Stereoselective Solid-Phase Synthesis of a Triaza Tricyclic Ring System: A New Chemotype for Lead Discovery

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Sequential pyrrolidine and hydantoin ring-forming reactions have been applied in the stereoselective solid-phase synthesis of a conformationally constrained, tricyclic triazacyclopenta[*c*]pentalene scaffold. These novel compounds share the structural complexity characteristic of certain alkaloid natural products and represent a source of chemical diversity that complements more traditional classes of heterocyclic compounds of interest as potential pharmaceutical agents. They are assembled in a 12-step reaction sequence from 4 variable building blocks by combining an intramolecular azomethine ylide cycloaddition reaction with a final cyclative cleavage from resin.

Introduction

Solid-phase synthesis methodologies have begun to reach a level of sophistication over the past two to three years whereby increasingly complex natural products can be confidently tackled through multistep reaction sequences comprising as many as 10 (or more) synthetic transformations.[1−3] That these syntheses can afford the targeted products in useful yields and acceptable purities without purification of numerous (resin-bound) intermediates is testimony to the frequently high conversions attainable for individual steps through use of large reagent excesses in the solid-phase approach. A well-optimized polymer-supported synthesis may both provide an efficient means to establish relationships between compound structure and biological activity and open the door to semisynthetic analogues having pharmacological and/or pharmaceutical properties superior to those of the natural product itself. Structural motifs evident in naturally occurring molecules are also providing inspiration for the design of new compound classes amenable to combinatorial synthesis. In particular, the construction of libraries of diverse, rigid, densely functionalized polycyclic compounds is being pursued with the goal of discovering novel active molecules in high-throughput bioassays.[4]

1,3-Dipolar cycloadditions of azomethine ylides to olefins provide a powerful method for the stereocontrolled synthesis of functionalized pyrrolidines.[5] We and others have capitalized on solid-phase intermolecular versions of this cycloaddition reaction to generate libraries of pyrrolidines on polymer supports using α-amino acid ester aldimines as ylide precursors.[6,7] Covalent linkage of the dipolarophile to the azomethine ylide through a variety of different attachment points sets up intramo-

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(1) For epothilones, see: (a) Nicolaou, K. C.; Vourloumis, D.; Li, T.; Pastor, J.; Winssinger, N.; He, Y.; Ninkovic, S.; Sarabia, F.; Vallberg, H.; Roschangar, F.; King, N. P.; Finlay, M. R. V.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2097. (b) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. *Nature* **1997**, *387*, 268. For (*S*)-zearalenone, see: (c) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2534. For (*dl*)-muscone, see: (d) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132. For prostaglandins, see: (e) Thompson, L. A.; Moore, F. L.; Moon, Y.-C.; Ellman, J. A. *J. Org. Chem.* **1998**, *63*, 2066. (f) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724. (g) Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943. For lavendustin A, see: (h) Devraj, R.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 9368. (i) Green, J. *J. Org. Chem.* **1995**, *60*, 4287. For mycotoxin alkaloid analogues, see: (j) van Loevezijn, A.; van Maarseveen, J. H.; Stegman, K.; Visser, G. M.; Koomen, G.-J. *Tetrahedron Lett.* **1998**, *39*, 4737. For actinomycin, see: (k) Tong, G.; Nielsen, J. *Bioorg. Med. Chem.* **1996**, *4*, 693.

(2) One may distinguish synthetic strategies in which the natural product template is assembled de novo by solid-phase methods (as in ref 1) from those in which a key scaffold building block is preformed in solution and then attached to resin for subsequent elaboration (vide infra). For antibacterial natural product derivatives, see: (a) Gordeev, M. F.; Luehr, G. W.; Hui, H. C.; Gordon, E. M.; Patel, D. V. *Tetrahedron* **1998**, *54*, 15879. (b) Senici, P.; Sizemore, C.; Islam, K.; Kocis, P. *Tetrahedron Lett.* **1996**, *37*, 6319. For antimitotic derivatives, see: (c) Nicolaou, K. C.; Winssinger, N.; Vourloumis, D.; Ohshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J.-Y.; Li, T. *J. Am. Chem. Soc.* **1998**, *120*, 10814. (d) Xiao, X.-Y.; Parandoosh, Z.; Nova, M. P. *J. Org. Chem.* **1997**, *62*, 6029. For alkaloid derivatives, see: (e) Koh, J. S.; Ellman, J. A. *J. Org. Chem.* **1996**, *61*, 4494. (f) Atuegbu, A.; Maclean, D.; Nguyen, C.; Gordon, E. M.; Jacobs, J. W. *Bioorg. Med. Chem.* **1996**, *4*, 1097. For steroid derivatives, see: (g) Tremblay, M. R.; Poirier, D. *Tetrahedron Lett.* **1999**, *40*, 1277. (h) Wess, G.; Bock, K.; Kleine, H.; Kurz, M.; Guba, W.; Hemmerle, H.; Lopez-Calle, E.; Baringhaus, K.-H.; Glombik, H.; Enhsen, A.; Kramer, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2222. (i) Lebl, M.; Krchnak, V.; Sepetov, N. F.; Seligmann, B.; Strop, P.; Felder, S.; Lam, K. S. *Peptide Sci.* **1995**, *37*, 177. (j) Boyce, R.; Li, G.; Nestler, H. P.; Suenaga, T.; Still, W. C. *J. Am. Chem. Soc.* **1994**, *116*, 7955.

(3) For a review of carbohydrate synthesis by polymer-supported methods, see: Sofia, M. J. *Mol. Diversity* **1998**, *3*, 75.

(4) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565. (b) Vojkovsky, T.; Weichsel, A.; Patek, M. *J. Org. Chem.* **1998**, *63*, 3162. (c) Bicknell, A. J.; Hird, N. W.; Readshaw, S. A. *Tetrahedron Lett.* **1998**, *39*, 5869. (d) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. *Tetrahedron Lett.* **1998**, *39*, 6815. (e) Powers, D. G.; Casebier, D. S.; Fokas, D.; Ryan, W. J.; Troth, J. R.; Coffen, D. L. *Tetrahedron* **1998**, *54*, 4085. (f) Bolton, G. L.; Hodges, J. C.; Rubin, J. R. *Tetrahedron* **1997**, *53*, 6611. (g) Swayze, E. E. *Tetrahedron Lett.* **1997**, *38*, 8643.

(5) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran D. P., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 3, p 161. (b) Padwa, A. Intermolecular 1,3-Dipolar Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. IV, p 1069. (c) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritsky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 25, p 231.

