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Formal synthesis of schulzeines B and C: A new route to Gurjar's lactams

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Abstract

Described is a formal synthesis of racemic schulzeines B and C that intercepts intermediates developed by Gurjar and co-workers. The synthetic sequence features an annulative coupling of a ketimine and acrylic acid enabling the construction of the benzoquinolizidine nucleus in a highly convergent manner. We also examined a continuous-flow version of the thermal aza-annulation, which proved less practical as compared to the batch processes.

KEYWORDS

2-piperidone, aza-annulation, benzoqionolizidine, marine alkaloid, schulzeine

1 | INTRODUCTION

α-Glucosidase is a hydrolase enzyme that selectively degrades carbohydrates to release glucose, and hence plays a vital role in oligosaccharide metabolism, glycoprotein processing, and other biological pathways.[1] Evidently, small molecules displaying potent inhibitory activities against α-glucosidase have been considered of enormous therapeutic potential for treating diabetes.[2] While the iminosugar-based α-glucosidase-inhibiting drugs have been developed such as acarbose, miglitol, and voglibose, the search for the new chemotypes endowed with an improved pharmacological profile is still highly desirable.[3] In 2004, Fusetani and co-workers reported that schulzeines A (**1**), B (**2**), and C (**3**) possess potent inhibitory activities against α-glucosidase (48–170 nM).[4] Compounds **1**–**3** are a new class of marine alkaloids isolated from extracts of the marine sponge *Penares schulzei*. The structure of schulzeines comprises of a benzo[*a*]quinolizidine framework appending with a tri-*O*-sulfated C28 fatty acid side chain (Figure 1). The promising bioactivities coupled with their unique structural features have drawn research efforts into the synthesis of **1**–**3** and their derivatives. In the past decades, a number of approaches have been successfully implemented to construct the tricyclic core of these alkaloids.[5] The design plans of these syntheses underscore the strategic uses of Pictet-Spengler-type cyclization, Bischler-Napieralski reaction, asymmetric allylic addition, aza-Claisen rearrangement, or dehydrative amination. The research endeavors devoted in the aforementioned works has provided us a great inspiration in formulating our synthesis plan. In order to facilitate further structure–activity-relationship (SAR) studies, we envisioned a facile and modular route to these biomedicinally relevant alkaloids is definitely advantageous. Herein, we describe a formal synthesis of schulzeines B (**2**) and C (**3**) by intercepting lactams **4** and **5** established by Gurjar and co-workers.[5]

In our retrosynthesis design (Scheme 1), Gurjar's lactams **4** and **5** were derived from a common achiral intermediate **A** through a two-step process involving an α-amination and a hydrogenation reaction. We envisioned that a formal (3 + 3) aza-cycloaddition of a ketimine **B** and acrylic acid derivatives could give rise to the benzo[*a*]quinolizidine ring system.[6] The

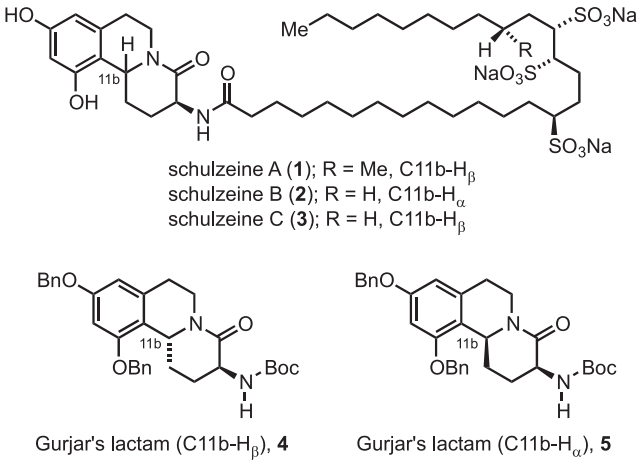
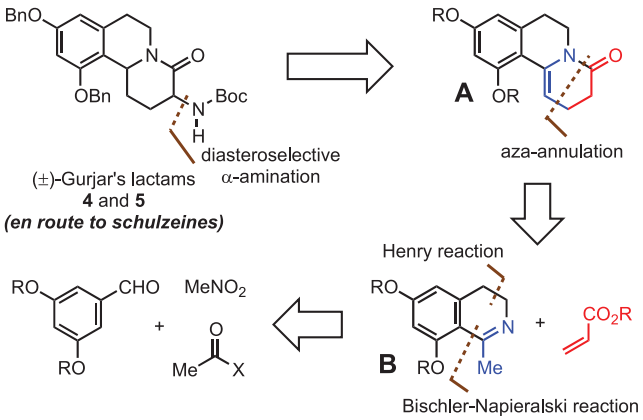


