ = 17.0 Hz, 1H), 3.79 (d, $^2J$ = 16.7 Hz, 1H), 4.33 (d, $^2J$ = 14.9 Hz, 1H), 4.87−5.04 (m, 3H), 5.54 (m, 1H), 6.78−7.36 (m, 20H). HPLC: $t_{ret}$ = 28.6 min. MS: $m/z$ = 460. HRMS: calcd, 460.2229; found, 460.2240.

**Compound 8fd.** $^1$H NMR ($CDCl_3$): $\delta$ 3.03 (m, 1H), 3.67 (dd, $^3J$ = 4.6 Hz, $^2J$ = 17.1 Hz, 1H), 3.85 (d, $^2J$ = 16.8 Hz, 1H), 4.31 (d, $^2J$ = 14.9 Hz, 1H), 5.01−5.12 (m, 2H), 5.64 (m, 1H), 6.58 (d, $^3J$ = 15.7 Hz, 1H), 6.85−7.62 (m, 14H), 8.05 (d, $^3J$ = 15.7 Hz, 1H). HPLC: $t_{ret}$ = 27.5 min. MS: $m/z$ = 430. HRMS: calcd, 430.1526; found, 430.1539.

**Compound 8fe.** $^1$H NMR ($CDCl_3$): $\delta$ 0.85−1.88 (m, 11H), 2.15 (d, $^3J$ = 6.7 Hz, 1H), 2.92 (m, 1H), 3.56 (dd, $^3J$ = 4.3 Hz, $^2J$ = 17.0 Hz, 1H), 3.82 (d, $^2J$ = 16.7 Hz, 1H), 4.32 (d, $^2J$ = 14.8 Hz, 1H), 4.96−5.08 (m, 2H), 5.5 (m, 1H), 6.82−7.33 (m, 10H). HPLC: $t_{ret}$ = 26.9 min. MS: $m/z$ = 390. HRMS: calcd, 390.2385; found, 390.2407.

**Compound 8ff.** $^1$H NMR ($CDCl_3$): $\delta$ 3.11 (m, 1H), 3.49 (dd, $^3J$ = 4.8 Hz, $^2J$ = 17.4 Hz, 1H), 2.36 (d, $^2J$ = 16.7 Hz, 1H), 4.04 (d, $^2J$ = 14.9 Hz, 1H), 4.68−5.02 (m, 3H), 6.38 (d, $^3J$ = 6.9 Hz, 1H), 6.81−7.96 (m, 18H). HPLC: $t_{ret}$ = 29.0 min. MS: $m/z$ = 482. HRMS: calcd, 482.1742; found, 482.1773.

**Compound 8fg.** $^1$H NMR ($CDCl_3$): $\delta$ 2.99 (m, 1H), 3.47 (m, 1H), 3.88 (d, $^2J$ = 16.6 Hz, 1H), 4.31 (d, $^2J$ = 15.1 Hz, 1H), 4.98−5.20 (m, 2H), 5.54 (m, 1H), 6.75−7.72 (m, 12H). HPLC: $t_{ret}$ = 28.7 min. MS: $m/z$ = 453. HRMS: calcd, 453.1089; found, 453.1096.

**Compound 8ga.** $^1$H NMR ($CDCl_3$): $\delta$ 2.89 (m, 1H), 3.54 (m, 1H), 3.65 (s, 2H), 3.77 (d, $^2J$ = 16.7 Hz, 1H), 4.64 (d, $^2J$ = 15.4 Hz, 1H), 4.86 (d, $^2J$ = 15.4 Hz, 1H), 5.20 (d, $^2J$ = 16.6 Hz, 1H), 5.52 (m, 1H), 6.72−7.69 (m, 13H). HPLC: $t_{ret}$ = 29.0 min. MS: $m/z$ = 520. HRMS: calcd, 520.1663; found, 520.1675.

**Compound 8gb.** $^1$H NMR ($CDCl_3$): $\delta$ 2.51−3.07 (m, 5H), 3.49 (dd, $^3J$ = 4.7 Hz, $^2J$ = 17.2 Hz, 1H), 3.79 (d, $^2J$ = 16.7 Hz, 1H), 4.71 (d, $^2J$ = 15.4 Hz, 1H), 4.82 (d, $^2J$ = 15.4 Hz, 1H), 5.21 (d, $^2J$ = 16.6 Hz, 1H), 5.52 (m, 1H), 6.76−7.77 (m, 13H). HPLC: $t_{ret}$ = 29.7 min. MS: $m/z$ = 534. HRMS: calcd, 534.1820; found, 534.1826.

**Compound 8gc.** $^1$H NMR ($CDCl_3$): $\delta$ 2.88 (m, 1H), 3.60 (dd, $^3J$ = 4.8 Hz, $^2J$ = 17.1 Hz, 1H), 3.77 (d, $^2J$ = 16.8 Hz, 1H), 4.61(d, $^2J$ = 15.4 Hz, 1H), 4.89 (d, $^2J$ = 15.4 Hz, 1H), 5.01 (s, 1H), 5.20 (d, $^2J$ = 16.6 Hz, 1H), 5.58 (m, 1H), 6.71−7.53 (m, 18H). HPLC: $t_{ret}$ = 33.3 min. MS: $m/z$ = 596. HRMS: calcd, 596.1976; found, 596.1986.

**Compound 8gd.** $^1$H NMR ($CDCl_3$): $\delta$ 3.01 (m, 1H), 3.71 (dd, $^3J$ = 4.8 Hz, $^2J$ = 17.2 Hz, 1H), 3.84 (d, $^2J$ = 16.8 Hz, 1H), 4.82 (dd, $^3J$ = 15.4 Hz, $^2J$ = 31.4 Hz, 2H), 5.28 (d, $^2J$ = 16.6 Hz, 1H), 5.68 (m, 1H), 6.56 (d, $^3J$ = 15.7 Hz, 1H), 6.79−7.72 (m, 12H), 8.05 (d, $^3J$ = 15.7 Hz, 1H). HPLC: $t_{ret}$ = 30.9 min. MS: $m/z$ = 566. HRMS: calcd, 566.1274; found, 566.1291.

**Compound 8ge.** $^1$H NMR ($CDCl_3$): $\delta$ 0.83−1.90 (m, 11H), 2.16 (d, $^3J$ = 6.8 Hz, 1H), 2.91 (dd, $^3J$ = 12.6 Hz, $^2J$ = 17.0 Hz, 1H), 3.58 (dd, $^3J$ = 4.6 Hz, $^2J$ = 17.2 Hz, 1H), 3.81 (d, $^2J$ = 16.7 Hz, 1H), 4.70 (d, $^2J$ = 15.3 Hz, 1H), 4.89 (d, $^2J$ = 15.3 Hz, 1H), 5.25 (d, $^2J$ = 16.8 Hz, 1H), 5.55 (m, 1H), 6.76−7.70 (m, 8H). HPLC: $t_{ret}$ = 30.8 min. MS: $m/z$ = 526. HRMS: calcd, 526.2133; found, 526.2175.

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**Supporting Information Available.** $^1$H NMR spectra of all compounds and examples of HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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