(6) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029.

(7) Kantorowski, E. J.; Kurth, M. J. *Mol. Diversity* **1996**, *2*, 207. (b) Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671. (c) Bicknell, A. J.; Hird, N. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2441. (d) Hollinshead, S. P. *Tetrahedron Lett.* **1996**, *37*, 9157. (e) Costero, A. M.; Pitarch, M.; Luz Cano, M. *J. Chem. Res. (S)* **1994**, 316.

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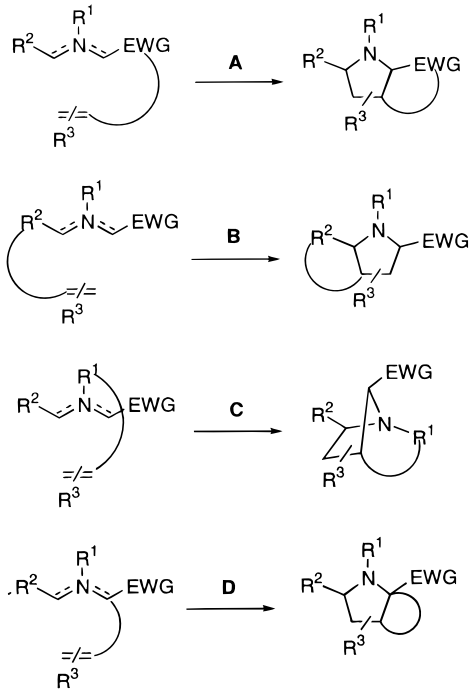
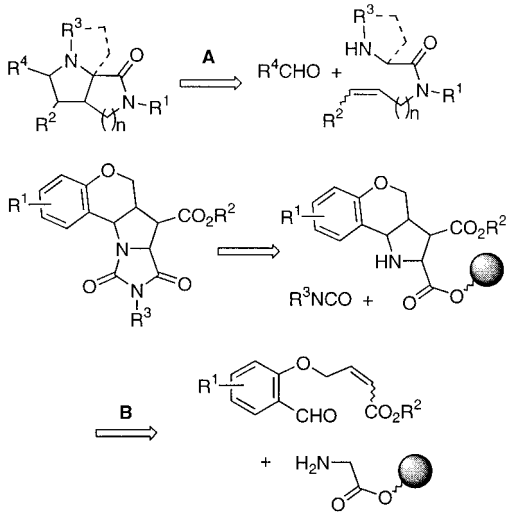
Scheme 1



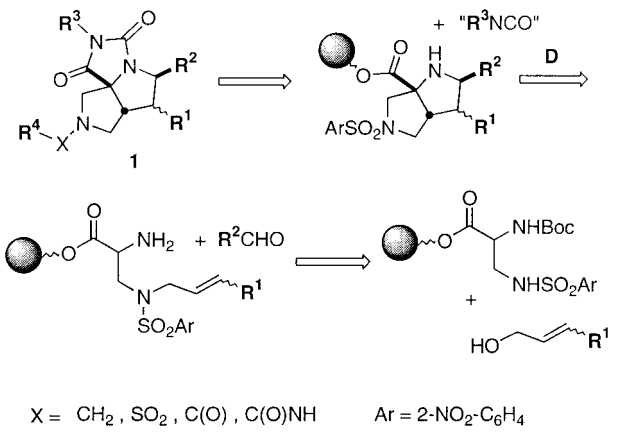
lecular cycloadditions that lead to formation of polycyclic products (see Scheme 1).[8]

These strategies provide inherently more complex structures than their intermolecular counterparts and have been successfully used in several studies directed at alkaloid natural products.[9] Recent publications from the Bartlett and Kurth groups describe interesting solid-phase adaptations of the intramolecular azomethine ylide cycloaddition reaction that feature complementary dipole–dipolarophile tethering constructs (approaches A and B, respectively, from Scheme 1).[10–12]

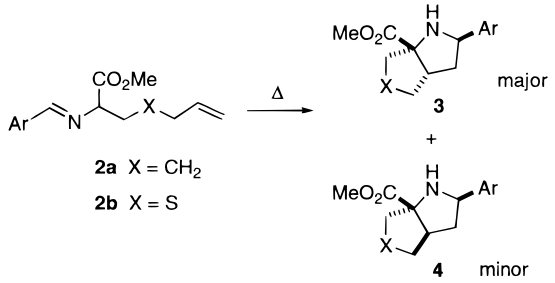


In this paper, we describe our independent efforts to exploit intramolecular [2 + 3] cycloadditions for fashioning molecules having rigid, conformationally well-defined structures and physicochemical characteristics consistent with attractive lead compounds for drug discovery. These

Scheme 2



Scheme 3



products, hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-diones **1**, are unprecedented tricyclic scaffolds reminiscent of angular triquinanes. They are assembled in a 12-step reaction sequence from 4 variable building blocks by combining cycloaddition strategy D (*supra*) with a final cyclative cleavage (see Scheme 2).

Results and Discussion

Grigg et al. have previously shown that aryl imines of alkenyl amino acid esters **2** undergo thermally promoted intramolecular cycloadditions to afford bicyclic pyrrolidines in which the cis-fused ring product **3** predominates (Scheme 3).[13] While intermolecular additions to stabilized ylides of this type require electron-withdrawing groups for activation of dipolarophile, the intramolecular versions appear comparatively insensitive to the electronic character of the olefin component.

(8) Wade, P. A. Intramolecular 1,3-Dipolar Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. IV, p 1069.

(9) For representative examples, see: (a) Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175. (b) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309. (c) Confalone, P. N.; Earl, R. A. *Tetrahedron Lett.* **1986**, *27*, 2695. (d) Garner, P.; Sunitha, K.; Ho, W. B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041. (e) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 3210. (f) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945. (g) Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056. (h) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 9616. (i) Overman, L. E.; Tellew J. E. *J. Org. Chem.* **1996**, *61*, 8338.