FIGURE 1 Structures of schulzeines A (**1**), B (**2**), and **C** (3) and Gurjar's lactams **4** and **5**

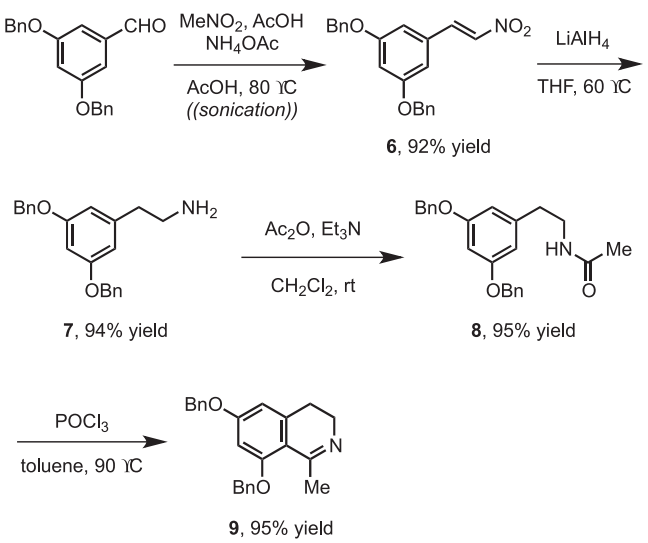


SCHEME 1 Retrosynthetic analysis of **4** and **5**

intermediate **B** could be prepared from readily available 3,5-dialkoxybenzaldehyde, nitromethane, and an acyl donor through a short sequence of reactions.

2 | RESULTS AND DISCUSSION

We commenced conducting the Henry reaction between nitromethane and 3,5-dibenzyloxybenzaldehyde at 80°C (Scheme 2). However, we found the reaction is difficult to scale up; the product was produced only in moderate yields (50–70%) along with a fair amount of intractable material. To our delight, the application of ultrasonication greatly improved the reaction efficiency whereby the gram-scale synthesis of nitrostyrene **6** could be reproducibly achieved (92% yield).[7] An exhaustive reduction of **6** with lithium aluminum hydride led to the formation of the corresponding primary amine **7** in excellent yield. An N-acetylation followed by a Bischler-Napieralski reaction furnished dihydroquinoline **9**. Overall, this four-step sequence is scalable, efficient, and operationally simple.

