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An Atom-Economical Approach to Conformationally Constrained Tricyclic Nitrogen Heterocycles via Sequential and Tandem Ugi/Intramolecular Diels−Alder Reaction of Pyrrole[1,2]

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An efficient approach to rigid tricyclic nitrogen heterocycles via sequential and tandem Ugi/intramolecular Diels−Alder (IMDA) cycloaddition of pyrrole is described. The one-pot Ugi four-component condensation (4CC) reaction was used as the key transformation to prepare trienes with a carboxamide substituent on the tether. The use of acrylic acid (**21**) and *N*-propyl- and *N*-benzylmaleamic acids (**24b** and **24C**) as the acid components provided trienes **22**, **25b**, and **25c**, respectively, which upon heating at 120 °C for 12 h yielded the corresponding [4 + 2] cycloaddition products. In the case of maleic acid derivative **24a**, heating the reaction mixture at 60 °C for 6 h promoted the cycloaddition reaction and provided the desired product **26a** in 78% yield. In contrast, fumaric acid monoethyl ester (**27a**) and 3-acetyl- and 3-(4-methylbenzoyl) acrylic acids (**27b**−**c**) directly yielded the corresponding Ugi/IMDA cycloaddition products **29a**−**c** in high yields at room temperature without any trace of initially formed trienes **28a**−**c**. The IMDA cycloaddition reactions proceed with excellent stereoselectivity with the formation of five stereogenic centers and three rings.

Introduction

The intramolecular Diels−Alder (IMDA) [4 + 2] cycloaddition reaction employing a cyclic diene partner has been established as a powerful synthetic tool for the construction of tricyclic ring system in a stereo- and regiocontrolled manner[3] and has been widely used in the preparation of a wide range of carbocyclic and heterocyclic compounds. Furan is one of the commonly used electron-rich diene partners known to undergo IMDA cycloaddition reaction with various alkene dienophiles to provide molecules with a 7-oxabicyclo[2.2.1]hept-2-ene (7-oxanorbornene) ring system.[4] Recently, we reported a one-pot approach to tricyclic compound **4** via acylation of *N*-benzylfurfurylamine **1** with fumaric anhydride **2** (Scheme 1).[4a] Acylation of amine **1** with anhydride **2** initially provided triene **3**, which immediately underwent IMDA cycloaddition to provide tricyclic compound **4** at room temperature. As an extension of this work, we set out to examine the intramolecular Diels−Alder reaction employing pyrrole as a diene partner to prepare tricyclic molecules possessing a 7-azabicyclo[2,2,2]hept-2-ene moiety.

Although significant progress has been recorded on the intermolecular Diels−Alder cycloaddition reaction of

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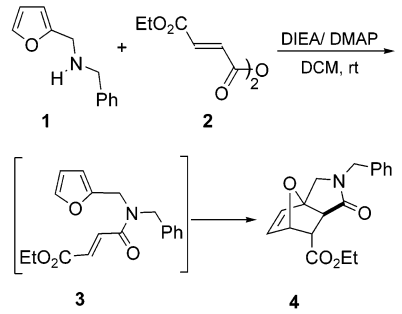
SCHEME 1



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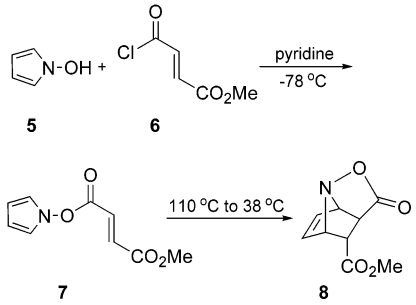
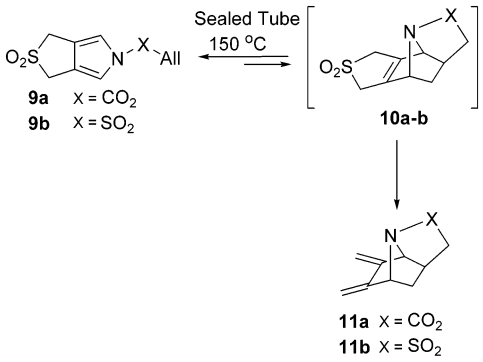


N-protected pyrroles,[5,6] IMDA cycloaddition reactions employing pyrrole as a diene partner have received very little attention. Furthermore, in comparison to the numerous work reported on IMDA reaction of furan only a few reports describing IMDA cycloaddition of pyrrole have appeared,[7,8] which may be due to the aromatic character of the pyrrole ring (resonance energy: pyrrole = 21 kcal mol^{-1}; furan = 16 kcal mol^{-1}).[9] The first example of IMDA cycloaddition of pyrrole was reported by the Jung group (Scheme 2).[7] Acylation of 1-hydroxypyrrole (**5**) with fumaroyl chloride **6** provided triene **7**, which upon heating provided the tricyclic compound **8**. Later, Takayama and co-workers reported the preparation of azanorbonanes **11a** and **11b** via IMDA cycloaddition of pyrrole followed by SO_2 extrusion (Scheme 3).[8] Despite the great potential of the IMDA reaction of

SCHEME 3



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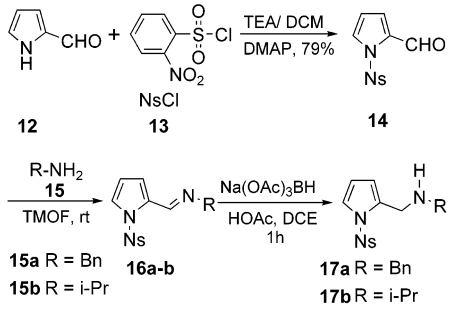

pyrrole to prepare polycyclic nitrogen heterocycles, the synthetic usefulness of IMDA reaction of pyrrole has not been fully exploited. Herein, we disclose our effort on the preparation of novel tricyclic molecules possessing a 7-azabicyclo[2.2.1]hept-2-ene ring system via IMDA reaction employing pyrrole as a diene partner.

Results and Discussion

The amine prepared from aldehyde **14** and amine **15a** was chosen as the initial test substrate for our IMDA cycloaddition study (Scheme 4). Condensation of aldehyde **14**, prepared from **12** and **13**, with benzylamine **15a** followed by reduction of the imine **16a** with sodium triacetoxyborohydride ($Na(OAc)_3BH$) provided amine **17a**. Acylation of the crude amine **17a** with anhydride **2** gave triene **18a** as the only product in 69% overall yield for a two-step reaction sequence. Upon heating in toluene at 80 °C for 15 h, triene **18a** underwent the IMDA cycloaddition to provide the desired tricylic compound **19a** as a single diastereoisomer in quantitative yield. Compound **19a** was fully characterized by ^1H and ^{13}C NMR and mass spectrometry. The relative trans stereochemistry at C-3 and C-4 of **19a** was assigned based on the vicinal coupling constant of H_3 and H_4 in the ^1H NMR spectrum ($J_{3,4}$ = 4.1 Hz). It is also interesting to mention that the examination of the ^1H NMR spectrum and LCMS of triene **18a** obtained at various time intervals over a period of 10 weeks clearly indicated that triene **18a** was slowly undergoing the cycloaddition reaction when stored at room temperature to give the cycloadduct **19a**. However, storing the triene **18a** at lower temperatures (<0 °C) slowed the rate of the cycloaddition and only a trace of the cycloaddition product formation was detected by ^1H NMR even after several weeks.