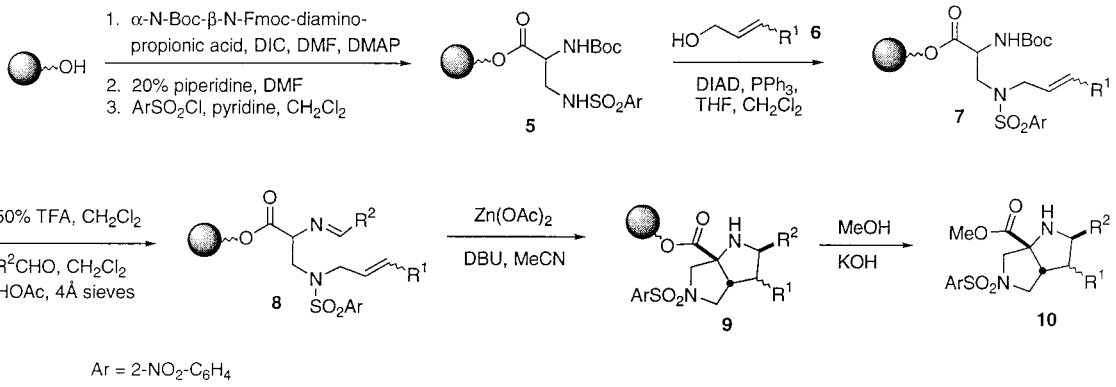
(10) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153.

(11) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081.

(12) For related solution-phase studies, see: (a) Najdi, S.; Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *Tetrahedron Lett.* **1998**, *39*, 1685. (b) Gong, Y.-D.; Kurth, M. J. *Tetrahedron Lett.* **1998**, *39*, 3379. (c) Gong, Y.-D.; Sohn, H.-Y.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 4854.

(13) Armstrong, P.; Grigg, R.; Jordan, M. W.; Malone, J. F. *Tetrahedron* **1985**, *41*, 3547. (b) Cabral, A. M. T. D. P. V.; Rocha Gonsalves, A. M. d'A.; Pinho e Melo, T. M. V. D. *Molecules* **1998**, *3*, 60. (c) Beja, A. M.; Paixão, J. A.; Ramos, Silva, M.; Alte da Veiga, L.; Rocha Gonsalves, A. M. d'A.; Pinho e Melo, T. M. V. D.; Cabral, A. M. T. D. P. V. *Acta Crystallogr.* **1998**, *C54*, 803.

Scheme 4

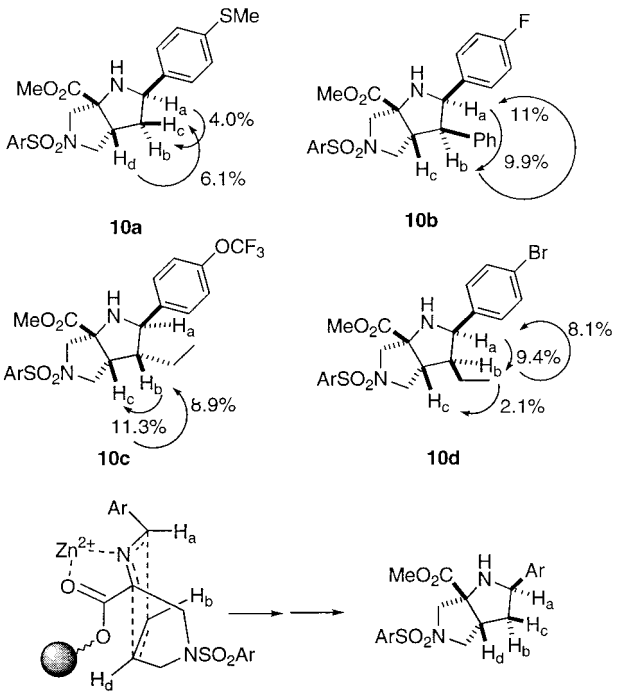


We planned to extend this concept by devising a combinatorial approach to the requisite unsaturated amino acid and performing the cyclization under mild conditions compatible with solid-phase synthesis. The experimental realization of this idea is summarized in Scheme 4.

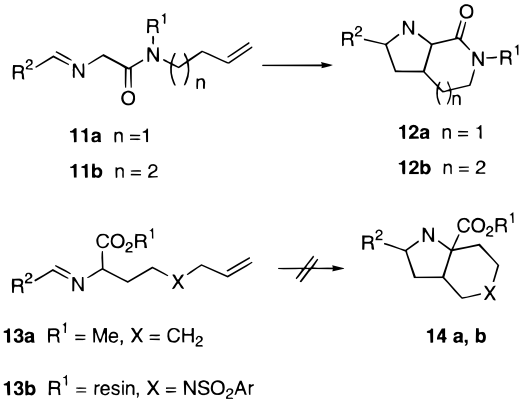
Hydroxymethyl polystyrene resin was acylated with α-*N*-Boc-*β*-*N*-Fmoc-diaminopropionic acid and the *β*-amino group reprotected as the *o*-nitrobenzenesulfonamide **5**. Chemospecific alkylation at this nitrogen via Mitsunobu reaction with allylic alcohols **6** afforded polymer-supported alkenyl amino esters **7**.[14,15] Boc deprotection followed by aryl imine formation under standard conditions provided the cycloaddition precursor **8**. To initiate azomethine ylide formation under ambient conditions, we explored a variety of Lewis acid/tertiary amine base combinations following the methods of Grigg.[5a] An equimolar mixture of zinc acetate and DBU in dry acetonitrile (10-fold excess relative to initial loading of resin) proved an optimal catalyst system, with reaction for 24 h giving efficient cyclization to the bicyclic pyrrolidines **9**. These products were characterized as methyl 2,7-diazabicyclo-[3.3.0]octane-1-carboxylates **10** after cleavage from resin with methoxide. Notably, the key cycloaddition step proceeded stereospecifically, yielding the target structures as *single* (racemic) diastereomers. Stereochemical assignments were secured via NOE difference studies of several representative products and confirmed the expected cis ring fusion in the bicyclic adducts (see Scheme 5). For compounds derived from substituted allylic alcohols, the initial double bond geometry was preserved in the cycloadducts, as exemplified by conversion of (*Z*)- and (*E*)-2-penten-1-ol to **10c** and **10d**, respectively. These results are consistent with a transition-state geometry in which the metalated ylide adopts the *E*,*E*-configuration and approaches the *exo* face of the olefin as observed previously for solution-phase reactions.[13] The intramolecular solid-phase reactions studied by Bartlett differ in that the *E*,*Z*-ylide configuration appears to be favored when the dipolarophile is tethered via the carboxamide rather than via the α-carbon of the ylide precursor.