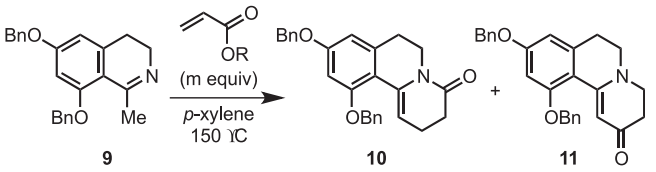


SCHEME 2 Gram-scale synthesis of dihydroisoquinoline **9**

We next investigated the key aza-annulation reaction by exploiting Compound **9** and acrylic acid as the coupling partners. Initially, we observed no noticeable reactions occurred in refluxing ethanol, acetonitrile, or dioxane. When the thermal reaction was conducted in *p*-xylene, the desired annulation product **10** and a regioisomer **11** were successfully obtained in 31 and 13% yields, respectively (Table 1, entry 1). The yield of the 1,2-piperidinone could be increased to 42% by using 2 equiv. of acrylic acid (Entries 2–4). Interestingly, methyl acrylate, in lieu of acrylic acid, proved to be an inferior three-carbon donor in the transformation (entries 5 and 6). We also surveyed a range of Lewis-acid additives (1 equiv. of ZnI_2, $FeCl_3$, $SnCl_4$, $Sc[OTf]_3$, $CeCl_3$, $AgNO_3$, or $LiClO_4$) in an attempt to alter the ratio of **10** to **11**, but the bond-forming events were mostly terminated in these trials. This scenario implies that the Lewis acids play a detrimental role in this reaction by taming the nucleophilic nitrogen. A plausible mechanism to account the formation of **10** and **11** was depicted in Scheme 3. We presumed the enamine (i.e., the tautomer of **9**) could engage with acrylic acid in two different reaction pathways leading to the isomeric piperidone products.

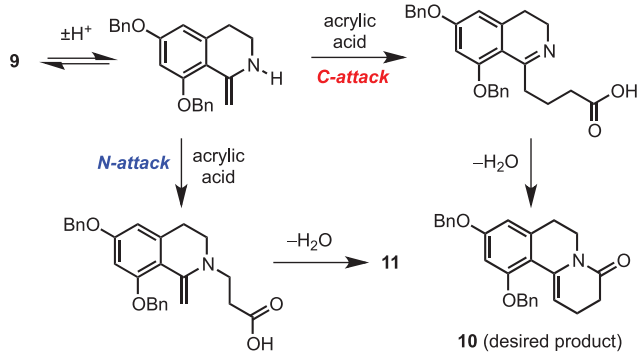
Over the last decade, continuous flow technology has proven highly relevant and beneficial to the production of specialty chemicals and active pharmaceutical ingredients.[8] Even by comparing with laboratory-scale batch processes, merits of the flow synthesis have been widely acknowledged. Since enhanced heat transfer is one of the commonly recognized features, we sought to examine a flow edition of the thermal aza-annulation reaction with a simple tubular reaction system (Scheme 4). Although

TABLE 1 Survey of conditions for the aza-annulation[a]

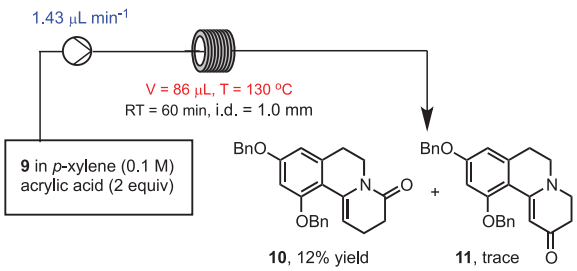


Entry	*R*	*m*	Time (hr)	Yield%[b] of 10	Yield%[b] of 11
1	H	1	6	31	13
2	H	2	6	42	16
3	H	5	6	30	23
4	H	10	6	17	24
5	Me	2	6	Trace	0
6	Me	7	41	29	9

[a]The reaction was conducted with 2.0 mmole of **9** under a nitrogen atmosphere.
[b]Isolated yields.