To examine the influence of a sterically bulky *N*-substituent on the cycloaddition reaction, triene with an

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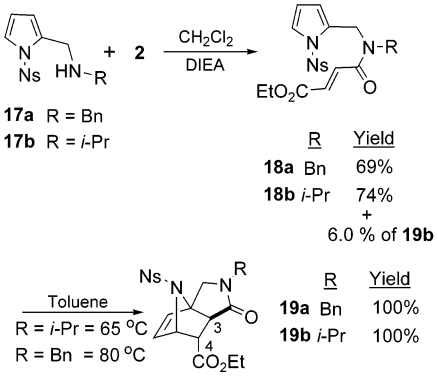
SCHEME 5

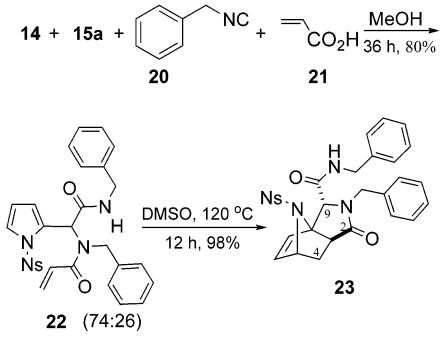


N-isopropyl substituent was prepared (Schemes 4 and 5). The presence of a bulky *N*-isopropyl substituent in **18b** was expected to increase the steric hindrance and simultaneously bring both the diene and dienophile closer to promote the cycloaddition under milder reaction conditions compared to the triene **18a** with a *N*-benzyl substituent. Treatment of crude amine **17b** with anhydride **2** yielded triene **18b** and cycloadduct **19b** in 74% and 6% yields, respectively. Heating the triene **18b** in toluene at 65 °C for 12 h promoted the cycloaddition and furnished compound **19b** as a single isomer in quantitative yield. When stored at room temperature, similar to triene **18a**, triene **18b** slowly (>8 weeks) undergoes IMDA cycloaddition to give the cyclized product **19b**. Comparison of the temperatures required to promote the cycloaddition reaction of trienes **18a** and **18b** (80 °C for **18a** and 65 °C for **18b**) clearly indicate that the presence of a *N*-isopropyl substituent slightly enhanced the rate of the cycloaddition reaction of triene **18b** compared to that of the triene **18a** with a *N*-benzyl group.

Having studied the cycloaddition reaction of pyrrole with *N*-benzyl and *N*-isopropyl trienes, attention was then turned to examine the impact of a substituent on the tether connecting the pyrrole diene and dienophile on the cycloaddition reaction. The Jung group and other research groups[4p−w] previously reported that a substituent on the tether accelerated the rate of IMDA cycloaddition due to the "internal angle compression effect"[4q] by bringing the diene and dienophile somewhat closer compared to a similar system with no substituent on the tether. Encouraged by the above reports and to examine the internal angle compression effect in our system, we proceeded to prepare trienes with a carboxamide substituent on the tether using the one-pot Ugi four-component condensation reaction (4CC).[10,11] The one-pot Ugi 4CC approach would provide triene with a carboxamide substituent on the tether in a single step and eliminate the need for a reductive amination and acylation reaction sequence.

Our initial optimization study was carried out using acrylic acid (**21**) as the acid component and MeOH was used as the solvent. Stirring a mixture of aldehyde **14**, benzylamine (**15a**), benzyl isocyanide (**20**), and acrylic acid (**21**) in MeOH at room temperature for 36 h provided triene **22** as a 74:26 mixture of amide rotational isomers in 80% combined yield (Scheme 6). Heating triene **22** in DMSO at 120 °C for 12 h promoted the cycloaddition and yielded the desired tricyclic lactam **23** as a single diastereoisomer in 98% yield.

SCHEME 6



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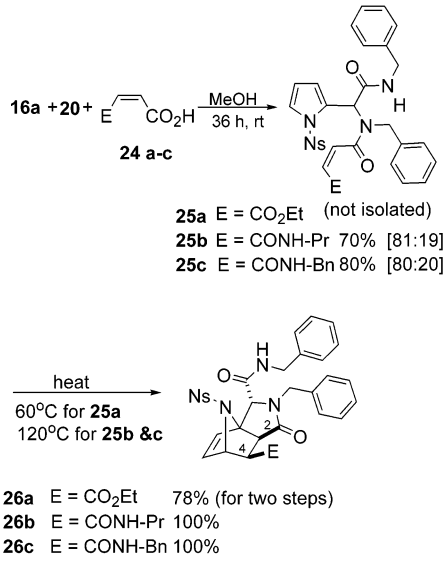

Encouraged with these results, we next examined the influence of electronically and geometrically different dienophile acids **24a**−**c** and **27a**−**c** on the Ugi/ IMDA reaction sequence (Schemes 7 and 8). Condensation of doubly activated dienophile acid **24a** with aldehyde **14**, amine **15a**, and isocyanide **20** in MeOH at room temperature provided the Ugi/IMDA reaction product **26a** as a

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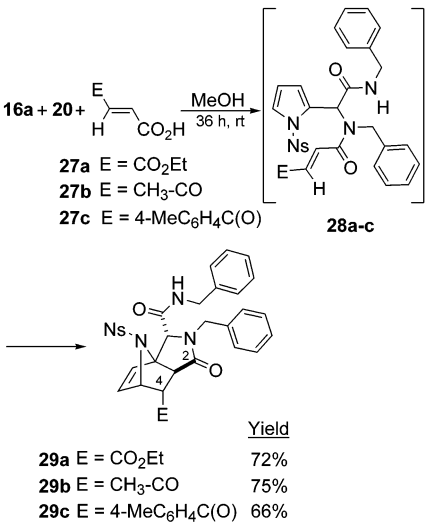
SCHEME 8