One further illustration (Scheme 6) of the different geometric constraints arising from these alternative

Scheme 5



Scheme 6

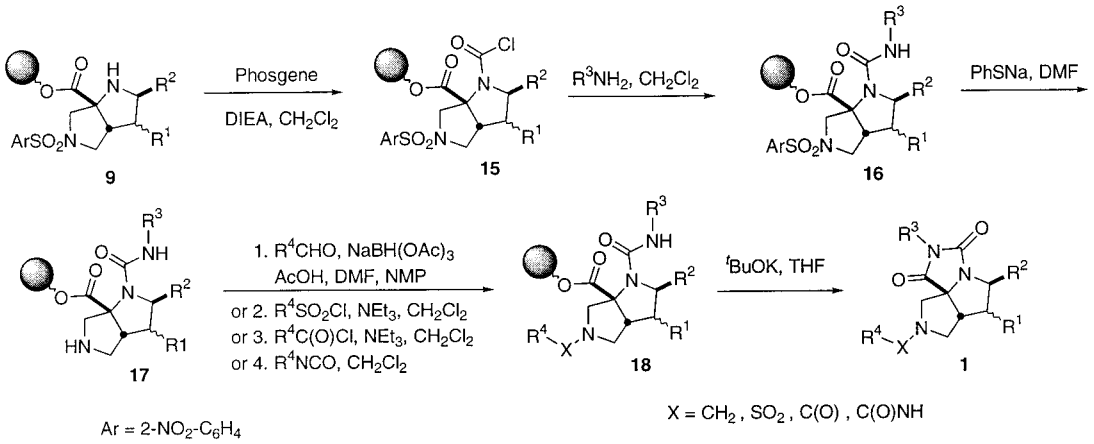


ylide−olefin linkage strategies is that while diazabicyclo-[4.3.0]nonane (**12a**) and diazabicyclo[5.3.0]decane (**12b**) skeletons are accessible through intramolecular cycloadditions of the homoallyl amide and 4-pentenyl amide compounds **11a** and **11b**,[9g,10] neither hexenyl glycine imine **13a** nor **13b** (the ornithine homologue of **8**) cyclize to ring-fused products **14** in solution and the solid phase, respectively.[13a]

(14) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

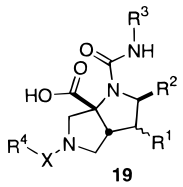
(15) For solid-phase adaptations of the Fukuyama amine synthesis, see: (a) Miller, S. C.; Scanlon, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301. (b) Yang, L.; Chiu, K. *Tetrahedron Lett.* **1997**, *38*, 7307. (c) Miller, S. C.; Scanlon, T. S. *J. Am. Chem. Soc.* **1998**, *120*, 2690. (d) Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **1998**, *39*, 1243.

Scheme 7



Returning to bicyclic adduct **9**, we next examined several common amine derivatization reactions to introduce additional functionality at N^2 of the pyrrolidine ring. Acylation with various acyl chlorides, carboxylic acid anhydrides, chloroformates, and isocyanates generally proceeded in low yield, if at all, and offered little hope for robust combinatorial diversification. Reductive alkylation with aromatic aldehydes and sulfonylation with aryl sulfonyl chlorides proved equally unsuccessful, further serving to highlight the significant steric congestion around this basic nitrogen center. Phosgene, however, was identified as a small, highly reactive electrophile capable of converting **9** to carbamoyl chlorides **15** in high yield for a wide range of R^1 and R^2 substituent groups (vide infra). This immediately suggested an interesting synthetic end game wherein elaboration of a urea moiety could set up a cyclative cleavage reaction that would concurrently liberate the product from resin and generate a third fused hydantoin ring.[11] This approach is summarized in Scheme 7.

Ureas **16** were obtained by displacement of **15** with primary amines in dichloromethane, and the *o*-nitrobenzenesulfonamide protecting group was removed by treatment with sodium thiophenoxide to give resin-bound secondary amines **17**. In contrast to the sterically hindered pyrrolidine nitrogen of **9**, the basic amine in **17** could be readily derivatized under standard conditions through reductive alkylation, sulfonylation, and acylation reactions to introduce a fourth site of diversity into the scaffold **18**. Predictably, the final cyclative cleavage step proved to be somewhat demanding as it involved hydantoin formation adjacent to a quaternary carbon center to deliver a rigid tricyclic ring system. While cyclizations of polymer-supported amino ester ureas to hydantoins under both basic and acidic conditions are well-known,[11,12,16] most of the literature methods failed to yield tricyclic products **1**, even at elevated temperatures. However, treatment of carefully dried resin **18** with potassium *tert*-butoxide in anhydrous THF ultimately afforded the hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-diones **1** in typically excellent purity (>90% as determined by HPLC). The most frequently observed byproducts corresponded to bicyclic ureas **19** formed via basic hydrolysis of **18** under less than rigorously anhydrous conditions.



19

A series of representative tricyclic compounds prepared through this reaction sequence are shown in Chart 1. Isolated yields averaged 22%, equal to an average yield per step of ~88% over the 12-step protocol. The remarkable product purities obtained from this synthesis reflect the "self-policing" nature of the cyclative cleavage process; i.e., only the faithfully assembled product precursors **18** are competent to undergo the hydantoin ring-forming reaction.[17] NOE difference spectra obtained for compounds **1a**−**d** further confirmed that the relative stereochemistry established in **9** by the cycloaddition reaction persisted through the cyclative cleavage step. This may be contrasted with Kurth's observation of kinetic and thermodynamic product mixtures arising during the base-catalyzed formation of pyrrolidinohydantoins that contain an epimerizable stereogenic center.[12]