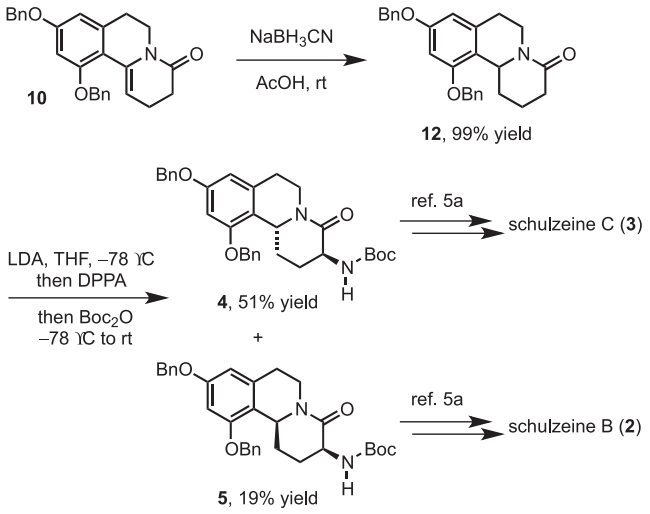


SCHEME 3 Proposed reaction courses to **10** and **11**



SCHEME 4 Continuous-flow synthesis of **10** and **11**

the conversion of **9** is rather fast, we found that Compound **10** was isolated in low yield, and only a trace amount of **11** was detected in the crude mixture by ^{1}H NMR. A quick survey of different residence times failed to improve the results; no further optimization of the process was performed. We presumed the enhanced heat transfer under flow conditions unfavorably accelerates the oligomerization of acrylic acid, thus hampering the desired aza-annulation.



SCHEME 5 Synthesis of Gurjar's lactams **4** and **5**

The successful reduction of enamide **10** with sodium cyanoborohydride[9] set the stage for the key α-amination of the benzo[*a*]quinolizidine core (Scheme 5). Following a procedure developed by Heimgartner et al.,[10] Boc-amino group was smoothly introduced at the α-position in moderate diastereoselectivity (~2.5:1 by crude NMR analysis), furnishing a separable mixture of the titled lactams. The spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra) of **4** and **5** are consistent with those reported by the Gurjar group, and therefore the formal synthesis of schulzeines B and C was achieved.[5]

3 | CONCLUSIONS

In conclusion, we have established the formal synthesis of schulzeines B and C from simple building blocks. Taking advantage of ultrasonication technique, the formation of side products was notably suppressed in the Henry reaction. The key aza-annulation was implemented in either batch or flow mode; the batch process stands out as a reliable access to the benzo[*a*]quinolizidine skeleton. The synthetic efforts pave a way for a rapid assembly of a library of schulzeine analogues, and have prompted an ongoing SAR investigation. The results will be disclosed in due course.

4 | EXPERIMENTAL

4.1 | General information

All air-sensitive reactions were carried out using oven-dried glassware under N_2 atmosphere. tetrahydrofuran, toluene, and dichloromethane were purified by passage over activated alumina using a commercial solvent

purification system. All other solvents and commercially obtained reagents were used without further purification. Reactions were monitored by TLC on silica gel 60 Å F254 plates visualized by UV and ceric ammonium molybdate or potassium permanganate staining solution. Flash chromatography was performed on silica gel (particle size 40–63 μm). Melting points are uncorrected. NMR spectra were measured at 500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra and calibrated from residual solvent signals (chloroform at 7.26 ppm for ^{1}H spectra; chloroform at 77.16 ppm for ^{13}C spectra). Infrared spectra were measured on KBr salt plates. High-resolution mass spectroscopy (HRMS) was performed on a TOF instrument with EI in positive ionization mode.