single diastereoisomer, albeit only in 27% yield after a tedious chromatographic purification due to unreacted starting materials and unidentified impurities. Recovery of the unreacted aldehyde **14** clearly revealed that there was incomplete imine formation, which is a key step in the Ugi reaction. In an alternative approach, the imine **16a**, prepared from aldehyde **14** and amine **15a** was dissolved in MeOH and allowed to react with isocyanide **20** and dienophile acid **24a** to undergo the Ugi/IMDA reaction sequence (Scheme 7). Examination of the ^{1}H NMR of an aliquot of the crude reaction mixture indicated the presence of a 1:1 mixture of triene **25a** and the desired cycloaddition product **26a** and the triene **25a** was present as a 81:19 mixture of amide rotational isomers. The reaction mixture was heated at 60 °C for 6 h in order to drive the cycloaddition reaction to completion. The above approach (preformed imine and heating) suppressed the side product formation and yielded the cycloaddition product **26a** as a single isomer in 78% yield. The cycloaddition reaction of triene **25a** proceeded with excellent control of diastereoselectivity and no trace of minor isomer was detected. This is the first reported example of IMDA reaction employing pyrrole as a diene partner to undergo IMDA cycloaddition under mild reaction conditions (rt to 60 °C) without the use of any Lewis acids or higher temperatures and pressures. The relative cis stereochemistry at C-3 and C-4 of **26a** was assigned based on the vicinal coupling constant of H_3 and H_4 in the ^{1}H NMR spectrum ($J_{3,4}$ = 9.9 Hz), and the relative stereochemistry of compound **26a** was assigned based on the X-ray crystal structure of compound **29a**.

Reaction of electronically different maleamic acids **24b** and **24c** with imine **16a** and isocyanide **20** provided only trienes **25b** and **25c** as 81:19 and 80:20 mixture of amide rotational isomers in 70% and 80% yields, respectively (Scheme 7). No expected cycloaddition products **26b** and **26c** were detected in the reaction mixture, which could be attributed to the fact that an amide group is less electron withdrawing than an ester group that makes maleamic acids **24b** and **24c** poor dienophiles compared to the dienophile acid **24a**. Hence, the reaction stopped at the Ugi reaction stage to yield only the trienes **25a** and **25b** without further undergoing the IMDA cycloaddition. However, heating the trienes **25b** and **25c** in DMSO at 120 °C for 10 h promoted the cycloaddition to give the corresponding tricyclic products **26b** and **26c**, respectively, as single isomers (Scheme 7). Comparison of the above results clearly indicate that the success of the IMDA cycloaddition reaction of a pyrrole diene tethered to a dienophile partner depends on the nature of the electron-withdrawing substituent at the β-position of the dienophile acid (ester vs amide substituent).

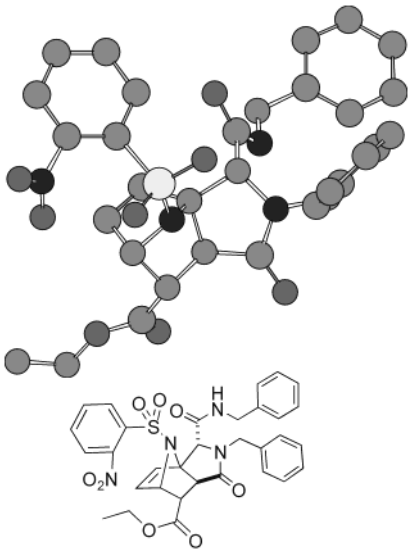


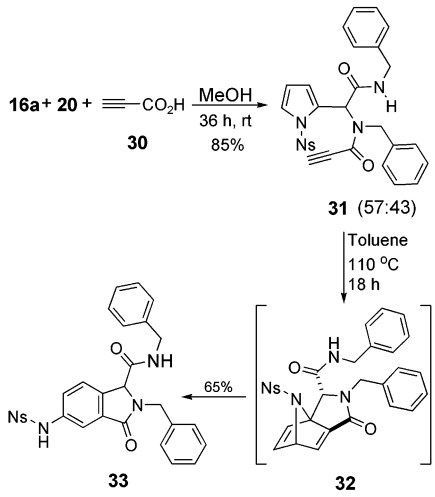
FIGURE 1. Chem3D representation of the X-ray crystal structure of **29a**.

In contrast to dienophile acids **24a**−**c** with *Z*-geometry, condensation of fumaric acid monoethyl ester (**27a**) with imine **16a** and isocyanide **20** in MeOH provided the corresponding Ugi/IMDA reaction product **29a** as a single isomer in 72% yield. No trace of the presumed triene intermediate **28a** was detected in the reaction mixture, as judged by the ^{1}H NMR spectrum of the crude reaction mixture, which clearly indicated that the triene **28a** containing a dienophile with *E*-geometry underwent the IMDA cycloaddition reaction faster than the triene **24a** containing dienophile with *Z*-geometry**.** The relative trans stereochemistry at C-3 and C-4 of **29a** was assigned on the basis of the vicinal coupling constant of H_3 and H_4 in the ^{1}H NMR spectrum ($J_{3,4}$ = 4.0 Hz). Our attempts to determine the relative stereochemistry of the carboxamide substituent at C-9 stereocenter of **29a** using various ^{1}H NMR experiments met with failure. However, the structure of the compound **29a** was unambiguously assigned based on the single-crystal X-ray analysis. Figure 1 shows the chem.3D representation of the X-ray crystal structure of compound **29a**. Comparison of the temperatures required to effect the IMDA cycloaddition reactions of trienes **18a** and **28a** (80 °C for **18a** and room temperature for **28a** (Schemes 5 and 8) clearly indicates that the presence of a carboxamide substituent on the tether influences the triene **28a** to undergo IMDA cyclization at room temperature. The Ugi/ IMDA reaction can be conveniently carried out on a multigram scale to afford compound **29a** in synthetically useful yield (>65%). In the case of large-scale synthesis, removal of the solvent followed by a diethyl ether wash and MeOH trituration provided compound **29a** in analytically pure form. To the best of our knowledge, this is the first example of

stereocontrolled construction of conformationally rigid tricyclic molecule with five stereocenters from readily available achiral starting materials under mild reaction conditions via Ugi 4CC and IMDA cycloaddition of pyrrole in a tandem fashion.[12,13] Since all the atoms, except one water molecule, of the reactants were incorporated into the final product in a regio- and stereocontrolled manner, this tandem Ugi 4CC/ IMDA cycloaddition approach is an excellent illustration for Trost's "atom economy" concept.[14] Similar to furmaric acid derivative, condensation of *trans*-3-acetyl- and 3-(4-methylbenzoyl)acrylic acids (**27b**,**c**) with imine **16a** and isocyanide **20** readily furnished the corresponding cycloaddition products **29b** and **29c** as single diastereoisomers in 75% and 66% yields, respectively (Scheme 8). In general, reactions involving doubly activated dienophile acids with trans geometry were remarkably clean and provided the desired Ugi/ IMDA cycloaddition products in good yields.