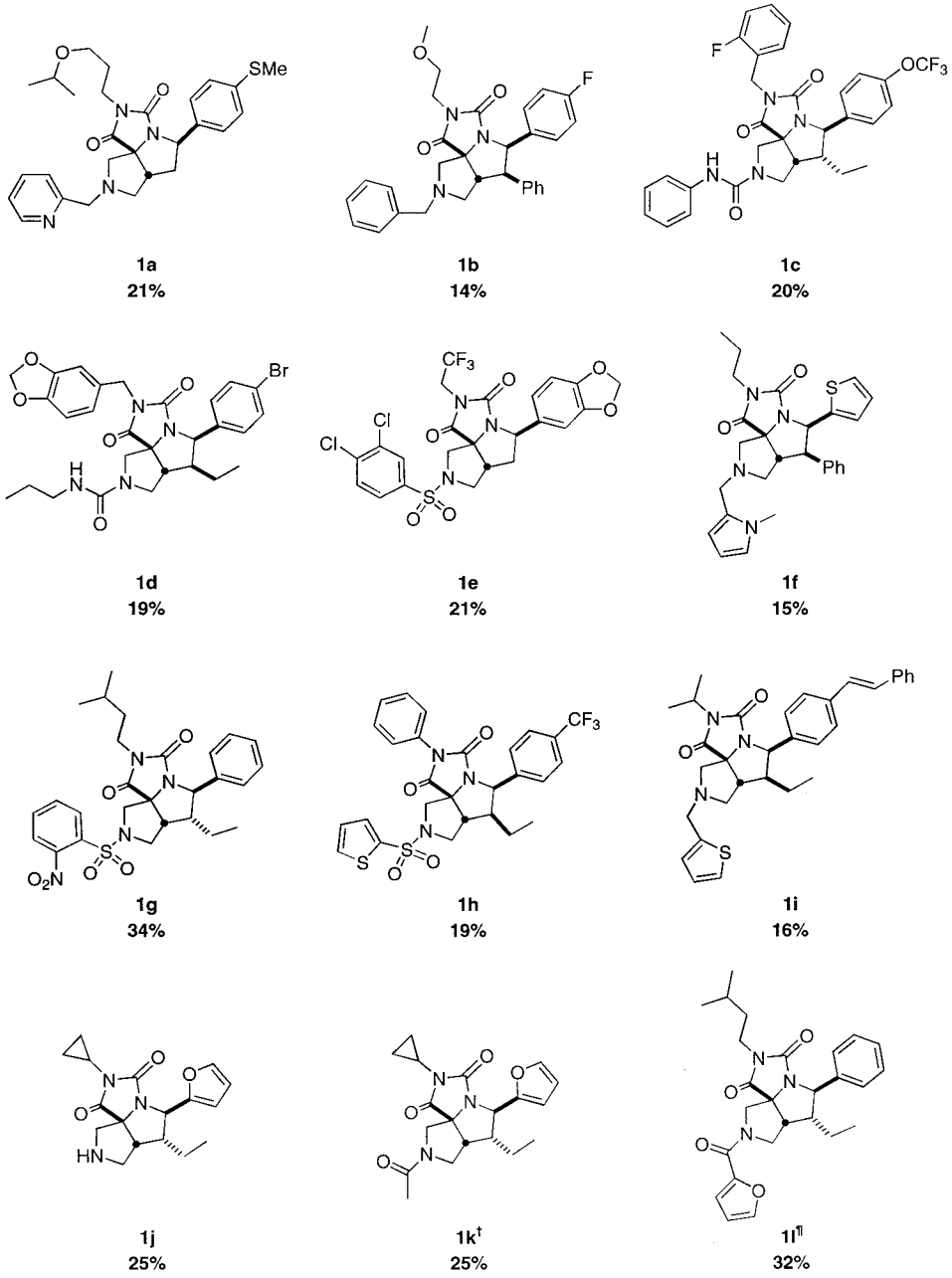
As a prelude to generating a combinatorial library of hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-diones, it was necessary to systematically evaluate the proclivity of monomers from each of the four building block classes to be successfully incorporated into these products (i.e., monomer "rehearsal"). For each monomer class, a series of representative structures (outlined in Scheme 8) prepared via the solid-phase route was analyzed by HPLC and LC−MS to determine the purity and fidelity of the reaction sequence.

The general structure−reactivity trends may be summarized as follows: (i) Of the limited number of commercially available allylic alcohols that were evaluated through the Mitsunobu alkylation and subsequent cycloaddition with the benzylidene azomethine, only the conjugatively unsaturated 2,4-hexadien-1-ol failed to yield a bicyclic pyrrolidine product. Cyclic allylic alcohols

(16) DeWitt, S. H.; Kieley, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909. (b) Patek, M.; Drake, B.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 2227. (c) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5835. (d) Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603. (e) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090.

(17) For a review of cyclative cleavage reactions in solid-phase synthesis, see: van Maarseveen, J. H. *Comb. Chem. High Throughput Screen.* **1998**, *1*, 185.

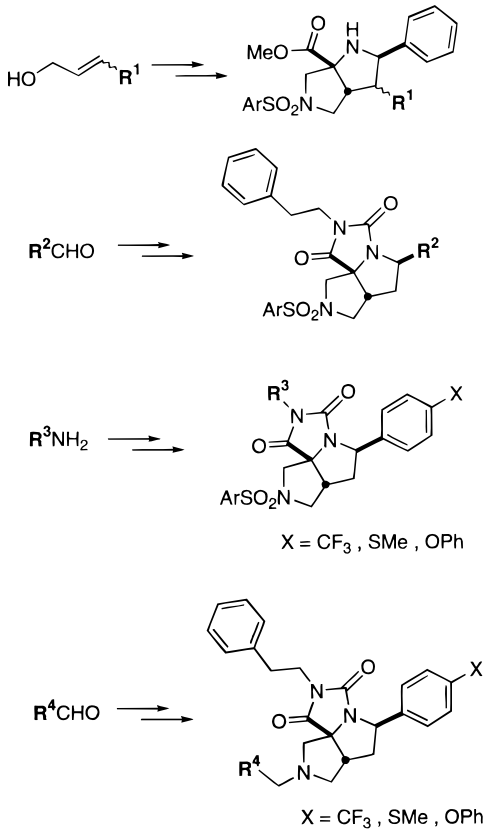
Chart 1. Isolated Yields for Representative Hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-diones 1[a]



[a] Notes: (†) product formed as a 2:1 mixture of isomers (amide bond rotamers), (¶) product formed as a mixture of isomers (amide bond rotamers) equilibrating at room temperature.

were not investigated. In subsequent rehearsal studies the simplest monomer (i.e., allyl alcohol itself) was used exclusively for preparing triazacyclopenta[*c*]pentalenes. (ii) Aromatic and heteroaromatic aldehydes were extensively examined as R^2 monomers. Aldehydes in resonance with electron-withdrawing or highly electron-releasing substituents generally gave little or none of the desired products. For example, 4-nitrobenzaldehyde and 4-pyridinecarboxaldehyde proved unsatisfactory, while the 3-nitrobenzaldehyde and 3-pyridinecarboxaldehyde monomers afforded the desired tricyclic products. Alkoxy-substituted benzaldehydes generally behaved well, while 4-(dialkylamino)benzaldehydes, 1-methyl-2-pyrrolecarboxaldehyde, and aldehydes containing unprotected polar groups (e.g., phenols, carboxylic acids) were not useful monomers. Steric encumberance in the form of *ortho*-disubstitution was not tolerated. Aliphatic aldehydes were generally not found to be useful in this reaction, most likely because tautomerization to enamine intermediates was competitive with azomethine ylide cycloaddition.[5] One exception proved to be the nonenolizable pivalaldehyde for which successful cyclization was observed. (iii) Primary amine R^3 monomers were evaluated in conjunction with multiple R^2 aldehydes. Sterically hindered amines (e.g., benzhydrylamine, adamantanamine) failed to yield the desired products, and poorly nucleophilic anilines proved incapable of reaction with the carbamoyl chloride **15**. Most other amines investigated reacted satisfactorily. (iv) We chose to rehearse reductive alkylation as the final diversification step in the triazacyclopenta[*c*]pentalene synthesis. A wide variety of aromatic and aliphatic R^4 aldehydes could be successfully incorporated into the target compounds

Scheme 8



under standard conditions.[18] The most distinctive failures were for aldehydes containing unprotected polar moieties, as noted above.