4.2 | Synthesis and spectral characterization of Compound 6

A mixture of 3,5-diphenoxybenzaldehyde (2.0 g, 6.3 mmol), ammonium acetate (1.0 g, 12 mmol), and acetic acid (1.0 ml, 21.1 mmol) in nitromethane (10 ml, 260.8 mmol) was placed at 80°C under sonication (power = 200 W; operating frequency = 40 KHz). After 7 hr, the solution was cooled to room temperature, and the excess of nitromethane was removed under reduced pressure. Methanol was added to the residue, and the resulting mixture was placed in refrigerator at −20°C for 12 hr to permit a process of recrystallization. After a filtration and rinsing with cold methanol, Compound **6** was obtained as white crystals (2.09 g, 92%). R_f = 0.5 (hexanes/CH_2Cl_2 = 10:1). IR (film): 1593, 1,374, 1,347 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 13.6 Hz, 1H), δ 7.50 (d, J = 13.6 Hz, 1H), 7.46–7.29 (m, 10H), δ 6.75 (s, 3H), 5.06 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.44, 139.09, 137.58, 136.27, 131.89, 128.79, 128.34, 127.57, 108.25, 105.90, 70.38; HRMS (EI, $[M]^+$) for $C_{22}H_{19}NO_4$ calcd. 361.1309, found: 361.1303.

4.3 | Synthesis and spectral characterization of Compound 7

Under N_2 atmosphere, to a suspension of lithium aluminum hydride (1.1 g, 28.9 mmol) in THF (12 ml) was added a solution of **6** (2.09 g, 5.8 mmol) in THF (10 ml) at 60°C over 2 hr via a syringe pump. After stirring at 60°C for 15 hr, the reaction was cooled to 0°C and then quenched by adding water (1.1 ml), 15% $NaOH_{(aq)}$ (1.1 ml) and water (3.3 ml) sequentially at 15 min intervals. The resulting mixture was filtered, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford **7** as a yellow oil (1.77 g, 92%). R_f = 0.5 (hexanes/CH_2Cl_2 = 10:1). IR (film): 3467, 1,595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.29 (m, 10H), 6.52 (s, 1H), 6.48 (s, 2H), 5.04 (s, 4H), 2.95 (t, J = 6.8 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.09, 142.30, 137.00, 128.66, 128.06, 127.63, 108.19, 99.92, 70.12, 43.34, 40.39; HRMS (EI, $[M]^+$) for $C_{22}H_{23}NO_2$ calcd. 333.1723, found: 333.1714.

4.4 | Synthesis and spectral characterization of Compound 8

Under N_2 atmosphere, to a stirring solution of Compound **7** (2.01 g, 5.31 mmol) and Et_3N (0.89 ml, 6.37 mmol) in CH_2Cl_2 (15 ml) was slowly added acetic anhydride (0.6 mmol, 3 equiv.). After stirring at room temperature for 3 hr, the resulting mixture was washed with water (20 ml ×2), and the water layers were separated and back-extracted with EtOAc (20 ml ×3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 50:1) to afford **8** as a white solid (1.87 g, 95%). R_f = 0.2 (hexanes/EtOAc = 1:1). IR (film): 3292, 1,651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.28 (m, 10H), 6.51 (br s, 1H), 6.44 (s, 2H), 5.03 (s, 4H), 3.49 (q, J = 6.6 Hz, 2H), 2.74 (t, J = 6.6 Hz, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.12, 160.02, 141.30, 136.73, 128.48, 127.90, 127.41, 107.81, 100.04, 69.89, 40.35, 35.75, 23.10; HRMS (EI, $[M]^+$) for $C_{24}H_{25}NO_3$ calcd. 375.1829, found: 375.1822.

4.5 | Synthesis and spectral characterization of Compound 9

Under N_2 atmosphere, a stirring solution of **8** (1.87 g, 4.99 mmol), phosphoryl chloride (3.26 ml, 35 mmol) in toluene (15 ml) was brought up to 90°C (oil bath), and stirred for 5 hr. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. The resulting mixture was basified with 15% $NaOH_{(aq)}$ until reaching pH = 10, and then extracted with EtOAc (10 ml ×2). The combined organic layers were washed with water (10 ml ×3), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford **9** (1.69 g, 95%) as a dark purple solid. R_f = 0.2 (hexanes/ EtOAc = 1:1). IR (film): 1673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.28 (m, 10H), 6.53 (s, 1H), 6.44 (s, 1H), 5.05 (s, 4H), 3.51 (t, J = 7.1 Hz, 2H), 2.60 (t, J = 7.1 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.83, 161.41, 158.52, 142.60, 136.34, 136.12, 128.73, 128.70, 128.27, 127.71, 127.54, 113.31, 105.56, 99.25, 70.85, 70.20, 45.75, 27.92, 27.63; HRMS (EI, $[M]^+$) for $C_{24}H_{23}NO_2$ calcd. 357.1723, found: 357.1725.