To demonstrate the versatility and to expand the synthetic scope of the sequential and tandem Ugi/ IMDA reaction strategy, the reaction was next examined using propiolic acid (**30**) as the acid component (Scheme 9).[15] Stirring a mixture of acid **30**, imine **16a**, and isocyanide **20** in MeOH at room temperature for 36 h provide the triene **31** as the Ugi condensation product as a 57:43 mixture of amide rotational isomers in 85% yield (Scheme 9). The structure of the triene **31** was unambiguously confirmed by the characteristic chemical shifts of the alkyne carbons in the ^{13}C NMR spectrum (major isomer, 76.4 and 82.5 ppm; minor isomer, 75.8 and 83.2 ppm). The isomeric mixture of triene **31** in toluene was heated at 110 °C for 18 h to promote the triene to undergo cycloaddition reaction. To our disappointment, under the reaction conditions, no desired tricyclic lactam **32** was isolated. Instead, isoindolone **33** was isolated in 65% yield. Presumably, the initially formed rigid cycloaddition product **32**, rearranges to a bicyclic compound at higher temperature via a sequential ring-opening/aromatization pathway.[16] The structure of compound **33** was determined on the basis of ^{1}H and ^{13}C NMR spectra. The

SCHEME 9



presence of an additional broad singlet (sulfonamide proton) at 11.5 ppm and the disappearance of the vinylic protons in the NMR spectrum clearly indicated the absence of the tricyclic ring skeleton. This synthetic approach could be used as a complementary route to the currently existing routes to isoindolones.

A recent report from the Schreiber group[11n] led us to initiate a synthetic effort to further elaborate compound **29a** into a tetracyclic compound **37** using a ring opening and ring closing metathesis (RORCM)[17,18] reaction sequence. The proposed synthetic approach to compound **37** is shown in Scheme 10. Hydrolysis of ester **29a** followed by coupling with amine **15a** gave amide **35** in 58% overall yield for two steps. To our disappointment, allylation of amide **35** under various reaction conditions failed to yield pure bis-allyl compound **36**. When the impure bis-allyl compound **36** was subjected to the RORCM reaction following Schreiber's reaction conditions using Grubb's second-generation catalyst[19] no desired tetracyclic product **37** was detected by LCMS. At this point, we strongly believe that the incompatibility of 2-nitrophenylsulfonyl protecting group (Ns) and the bases used in the allylation reaction may have attributed for the failure to isolate the pure bis-allyl compound.[20] We are currently examining alternative synthetic routes to bis-allyl compound **36,** and our results will be reported in due course.

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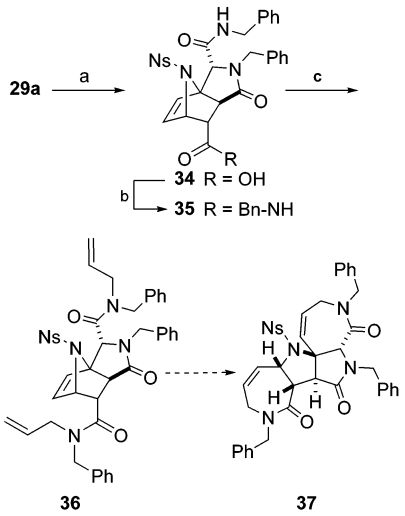
SCHEME 10[a]



[a] Reagents and conditions: (a) LiOH, THF/H_2O, rt, 10 h; (b) DIC, $BnNH_2$, DMAP DMF; (c) LHMDS, allyl bromide, −78 °C, THF.

Conclusions

In summary, the preparation of rigid tricyclic nitrogen heterocyles via sequential and tandem 4CC/IMDA reaction employing pyrrole as a diene partner is described. The key to the success of the Ugi/ IMDA cycloaddition strategy is the selection of *N*-protected pyrrole aldehyde and activated dienophile acid as the aldehyde and acid components, respectively. The attractive feature of this approach is the stereocontrolled generation of five stereocenters, including a quaternary center, and two rings in a single chemical transformation from readily available achiral starting materials. Considering the mild reaction conditions, and convergent and stereochemical control associated with the Ugi/IMDA cycloaddition reaction sequence, we strongly believe that this methodology will find widespread use in organic synthesis for the preparation of polycylic drug- and natural product-like molecules. Furthermore, this study represents a promising starting point for further expansion of the relatively unexplored IMDA cycloaddition reaction employing pyrrole as a diene partner in organic synthesis.

Experimental Section

Aldehyde 14. To a solution of pyrrole-2-carboxaldehyde (**12**) (20.00 g, 210.30 mmol, 1.1 equiv) in CH_2Cl_2 (750 mL) were added TEA (29.00 g, 286.77 mmol, 1.5 equiv), 2-nitrobenzenesulfonyl chloride (**13**) (42.40 g, 191.18 mmol, 1.0 equiv), and DMAP (cat), and the reaction mixture was stirred at rt for 15 h. Solvent was removed, and the residue was purified by column chromatography (CH_2Cl_2/EtOAc) to give aldehyde **14** (42.3 g, 79%): ^{1}H NMR (DMSO-d_6) δ 6.67 (t, J = 3.3 Hz, 1H), 7.49 (dd, J = 3.3, 1.8 Hz, 1H), 7.86 (m, 1H), 7.92 (td, J = 7.7, 1.1 Hz, 1H), 8.01 (m, 2H), 8.13 (dd, J = 7.7, 1.1 Hz, 1H), 9.55 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 112.7, 125.3, 129.1, 130.2, 131.0, 131.6, 133.2, 133.3, 136.3, 147.2, 178.2; MS (EI) m/z 281 (M^+).

General Procedure for the Preparation of Compounds 19a and 19b. Representative Procedure for Compound 19b. To a solution of aldehyde **14** (3.0 g, 10.68 mmol, 1 equiv) in TMOF (55 mL) was added isopropylamine (**15b**) (0.7 g, 11.74 mmol, 1.1 equiv), and the reaction mixture was stirred at room temperature for 24 h. Removal of TMOF under vacuum gave the crude imine **16b**, which was used in the next step without further characterization. To a solution of imine **16b** in dichloroethane (DCE, 55 mL) were added $Na(OAc)_3BH$ (3.4 g, 16.02 mmol, 1.5 equiv) and HOAc (1.6 mL), and the reaction was stirred at rt. After 1 h, solvent was removed, and the residue was carefully neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc (2 × 150 mL). The combined organic layer was dried ($MgSO_4$) and evaporated to give the crude amine **17b**. To a solution of the crude amine **17b** (10.68 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) were added DIEA (2.10 g, 16.02 mmol, 1.5 equiv), fumaric anhydride (12.82 mmol,1.2 equiv) in CH_2Cl_2 (20 mL), and DMAP (cat.), and the reaction mixture was stirred at rt for 10 h. The reaction mixture was washed saturated aqueous $NaHCO_3$ and 10% HCl, dried ($MgSO_4$), and evaporated to give a residue, which was purified to give triene **18b** (3.6 g, 74%). A solution of triene **18b** (100 mg) in toluene was heated at 65 °C for 12 h. Evaporation of the solvent provided compound **19b** in quantitative yield.