This tandem intramolecular cycloaddition−cyclative cleavage chemistry has been used to prepare combinatorial libraries containing thousands of new tricyclic products. We shall defer a more detailed description of these libraries until disclosure of pharmacologically active compounds identified in our proprietary screening programs. In conclusion, stereospecific solid-phase synthesis of a conformationally constrained tricyclic scaffold has been developed that can provide numerous novel molecules for high-throughput screening. These compounds share the structural complexity characteristic of certain alkaloid natural products and represent a source of diversity that complements more traditional classes of heterocyclic compounds of interest as potential pharmaceutical agents.

Experimental Section

General Methods. Reagents were purchased from Aldrich, Sigma, Bachem Biosciences, Fluka, and NovaBiochem and used as received. Compound purification by preparative TLC was performed with Whatman preparative silica thin-layer chromatography plates.

Preparation of Resin 5. 1,3-Diisopropylcarbodiimide (DIC; 2.19 mL, 14.0 mmol) and 4-(dimethylamino)pyridine (DMAP; 49 mg, 0.4 mmol) were added to a suspension of hydroxymethyl polystyrene resin (2.0 mmol, i.e., 3.0 g of resin, hydroxyl group loading 0.67 mmol/g) and α-*N*-Boc-*β*-*N*-Fmoc-diaminopropionic acid (5.98 g, 14.0 mmol) in anhydrous DMF (20 mL), and the reaction mixture was agitated at room temperature for 24 h. The resin was filtered and washed with anhydrous DMF, MeOH, CH_2Cl_2, and THF and then dried in vacuo. Resin loading was determined to be 0.47 mmol/g by quantitative Fmoc measurement.

A 20% v/v piperidine/DMF solution (20 mL) was added to 1.0 g (0.47 mmol) of the above resin, and after shaking the reaction mixture at room temperature for 30 min, the resin was filtered and washed with anhydrous DMF, MeOH, and CH_2Cl_2. The resin was suspended in CH_2Cl_2 (9 mL), and then pyridine (0.38 mL, 5.1 mmol) and 2-nitrobenzenesulfonyl chloride (0.95 g, 4.7 mmol) were added. The reaction mixture was agitated at room temperature for 16 h and then the resin filtered and washed with anhydrous DMF, MeOH, and CH_2Cl_2. A qualitative ninhydrin test showed no blue coloration.

Preparation of Resin 7. Sulfonamide resin **5** (1.0 g, ∼0.47 mmol) was suspended in 1:1 v/v anhydrous THF/CH_2Cl_2 (15 mL), and triphenylphosphine (2.46 g, 9.4 mmol) and the allylic alcohol **6** (9.4 mmol) were added. The reaction mixture was cooled to 0 °C under nitrogen, and diisopropyl azodicarboxylate (DIAD; 1.85 mL, 9.4 mmol) in 1:1 v/v anhydrous THF/CH_2Cl_2 (3 mL) was added dropwise (reaction was initially exothermic). After addition was complete, the reaction mixture was agitated at room temperature for 3 h. The resin was filtered, washed with anhydrous DMF, MeOH, and CH_2Cl_2, and dried in vacuo.

Formation of Bicyclic Pyrrolidine Resin 9. A 50% v/v solution of TFA in CH_2Cl_2 (20 mL) was added to resin **7** (1.0 g, ∼0.47 mmol) and the reaction mixture agitated at room temperature for 1 h. The resin was filtered and washed with anhydrous CH_2Cl_2. The resin was suspended in anhydrous CH_2Cl_2 (9.4 mL), and the aldehyde (4.7 mmol) and acetic acid (0.28 mL, 4.7 mmol) were added followed by fresh 4 Å molecular sieves (2 g). The reaction mixture was shaken at 55 °C for 16 h and then the resin filtered, washed with anhydrous CH_2Cl_2, and dried in vacuo. To a suspension of this resin in anhydrous acetonitrile were added zinc acetate (0.86 g, 4.7 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.70 mL, 4.7 mmol). After the reaction mixture was shaken at room temperature for 24 h, the resin was filtered, washed with anhydrous DMF, MeOH, and CH_2Cl_2, and dried in vacuo.

Preparation of Methyl 2,7-Diazabicyclo[3.3.0]octane-1-carboxylates 10. Bicyclic pyrrolidine resin **9** (1 g, ∼0.47 mmol) was shaken with potassium hydroxide in MeOH (0.1N, 7 mmol) at room temperature for 24 h. The resin was filtered and washed with CH_2Cl_2. The combined filtrates were concentrated, and the product **10** was purified by preparative TLC (ethyl acetate/hexanes).

Methyl (1*R,3*S**,5*S**)-3-(4-(Methylthio)phenyl)-7-(2-nitrobenzenesulfonyl)-2,7-diazabicyclo[3.3.0]octane-1-carboxylate (10a).** The product was isolated as described above in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.05−8.02 (m, 1H), 7.76−7.70 (m, 2H), 7.67−7.64 (m, 1H), 7.26−7.21 (m, A_2B_2, 4H), 4.42 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.77 (m, 1H), 3.76 (s, 3H), 3.56 (d, *J* = 10.8 Hz, 1H), 3.43 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.17 (m, 1H), 2.46 (s, 3H), 2.10 (m, 1H), 1.98−1.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 173.7, 148.5, 138.8, 137.5, 133.9, 131.7, 131.0, 127.2, 126.8, 124.2, 75.3, 62.0, 58.8, 54.0, 53.2, 48.7, 41.1, 16.3. HR-FABMS: *m*/*z* calcd for MH^+ ($C_{21}H_{24}N_3O_6S_2$) 478.1107, found 478.1108.