4.6 | Synthesis and spectral characterization of Compounds 10 and 11

[The Batch Procedure] Under N_2 atmosphere, to a refluxing solution of **9** (1.07 g, 3 mmol) in *p*-xylene (30 ml) was added acrylic acid (0.41 ml, 6 mmol) over 1 hr via a syringe pump. After stirring at 150°C for 6 hr, the resulting mixture was washed with water (20 ml ×2). The water layers were back-extracted with EtOAc (20 ml ×3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 25:1) to afford **10** (520 mg, 42%) and **11** (200 mg, 16%). [The Flow Procedure] A *p*-xylene solution (0.1 M, 1 ml) of Compound **9** (0.1 mmol, 35.7 mg), acrylic acid (2 equiv., 13.7 μl) was prepared and then pumped into a stainless-steel tubing reactor (flow rate: 1.433 μl/min; volume: 0.086 ml; i.d.: 0.1 cm) that was placed in a sand bath (130°C). The reaction mixture eluted from the outlet was discarded for the first 8.3 min (11.9 μl) and the subsequent portion was collected for 505.2 min (724 μl). The crude mixture was purified by flash column chromatography (CH_2Cl_2/MeOH = 25:1) to give **10** (5 mg, 12%). **10**: Brown solid. R_f = 0.4 (hexanes/ EtOAc = 4:1). IR (film): 1695, 1,645, 1,602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.31 (m, 10H), 6.55 (s, 1H), 6.41 (s, 1H), 6.27 (t, J = 7.3 Hz,) 5.09 (s, 2H), 5.04 (s, 2H), 3.82 (t, J = 5.8 Hz, 2H), 2.79 (t, J = 5.8 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 2.36 (dt, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.50, 158.65, 157.38, 138.81, 136.74, 136.72, 131.48, 128.81, 128.76, 128.28, 128.14, 127.66, 127.35, 113.78, 107.92, 105.82, 100.24, 70.94, 70.27, 38.90, 31.57, 30.69, 20.09; HRMS (EI, $[M]^+$) for $C_{27}H_{25}NO_3$ calcd. 411.1829, found: 411.1825. **11**: Brown solid. R_f = 0.4 (hexanes/ EtOAc = 4:1). IR (film): 1736, 1,602, 1,580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.29 (m, 10H), 6.47 (s, 1H), 6.39 (s, 1H), 6.34 (s, 1H), 5.12 (br s, 2H), 4.99 (br s, 2H), 3.60 (m, 2H), 3.28 (m, 2H), 2.84 (m, 2H), 2.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.36, 160.83, 159.03, 155.65, 140.27, 140.25, 136.16, 136.15, 128.66, 128.21, 127.89, 127.46, 126.82, 112.45, 106.19, 100.44, 100.25, 70.79, 70.07, 51.40, 48.34, 36.19, 30.92; HRMS (EI, $[M]^+$) for $C_{27}H_{25}NO_3$ calcd. 411.1829, found: 411.1824.