Compound 18a: ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 1.29 (t, J = 7.1 Hz, 3H), 4.25 (m, 2H), 4.59 (s, 1H), 4.63 (s, 2H), 4.70 (s, 1H), 6.18 (b, 1H), 6.32 (dt, J = 15.2, 4.4 Hz, 0.5 H), 6.36 (dt, J = 15.2, 4.4 Hz, 0.5 H), 6.86 (d, J = 15.2 Hz, 0.5 H), 6.90 (d, J = 15.2 Hz, 0.5 H), 7.08−7.36 (m, 8H), 7.65−7.82 (m, 2H), 7.86−7.91 (m, 1H); ^{13}C NMR ($CDCl_3$) (mixture of isomers) δ 14.5, 43.2, 45.1, 49.5, 51.5, 61.5, 61.6, 112.3, 112.7, 114.2, 115.1, 124.9, 125.1, 125.6, 125.9, 126.7, 128.0, 128.2, 128.3, 128.5, 128.9, 129.0, 129.2, 130.4, 131.1, 132.7, 133.0, 133.1, 133.2, 133.4, 133.6, 133.8, 135.1, 135.4, 135.8, 136.4, 147.4, 165.4, 165.5, 165.6; MS (EI) m/z 498 (M^+).

Compound 18b: ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 1.07 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.28 (t, J = 6.8 Hz, 1.5H), 1.33 (t, J = 6.8 Hz, 1.5 H), 4.19 (q, J = 6.8 Hz, 1 H), 4.27 (q, J = 6.8 Hz, 1H), 4.49 (s, 1H), 4.54 (s, 1H), 4.85 (m, 1H), 6.09 (d, J = 1.6 Hz, 0.5 H), 6.18 (d, J = 1.6 Hz, 0.5 H), 6.31 (t, J = 3.4 Hz, 0.5 H) 6.35 (t, J = 3.4 Hz, 0.5 H), 6.73 (d, J = 15.6 Hz, 0.5 H), 6.85 (d, J = 15.2 Hz, 0.5 H), 6.97 (d, J = 15.2 Hz, 1H), 7.14 (dd, J = 7.2, 1.6 Hz, 1H), 7.22 (b, 0.5 H), 7.29 (b, 0.5 H), 7.47 (d, J = 15.6 Hz, 0.5 H), 7.74 (m, 1H), 7.83 (m, 1H), 7.96 (m, 1H); ^{13}C NMR ($CDCl_3$) (mixture of isomers) δ 14.1, 14.2, 20.0, 21.2, 38.8, 40.7, 46.4, 49.7, 61.0, 61.2, 112.3, 112.5, 113.1, 114.6, 123.5, 124.5, 125.4, 125.7, 128.3, 128.7, 131.1, 132.2, 132.8, 133.3, 133.4, 133.5, 133.7, 133.8, 134.1, 134.4, 134.5, 135.0, 165.0, 165.2, 165.6; MS (EI) m/z 450 (M^+).

Compound 19a: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 2.96 (d, J = 4.1 Hz, 1H), 3.6 (t, J = 4.3 Hz, 1H), 3.78 (d, J = 14.5 Hz, 1H), 3.89 (d, J = 12.5 Hz, 1H), 4.16 (m, 2H), 4.21 (d, J = 12.5 Hz, 1H), 4.95 (d, J = 14.5 Hz, 1H), 5.22 (dd, J = 4.3, 2.0 Hz, 1H), 6.04 (dd, J = 5.8, 2.0 Hz, 1H), 6.39 (d, J = 5.8 Hz, 1H), 7.23−7.37 (m, 5H), 7.65−7.76 (m, 3H), 7.91 (dd, J = 7.8, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 44.1, 47.4, 47.6, 54.8, 62.0, 67.1, 77.5, 124.9, 128.2, 128.5, 129.2, 131.0, 132.6, 132.9, 133.4, 135.0, 136.1, 136.2, 148.3, 170.1, 171.5; MS (EI) m/z 498 (M^+).

Compound 19b: ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 2.92 (d, J = 4.1 Hz, 1H), 3.56 (dd, J = 4.1, 4.2 Hz, 1H), 3.88 (d, J = 12.5 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 4.30 (d, J = 12.5 Hz, 1H), 4.34 (m, 1H), 5.20 (b, 1H), 6.04 (d, J = 5.6 Hz, 1H), 6.48 (d, J = 5.6 Hz, 1H), 7.65−7.73 (m, 3H), 7.99 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 19.5, 20.3, 42.4, 43.2, 43.8, 55.3, 61.9, 67.4, 77.4, 124.9, 130.9, 132.6, 133.1, 134.8, 136.4, 148.2, 170.2, 170.5; MS (EI) m/z 450 (M^+).

Compound 23. To a solution of aldehyde **14** (500 mg, 1.79 mmol, 1.0 equiv) in MeOH (15 mL) were added amine **15a** (190 mg, 1.79 mmol, 1 equiv), isocyanide **20** (210 mg, 1.79 mmol, 1

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equiv), and acid **21** (130 mg, 1.79 mmol, 1 equiv), and the reaction mixture was stirred at rt for 36 h. Evaporation of the solvent followed by column chromatography purification (EtOAc/hexane) provided the triene **22** (800 mg, 80% yield). Heating a solution of triene **22** (100 mg) in DMSO at 120 °C for 12 h followed by removal of the solvent gave the cycloaddition product **23**.

Compound 22: ^{1}H NMR (DMSO-d_6) (mixture of isomers) δ 3.85−4.31 (m, 3H), 4.58−4.77 (m, 2H), 5.62 (minor) (d, J = 10.4 Hz, 0.26H), 5.68 (major) (d, J = 10.4 Hz, 0.74H), 5.87−6.67 (m, 5H), 6.92−7.28 (m, 11H), 7.74 (m, 1H), 7.92 (t, J = 7.7 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.69 (major) (b, 0.76H), 8.77 (minor) (b, 0.24H); ^{13}C NMR ($CDCl_3$) (major isomer) δ 43.7, 49.1, 54.3, 111.8, 119.4, 125.4, 126.1, 127.1, 127.5, 127.6, 128.0, 128.5, 128.7, 130.1, 130.5, 133.3, 135.3, 137.1, 137.9, 147.4, 161.4, 168.0, 168.3; (minor isomer) δ 33.2, 42.1, 60.6, 112, 125.5, 125.6, 127.1, 127.8, 127.9, 128.2, 128.3, 128.6, 128.7, 128.8, 128.9, 130.3, 131.3, 132.6, 132.7, 135.4, 136.7, 137.8, 165.0, 166.1, 172.0; HRMS (FAB) calcd for $C_{29}H_{27}N_4O_6S$ (M + H) 559.1651, found 559.1653.