Methyl (1*R,3*S**,4*R**,5*S**)-3-(4-Fluorophenyl)-7-(2-nitrobenzenesulfonyl)-4-phenyl-2,7-diazabicyclo[3.3.0]octane-1-carboxylate (10b).** The product was isolated as described above in 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.05−8.03 (m, 1H), 7.76−7.68 (m, 3H), 7.07−7.05 (m, 3H), 6.87−6.84 (m, 2H), 6.83−6.74 (m, 4H), 4.85 (d, *J* = 7.0 Hz, 1H), 3.96 (d, *J* = 11.0 Hz, 1H), 3.81 (s, 3H), 3.78−3.64 (m, 3H), 3.54 (t, *J* = 7.0 Hz, 1H), 3.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 173.7, 161.6 (d, J_{CF} = 243.4 Hz), 148.5, 138.7, 135.3 (d, J_{CF} = 3.0 Hz), 134.0, 131.7, 131.1, 128.7, 128.6, 128.5, 128.1, 126.8, 124.3, 114.7 (d, J_{CF} = 21.2 Hz), 74.5, 66.6, 59.5, 56.7, 54.0, 53.4, 53.1. HR-FABMS: *m*/*z* calcd for MH^+ ($C_{26}H_{25}FN_3O_6S$) 526.1449, found 526.1456.

Methyl (1*R,3*S**,4*S**,5*S**)-4-Ethyl-7-(2-nitrobenzenesulfonyl)-3-(4-(trifluoromethoxy)phenyl)-2,7-diazabicyclo[3.3.0]octane-1-carboxylate (10c).** The product was

(18) For a recent report of an optimized protocol for reductive alkylation of polymer-supported substrates, see: Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *J. Org. Chem.* **1999**, *64*, 2219.

isolated as described above in 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08−8.06 (m, 1H), 7.77−7.66 (m, 3H), 7.36−7.23 (m, 3H), 7.11 (d, J = 8.1 Hz, 1H), 3.98 (d, J = 10.6 Hz, 1H), 3.90 (d, J = 10.0 Hz, 1H), 3.82 (s, 3H), 3.68−3.59 (m, 3H), 3.23 (dd, J = 15.1, 6.6 Hz, 1H), 2.44 (br, 1H), 2.09−2.00 (m, 1H), 1.37−1.26 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 149.4, 148.4, 144.6, 133.9, 131.8, 131.0, 129.9, 125.7, 124.3, 120.5 (q, J_{CF} = 255 Hz), 120.1, 119.8, 74.0, 67.2, 59.2, 53.3, 52.6, 50.9, 47.8, 20.6, 13.0. HR-FABMS: *m/z* calcd for MH^+ ($C_{23}H_{25}F_3N_3O_7S$) 544.1366, found 544.1373.

Methyl (1*R,3*S**,4*R**,5*S**)-3-(4-Bromophenyl)-4-ethyl-7-(2-nitrobenzenesulfonyl)-2,7-diazabicyclo[3.3.0]octane-1-carboxylate (10d).** The product was isolated as described above in 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.6 Hz, 1H), 7.75−7.64 (m, 3H), 7.43 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 4.60 (d, J = 6.4 Hz, 1H), 3.84 (d, J = 10.4 Hz, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.55−3.49 (m, 2H), 2.99−2.95 (m, 1H), 2.06−2.01 (m, 1H), 0.97−0.90 (m, 2H), 0.74 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 148.5, 139.1, 133.9, 131.7, 131.4, 131.1, 129.0, 124.3, 121.0, 74.3, 65.0, 59.4, 54.1, 53.3, 52.1, 51.7, 22.2, 12.5. HR-FABMS: *m/z* calcd for MH^+ ($C_{22}H_{25}BrN_3O_6S$) 538.0848, found 538.0622.

Preparation of Resin 16. Bicyclic pyrrolidine resin **9** (1 g, ∼0.47 mmol) was suspended in anhydrous CH_2Cl_2 (4.5 mL) and *N*,*N*-diisopropylethylamine (1.63 mL, 9.4 mmol) added. The reaction mixture was cooled to 0 °C under nitrogen, and a solution of phosgene in toluene (1.93M, 4.9 mL, 9.4 mmol) was added dropwise. After addition was complete, the reaction mixture was shaken at room temperature for 1 h. The resin was filtered and washed with anhydrous CH_2Cl_2. The resin was resuspended in CH_2Cl_2 (9.4 mL) and the primary amine (9.4 mmol) added. After the reaction mixture was shaken at room temperature for 1 h, the resin was filtered, washed with anhydrous DMF, MeOH, and CH_2Cl_2, and then dried in vacuo.

Preparation of Resin 17. Urea resin **16** (1.0 g, ∼0.47 mmol) was suspended in anhydrous DMF (4.9 mL), and a solution of PhSNa in DMF (4.9 mL, 1 M solution) was added. The reaction mixture was shaken at room temperature for 1 h, and then the resin was filtered and washed with anhydrous DMF. The above procedure was repeated, and the resin was shaken for another 16 h. The resin was filtered, washed with anhydrous DMF, MeOH, and CH_2Cl_2, and then dried in vacuo.

General Procedure for Reductive Alkylation of 17. Amine resin **17** (1.0 g, ∼0.47 mmol) was suspended in anhydrous DMF (4.7 mL), and the aldehyde (9.4 mmol) and acetic acid (0.56 mL, 0.94 mmol) were added. The mixture was shaken at room temperature for 20 min, and then sodium triacetoxyborohydride (1.99 g, 9.4 mmol) in 1-methyl-2-pyrrolidinone (NMP) (4.7 mL) was added. The reaction mixture was shaken at room temperature for 1 h. The resin was filtered and washed with MeOH, DMF, MeOH, CH_2Cl_2, and THF. The resin was dried in vacuo for 24 h.

General Procedure for Sulfonylation of 17. Amine resin **17** (1.0 g, ∼0.47 mmol) was suspended in anhydrous CH_2Cl_2 (9.4 mL), and the sulfonyl chloride (4.7 mmol) and triethylamine (4.7 mL) were added. The reaction mixture was shaken at room temperature for 16 h and then the resin filtered and washed with MeOH, DMF, MeOH, CH_2Cl_2, and THF. The resin was dried in vacuo for 24 h.

General Procedure for Urea Formation from 17. Amine resin **17** (1.0 g, ∼0.47 mmol) was suspended in anhydrous CH_2Cl_2 (4.7 mL), and the isocyanate (4.7 mmol) was added. The reaction mixture was shaken at room temperature for 24 h and then the resin filtered and washed with MeOH, DMF, MeOH, CH_2Cl_2, and THF. The resin was dried in vacuo for 24 h.