4.7 | Synthesis and spectral characterization of Compound 12

Under N_2 atmosphere, to a stirring solution of **10** (230 mg, 0.66 mmol) in acetic acid (6 ml) was added sodium cyanoborohydride (0.12 g, 1.98 mmol). After stirring at room temperature for 3 hr, the reaction mixture was basified by adding 15% $NaOH_{(aq)}$ until reaching pH = 10, and then extracted with EtOAc (10 ml ×2). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 25:1) to afford **12** as a brown solid (230 mg, 99%). R_f = 0.4 (hexanes/ EtOAc = 4:1). IR (film): 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.31 (m, 10H), 6.51 (s, 1H), 6.38 (s, 1H), 5.10–5.02 (m, 4H), 4.97–4.93 (m, 1H), 4.80–4.76 (m, 1H), 2.97–2.35 (m, 6H), 1.86–1.80 (m, 2H), 1.41–1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.34, 158.30, 156.67, 138.30, 136.92, 128.79, 128.77, 128.21, 128.13, 127.67, 127.10, 118.61, 106.10, 99.17, 70.19, 70.10, 54.45, 38.68, 31.86, 30.62, 30.11, 19.68; HRMS (EI, $[M]^+$) for $C_{27}H_{27}NO_3$ calcd. 413.1985, found: 413.1987.

4.8 | Synthesis and spectral characterization of Compounds 4 and 5

A solution of lithium diisopropylamide (LDA) was prepared by slowly adding 2.5 M *n*-butyl lithium (0.2 ml, 0.5 mmol) to a stirring solution of diisopropylamine (0.08 ml, 0.06 mmol) in THF (5 ml) at −78°C. After 15 min, the LDA solution was transferred to a solution of **10** (0.18 g, 0.5 mmol) at −78°C over 15 min via a syringe pump. The resulting mixture was stirred at −78°C for 1 hr. Diphenylphosphoryl azide (DPPA; 0.12 ml, 0.55 mmol) was then added, and the mixture was stirred for another 0.5 hr. After adding di-*tert*-butyl dicarbonate (0.23 ml, 1.0 mmol), the reaction was allowed to warm to room temperature. After 7 hr, 1 M $NH_4Cl_{(aq)}$ (1 ml) was added to quench the reaction, and the mixture was extracted with EtOAc (10 ml ×2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ EtOAc = 1:1) to give Compounds **4** (130 mg, 51%) and **5** (50 mg, 19%). **4**: Brown solid. R_f = 0.4 (hexanes/ EtOAc = 4:1). IR (film): 3401, 1712, 1,647,1,607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (m, 10H), 6.51 (s, 1H), 6.37 (s, 1H), 5.35 (br s, 1H), 5.03–4.90 (m, 4H), 4.96–4.90 (m, 1H), 4.81–4,78 (m, 2H), 4.13–3.93 (m, 1H), 3.09–2.74 (m, 2H), 2.66–2.42 (m, 3H), 1.87–1.67 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.90, 158.32, 156.90, 156.29, 138.03, 136.85, 136.59, 128.80, 128.75, 128.20, 127.63, 127.25, 118.47, 106.21, 99.25, 79.66, 70.30, 70.25, 56.27, 52.89, 39.66, 30.73, 28.50, 28.14; HRMS (EI, $[M]^+$) for $C_{32}H_{36}N_2O_5$ calcd. 528.2619, found: 528.2610. **5**: Brown solid. R_f = 0.4 (hexanes/ EtOAc = 4:1). IR (film): 3407, 1714, 1,658, 1,608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (m, 10H), 6.48 (s, 1H), 6.38

(s, 1H), 5.74 (s, 1H), 5.07 (s, 2H), 5.00 (s, 2H), 4.95–4.87 (m, 1H), 4.77–4.69 (m, 1H), 4.35–4.30 (m, 1H), 2.87–2.48 (m, 5H), 1.46 (s, 9H), 1.41–1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.59, 158.43, 155.93, 155.76, 137.28, 136.70, 136.45, 129.75, 128.79, 128.62, 128.13, 128.08, 127.50, 127.13, 117.35, 105.81, 99.01, 79.47, 70.14, 49.76, 48.80, 38.85, 29.72, 28.50, 28.39; HRMS (EI, $[M]^+$) for $C_{32}H_{36}N_2O_5$ calcd. 528.2619, found: 528.2610.

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