Compound 23:. ^{1}H NMR (DMSO-d_6) δ 1.52 (t, J = 11.4 Hz, 1H), 2.39 (dt, J = 11.4, 3.7 Hz, 1H), 2.84 (dd, J = 9.5, 3.7 Hz, 1H), 4.19 (dd, J = 14.7, 5.5 Hz, 1H), 4.32 (dd, J = 14.7, 5.5 Hz, 1H) 4.40 (d, J = 14.7 Hz, 1H), 4.53 (d, J = 14.7 Hz, 1H), 4.92 (s, 1H), 4.96 (s, 1H), 6.09 (m, 1H), 6.39 (m, 1H), 7.11 (d, J = 7.0 Hz, 2H), 7.20 (m, 8 H), 7.55 (d, J = 7.7 Hz, 1H), 7.64 (m, 1H), 7.85 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.0, 43.7, 47.0, 49.8, 61.3, 65.7, 78.1, 124.1, 127.6, 127.8, 127.9, 128.57, 128.6, 128.7, 131.2, 132.0, 132.4, 132.6, 134.1, 134.7, 135.4, 137.7, 148.0, 167.5, 173.9; HRMS (FAB) calcd $C_{29}H_{27}N_4O_6S$ (M + H) 559.1651, found 559.1664.

Preparation of Compound 26a. To a solution of aldehyde **14** (1.0 g, 3.57 mmol, 1 equiv) in benzene (20 mL) was added benzylamine (**15a**) (380 mg, 3.57 mmol, 1 equiv), and the reaction mixture was stirred at rt for 15 h. Removal of benzene provided the crude imine **16a**. To a solution of the crude imine **16a** in MeOH (20 mL) were added isocyanide **20** (420 mg, 3.57 mmol, 1 equiv) and acid **24a** (510 mg, 3.57 mmol, 1 equiv), and the reaction mixture was stirred at room temperature. After 36 h, the reaction flask was heated at 65 °C for 6 h to drive the IMDA reaction to completion. Removal of MeOH provided the crude material, which was purified by column (CH_2Cl_2/EtOAc) to give the lactam **26a** as a solid (1.75 g, 78% yield).

Compound 26a: mp 219−221 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (t, J = 7.0 Hz, 3H), 2.63 (d, J = 9.9 Hz, 1H), 3.27 (d, J = 9.9 Hz, 1H), 4.09 (m, 3H), 4.29 (dd, J = 15.0, 5.9 Hz, 1H), 4.34 (s, 2H), 4.90 (d, J = 2.2 Hz, 1H), 5.08 (s, 1H), 5.73 (d, J = 5.5 Hz, 1H), 6.11 (dd, J = 5.5, 2.2 Hz, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.28 (m, 8H), 7.63 (td, J = 8.0, 1.1 Hz, 1H), 7.87 (td, J = 8.0, 1.1 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 8.13 (dd, J = 8.0, 1.1 Hz, 1H), 9.31 (t, J = 5.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 13.9, 41.4, 42.7, 46.0, 52.1, 59.9, 60.3, 67.6, 76.7, 124.3, 127.1, 127.3, 127.5, 127.8, 128.2, 128.4, 130.9, 132.2, 133.1, 135.1, 135.2, 135.8, 138.5, 147.8, 167.1, 170.2, 170.5; HRMS (FAB) calcd for $C_{32}H_{31}N_4O_8S$ (M + H) 631.1863, found 631.1880.

General Procedure for the Preparation of Trienes 25b, 25c, and 31. Representative Procedure for Triene 25c. To a solution of the crude imine **16a** (1.63 mmol, 1 equiv), prepared as before, in MeOH (10 mL) were added benzyl isocyanide (**20**) (171 mg, 1.63 mmol, 1 equiv) and *N*-benzyl-maleamic acid (**24c**) (334 mg, 1.63 mmol, 1 equiv), and the reaction mixture was stirred at room temperature for 36 h. Removal of MeOH gave the crude material, which was then purified by column (hexane and EtOAc) to give the triene **25c** as a solid (900 mg, 80%).

Compound 25b: ^{1}H NMR (DMSO-d_6) (major) δ 0.79 (t, J = 7.3 Hz, 3H), 1.37 (m, 2H), 2.98 (m, 2H), 4.34 (d, J = 6.4 Hz, 2H), 4.46 (d, J = 17.2 Hz, 1H), 4.67 (d, J = 17.2 Hz, 1H), 6.05 (d, J = 11.7 Hz, 1H), 6.24 (m, 1H), 6.42 (d, J = 11.7 Hz, 1H), 6.48 (m, 1H), 6.88 (m, 2H), 6.99 (m, 1H), 7.09−7.33 (m, 11H), 7.82 (m, 1H), 7.94 (t, J = 7.7 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.56 (t, 6.0 Hz, 1H), 9.33 (t, J = 6.4 Hz, 1H); ^{13}C NMR (major) ($CDCl_3$) δ 11.6, 22.6, 41.6, 44.1, 50.4, 55.1, 112.4, 119.7, 125.0, 125.4, 126.2, 126.5, 127.2, 128.0, 128.4, 128.5, 128.6, 129.2, 130.1, 133.2, 133.8, 134.3, 134.8, 136.4, 139.1, 147.3, 164.4, 168.2, 169.6; HRMS (FAB) calcd for $C_{33}H_{34}N_5O_7S$ (M + H) 644.2179, found 644.2188.

Compound 25c: ^{1}H NMR (DMSO-d_6) (major isomer) δ 4.18−4.36 (m, 4H), 4.46 (d, J = 17.6 Hz, 1H), 4.69 (d, J = 17.6 Hz, 1H), 6.11 (d, J = 11.7 Hz, 1H), 6.24 (t, J = 3.5 Hz, 1H), 6.40 (s, 1H), 6.48 (s, 2H), 6.89 (m, 2H), 6.98 (m, 2H), 7.08−7.32 (m, 12 H), 7.81 (t, J = 7.7 Hz, 1H), 7.94 (t, J = 7.7 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 9.09 (t, J = 5.5 Hz, 1H), 9.30 (t, J = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) (major isomer) δ 43.6, 44.1, 50.4, 55.0, 112.3, 119.5, 124.7, 125.3, 125.6, 126.3, 127.0, 127.5, 127.6, 128.0, 128.2, 128.4, 128.5, 128.6, 129.8, 133.1, 133.5, 133.7, 134.1, 134.7, 136.0, 137.8, 138.8, 146.9, 164.1, 168.0, 169.8; HRMS (FAB) calcd for $C_{37}H_{34}N_5O_7S$ (M + H) 692.2179, found 692.2175.

Compound 31: ^{1}H NMR (DMSO-d_6) (mixture of isomers) δ 4.00−4.31 (m, 3H), 4.36 (d, J = 17.2 Hz, 0.43H), 4.56 (s, 0.57H), 4.57 (s, 0.43H), 4.70 (d, J = 17.2 Hz, 0.57H), 4.74 (d, J = 17.2 Hz, 0.43H), 4.97 (d, J = 17.2 Hz, 0.57H), 6.31 (m, 1H), 6.40 (m, 1H), 6.50 (m, 1H), 6.89−7.34 (m, 11H), 7.75 (m, 1H), 7.93 (m, 1H), 8.16 (m, 1H), 8.75 (t, J = 5.9 Hz, 0.57 H), 8.81 (t, J = 5.9 Hz, 0.43 H); ^{13}C NMR (mixture of isomers) (DMSO-d_6) δ 42.4, 42.8, 47.0, 50.2, 53.7, 58.7, 75.8, 76.4, 82.5, 83.2, 112.47, 112.5, 118.1, 118.5, 125.5, 125.6, 125.7, 125.8, 126.4, 126.6, 126.7, 126.8, 126.86, 126.9, 127.1, 127.2, 127.3, 127.6, 127.7, 128.0, 128.2, 128.4, 129.5, 130.4, 131.7, 132.0, 133.8, 133.9, 135.8, 136.0, 136.5, 136.9, 138.6, 138.8,146.5, 146.7, 154.1, 154.6, 166.9, 167.2; HRMS (FAB) calcd for $C_{29}H_{25}N_4O_6S$ (M + H) 557.1497, found 557.1509.

General Procedure for the Preparation of Compounds 26b and 26c. Representative Procedure for Compound 26c. A solution of triene **25c** (100 mg) in DMSO (10 mL) was heated at 120 °C for 10 h to undergo IMDA reaction. Evaporation of the solvent provided the lactam **26c** (100 mg, 100% crude yield).

Compound 26b: ^{1}H NMR (DMSO-d_6) δ 0.88 (t, J = 7.5 Hz, 3H), 1.45 (m, 2H), 2.48 (d, J = 9.9 Hz, 1H), 3.05 (m, 2H), 3.10 (d, J = 9.9 Hz, 1H), 4.08 (dd, J = 14.7, 5.5 Hz, 1H), 4.26 (s, 2H), 4.27 (dd, J = 14.7, 5.5 Hz, 1H), 4.85 (d, J = 2.0 Hz, 1H), 4.97 (s, 1H), 5.78 (d, J = 5.9 Hz, 1H), 6.20 (dd, J = 5.9, 2.0 Hz, 1H), 7.18 (m, 4H), 7.29 (m, 6H), 7.64 (td, J = 8.0, 1.1 Hz, 1H), 7.79 (t, J = 5.5 Hz, 1H), 7.86 (td, J = 8.0, 1.1 Hz, 1H), 7.94 (dd, J = 8.0, 1.1 Hz, 1H), 8.33 (dd, J = 8.0, 1.1 Hz, 1H), 9.25 (t, J = 5.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 11.7, 22.3, 40.4, 40.8, 42.1, 42.6, 45.9, 51.5, 59.7, 68.0, 76.4, 124.1, 126.9, 127.0, 127.3, 127.5, 127.9, 128.1, 130.8, 131.2, 132.0, 133.2, 134.7, 135.5, 135.7, 138.2, 147.4, 166.9, 168.0, 170.5; HRMS (FAB) calcd for $C_{33}H_{34}N_5O_7S$ (M + H) 644.2179, found 644.2181.

Compound 26c: ^{1}H NMR (DMSO-d_6) δ 2.57 (d, J = 9.9 Hz, 1H), 3.14 (d, J = 9.9 Hz, 1H), 4.08 (dd, J = 15.0, 5.5 Hz, 1H), 4.28 (m, 4H), 4.41 (dd, J = 15.0, 5.5 Hz, 1H), 4.89 (d, J = 1.8 Hz, 1H), 4.97 (s, 1H), 5.79 (d, J = 5.5 Hz, 1H), 6.23 (dd, J = 5.5, 1.8 Hz, 1H), 7.15−7.36 (m, 12H), 7.39 (d, J = 7.7 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.86 (t, J = 7.7 Hz, 1H), 7.94 (d, J = 7.7 Hz, 1H), 8.36 (m, 2H), 9.26 (t, J = 5.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 42.1, 42.5, 42.6, 45.9, 51.5, 59.7, 68.0, 76.4, 124.1, 126.5, 126.8, 127.0, 127.1, 127.3, 127.5, 127.9, 128.0, 128.1, 130.7, 131.3, 132.0, 133.2, 134.6, 135.6, 138.2, 138.9, 147.4, 166.9, 168.3, 170.6; HRMS (FAB) calcd for $C_{37}H_{34}N_5O_7S$ (M + H) 692.2179, found 692.2181.

General Procedure for the Preparation of Compounds 29a−c. Representative Procedure for Lactam 29a. To a solution of the crude imine **16a** (1.63 mmol, 1 equiv), prepared as before, in MeOH (10 mL) were added benzyl isocyanide (**20**) (171 mg, 1.63 mmol, 1 equiv) and fumaric acid monoethyl ester (**27a**) (235 mg, 1.63 mmol, 1 equiv), and the reaction mixture was stirred at room temperature for 36 h. Removal of MeOH

gave the crude material, which was then purified by column (EtOAc/hexane) to give the lactam **29a** as a solid (720 mg, 72%).

Compound 29a: mp 212−214 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 3H), 3.25 (d, J = 4.0 Hz, 1H), 3.60 (dd, J = 4.4, 4.0 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 4.27 (m, 2H), 4.38 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 15.0 Hz, 1H), 4.93 (s, 1H), 5.21 (dd, J = 4.4, 2.0 Hz, 1H), 5.98 (dd, J = 5.5, 2.0 Hz, 1H), 6.17 (d, J = 5.5 Hz, 1H), 6.36 (b, 1H), 7.12 (m, 2H), 7.28 (m, 8H), 7.60 (m, 1H), 7.70 (m, 2H), 7.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 44.1, 44.5, 47.6, 53.7, 61.6, 61.9, 66.9, 78.9, 124.2, 127.8, 127.9, 128.0, 128.7, 128.8, 128.9, 131.3, 132.3, 132.4, 133.1, 134.3, 134.4, 135.1, 137.2, 147.9, 166.9, 169.5, 172.4; HRMS (FAB) calcd for $C_{32}H_{31}N_4O_8S$ (M + H) 631.1863, found 631.1874.

Compound 29b: mp 204−206 °C; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.12 (d, J = 4.6 Hz, 1H), 3.62 (t, J = 4.6 Hz, 1H), 4.29 (d, J = 5.5 Hz, 2H), 4.49 (s, 2H), 4.89 (s, 1H), 5.12 (m, 1H), 5.99 (dd, J = 5.9, 1.8 Hz, 1H), 6.05 (d, J = 5.9 Hz, 1H), 6.59 (t, J = 5.5 Hz, 1H), 7.13−7.33 (m, 10H), 7.59 (dd, J = 7.7, 1.5 Hz, 1H), 7.69 (m, 2H), 7.88 (dd, J = 7.7, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.9, 44.1, 47.5, 53.0, 53.1, 61.6, 66.7, 78.9, 124.5, 128.0, 128.2, 128.92, 128.94, 129.0, 131.4, 132.5, 132.8, 133.5, 134.0, 134.4, 135.2, 137.3, 147.9, 167.3, 172.7, 204.9; HRMS (FAB) calcd for $C_{31}H_{29}N_4O_7S$ (M + H) 601.1757, found 601.1764.

Compound 29c: mp 205−208 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.35 (d, J = 4.4 Hz, 1H), 4.10 (dd, J = 15.0, 5.6 Hz, 1H), 4.29 (dd, J = 15.0, 5.6 Hz, 1H), 4.34 (d, J = 15.6 Hz, 1H), 4.38 (t, J = 4.4 Hz, 1H), 4.43 (d, J = 15.6 Hz, 1H), 5.11 (s, 1H), 5.12 (dd, J = 4.4, 1.8 Hz, 1H), 5.77 (d, J = 5.9 Hz, 1H), 5.94 (dd, J = 5.9, 1.8 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.24−7.33 (m, 8H), 7.39 (d, J = 8.0 Hz, 2H), 7.66 (t, J = 8.0 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 8.13 (m, 3H), 9.33 (t, J = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 22.0, 44.0, 47.6, 49.2, 53.3, 61.3, 67.9, 79.6, 124.5, 127.9, 128.0, 128.2, 128.9, 129.0, 129.5, 129.8, 131.4, 132.5, 132.8, 132.9, 134.4, 135.2, 135.3, 137.3, 145.2, 147.9, 167.3, 173.1, 196.2; HRMS (FAB) calcd for $C_{37}H_{33}N_4O_7S$ (M + H) 677.2070, found 677.2057.

Preparation of Compound 33. Heating a solution of triene **31** (200 mg) in toluene (20 mL) at 110 °C for 18 h followed by evaporation of the solvent and purification (EtOAc/hexane) provided compound **33** (130 mg, 65% yield).

Compound 33: ^{1}H NMR (DMSO-d_6) δ 3.97 (d, J = 15.3 Hz, 1H), 4.23 (dd, J = 15.0, 5.9 Hz, 1H), 4.35 (dd, J = 15.0, 5.9 Hz, 1H), 4.90 (s, 1H), 5.16 (d, J = 15.3 Hz, 1H) 7.16−7.44 (m, 13 H), 7.85 (m, 2H), 8.01 (m, 2H), 9.06 (t, J = 5.9 Hz, 1H), 11.13 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 42.5, 44.5, 61.9, 114.1, 123.4, 123.7, 124.6, 126.8, 127.0, 127.3, 127.7, 128.1, 128.5, 129.6, 131.0, 132.2, 132.5, 134.6, 136.2, 137.1, 137.3, 138.4, 147.6, 165.9, 166.9; HRMS (FAB) calcd for $C_{29}H_{25}N_4O_6S$ (M + H) 557.1497, found 557.1504.

Compounds 35. To a solution of ester **29a** (5.0 g, 7.94 mmol, 1 equiv) in 3:1 THF/H_2O (45 mL/15 mL) was added $LiOH\cdot H_2O$ (1.0 g, 23.81 mmol, 3.0 equiv), and the reaction mixture was stirred at rt for 12 h. THF was removed under vacuum, and additional H_2O (50 mL) was added to the reaction mixture. The reaction mixture was washed with ether and then acidified with 10% HCl, and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layer was dried ($MgSO_4$) and evaporated to give the acid **34** (4.8 g, 100%), which was used in the next step without purification. To a solution of the acid **34** (2.0 g, 3.32 mmol, 1 equiv) in DCM (30 mL) were added amine **15a** (430 mg, 3.99 mmol, 1.2 equiv), DIC (503 mg, 3.99 mmol, 1.2 equiv), and DMAP (cat.), and the reaction mixture was stirred for 12 h. Solvent was removed, and the reaction mixture was purified by column chromatography (EtOAc/hexane) to give the amide **35** (1.4 g, 61% yield).

Compound 34: ^{1}H NMR (DMSO-d_6) δ 3.15 (d, J = 4.4 Hz, 1H), 3.31 (t, J = 4.4 Hz, 1H), 4.06 (dd, 14.8, 5.6 Hz, 1H), 4.20 (d, J = 15.2 Hz, 1H), 4.25 (dd, J = 14.8, 5.6 Hz, 1H), 4.36 (d, J = 15.2 Hz, 1H), 4.97 (dd, J = 4.4, 2.0 Hz, 1H), 5.00 (s, 1H), 5.84 (d, J = 5.6 Hz, 1H), 6.01 (dd, J = 5.6, 2.0 Hz, 1H), 7.11−7.29 (m, 10 H), 7.63 (td, J = 7.2, 1.2 Hz, 1H), 7.85 (td, J = 7.2, 1.2 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 8.08 (dd, J = 7.2, 1.2 Hz, 1H), 9.26 (t, J = 5.6 Hz, 1H), 13.0 (b, 1H); ^{13}C NMR (DMSO-d_6) δ:43.3, 44.7, 46.9, 53.8, 61.3, 67.1, 79.0, 125.2, 127.7, 128.0, 128.2, 128.5, 128.9, 129.0, 131.2, 131.4, 133.0, 133.6, 134.6, 136.2, 136.5, 139.0, 148.3, 167.7, 171.5, 172.8; HRMS (FAB) calcd $C_{30}H_{26}N_4O_8S$ (M + H) 603.1549, found 603.1550.

Compound 35: ^{1}H NMR ($CDCl_3$) δ 3.12 (d, J = 5.1 Hz, 1H), 3.40 (m, 1H), 4.19−4.47 (m, 6H), 4.91 (s, 1H), 5.12 (d, J = 3.7 Hz, 1H), 6.07 (S, 2H), 6.68 (t, J = 5.9 Hz, 1H), 6.82 (t, J = 5.9 Hz, 1H), 7.12−7.31 (m, 15 H), 7.53 (dd, J = 7.7, 1.5 Hz, 1H), 7.58−7.67 (m, 2H), 7.88 (dd, J = 7.7, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.9, 44.1, 45.7, 47.3, 55.6, 61.8, 67.4, 78.7, 124.3, 127.5, 127.67, 127.7, 127.8, 127.9, 128.6, 128.7, 128.8, 131.2, 132.3, 132.5, 133.0, 134.1, 134.2, 134.9, 137.2, 137.7, 147.5, 166.9, 169.0, 173.0; HRMS (FAB) calcd $C_{37}H_{33}N_5O_7S$ (M + H) 692.2180, found 692.2178.

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Supporting Information Available: Complete X-ray crystallography data for compound **29a** and photocopies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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