General Procedure for Amide Formation from 17. Amine resin **17** (1.0 g, ∼0.47 mmol) was suspended in anhydrous CH_2Cl_2 (9.4 mL), and the acyl chloride (4.7 mmol) and triethylamine (4.7 mL) were added. The reaction mixture was shaken at room temperature for 16 h and then the resin filtered and washed with MeOH, DMF, MeOH, CH_2Cl_2, and THF. The resin was dried in vacuo for 24 h.

Formation of 1 by Cyclative Cleavage. Powdered potassium *tert*-butoxide (0.26 g, 2.35 mmol) was added to resin **18** (1.0 g, ∼0.47 mmol) followed by anhydrous THF (3 mL). The reaction mixture was shaken at room temperature for 1 h, and then the resin was filtered and washed with CH_2Cl_2. The combined filtrates were concentrated, and the product **1** was purified by preparative TLC (ethyl acetate/hexanes).

(4*R,5a*R**,8a*S**)-2-(3-Isopropoxypropyl)-4-(4-(methylthio)phenyl)-7-(pyridin-2-ylmethyl)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1a).** The product was isolated as described above in 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 4.0 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.39 (m, 2H), 7.30 (m, 3H), 5.17 (dd, J = 10.8 Hz, 5.6 Hz, 1H), 3.90 (AB quartet, 2H), 3.59 (m, 3H), 3.44 (m, 2H), 3.26 (d, J = 9.9 Hz, 1H), 3.19 (t, J = 9.2 Hz, 1H), 3.04 (m, 2H), 2.91 (dd, J = 9.2, 7.3 Hz, 1H), 2.60 (s, 3H), 2.48 (m, 1H), 2.28 (ddd, J = 12.8, 5.9, 1.5 Hz, 1H), 1.87 (m, 2H), 1.19 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 158.2, 156.7, 149.1, 138.6, 136.6, 131.5, 129.1, 125.8, 122.6, 122.2, 71.6, 65.6, 64.0, 63.8, 61.5, 61.1, 44.8, 40.7, 36.9, 28.6, 22.3, 22.2, 15.7. HR-FABMS: *m/z* calcd for MH^+ ($C_{27}H_{35}N_4O_3S$) 495.2431, found 495.2432.

(4*R,5*S**,5a*R**,8a*S**)-7-Benzyl-4-(4-fluorophenyl)-2-(2-methoxyethyl)-5-phenylhexahydro-2,3a,7-triazacyclopenta[c]pentalene-1,3-dione (1b).** The product was isolated as described above in 14% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.38 (m, 5H), 7.25−7.22 (m, 3H), 6.92−6.80 (m, 6H), 5.38 (d, J = 7.6 Hz, 1H), 4.44 (t, J = 8.0 Hz, 1H), 3.93−3.66 (m, 6H), 3.55−3.45 (m, 2H), 3.51 (s, 3H), 3.10 (d, J = 9.5 Hz, 1H), 2.99 (d, J = 10.3 Hz, 1H), 2.89 (dd, J = 9.5, 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 162.1 (d, J_{CF} = 244.2 Hz), 157.0, 138.6, 137.1, 131.2 (d, J_{CF} = 3.1 Hz), 130.3 (d, J_{CF} = 8.3 Hz), 128.6, 128.5, 128.5, 128.3, 127.3, 127.1, 114.7 (d, J_{CF} = 21.2 Hz), 68.9, 68.5, 65.2, 59.4, 58.8, 58.8, 58.6, 57.7, 48.2, 38.7. HR-FABMS: *m/z* calcd for MH^+ ($C_{30}H_{31}FN_3O_3$) 500.2350, found 500.2358.

(4*R,5*R**,5a*R**,8a*S**)-5-Ethyl-2-(2-fluorobenzyl)-7-(phenylcarbamoyl)-4-(4-(trifluoromethoxy)phenyl)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1c).** The product was isolated as described above in 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.38 (m, 3H), 7.33−7.21 (m, 7H), 7.11−7.01 (m, 3H), 6.28 (s, 1H), 4.68 (AX quartet, 2H), 4.32 (d, J = 11.2 Hz, 1H), 3.97 (d, J = 11.2 Hz, 1H), 3.90 (m, 1H), 3.86 (m, 1H), 3.73 (dd, J = 11.2, 8.8 Hz, 1H), 3.39−3.34 (m, 1H), 2.47−2.39 (m, 1H), 1.43−1.32 3 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 160.6 (d, J_{CF} = 245.7 Hz), 156.1, 153.7, 149.1, 138.4, 135.3, 130.4 (d, J_{CF} = 3.8 Hz), 130.0 (d, J_{CF} = 7.6 Hz), 129.7, 129.0, 127.9, 124.4 (d, J_{CF} = 3.8 Hz), 123.6, 121.7 (d, J_{CF} = 13.7 Hz), 120.5 (q, J_{CF} = 255 Hz), 120.0, 115.8 (d, J_{CF} = 20.5 Hz), 68.1, 56.7, 51.0, 46.4, 46.0, 37.3 (d, J_{CF} = 3.8 Hz), 20.7, 12.7. HR-FABMS: *m/z* calcd for MH^+ ($C_{31}H_{29}F_4N_4O_4$) 597.2126, found 597.2128.

(4*R,5*S**,5a*R**,8a*S**)-4-(4-Bromophenyl)-5-ethyl-2-[(3,4-(methylenedioxy)phenyl)methyl]-7-(propylcarbamoyl-)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1d).** The product was isolated as described above in 19% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 6.82−6.72 (m, 4H), 5.99 (dd, J = 10.4, 1.2 Hz, 2H), 4.91 (d, J = 8.0 Hz, 1H), 4.43 (AB quartet, 2H), 4.25 (t, J = 5.2 Hz, 1H), 3.83 (d, J = 10.8 Hz, 1H), 3.69−3.59 (m, 3H), 3.21 (dt, J = 7.2, 5.6 Hz, 1H), 2.71 (m, 2H), 1.54 (m, 2H), 1.31−1.25 (m, 1H), 0.95−0.84 (m, 4H), 0.74 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 156.6, 156.5, 147.7, 147.6, 135.0, 131.9, 129.8, 129.7, 123.0, 122.4, 110.0, 108.5, 101.5, 76.3, 66.4, 54.8, 48.6, 48.0, 43.0, 42.9, 30.1, 24.0, 22.3, 12.7, 11.9. HR-FABMS: *m/z* calcd for MH^+ ($C_{28}H_{32}BrN_4O_5$) 583.1757, found 583.1529.

(4*R,5a*R**,8a*S**)-7-(3,4-Dichlorobenzenesulfonyl)-4-(3,4-(methylenedioxy)phenyl)-2-(2,2,2-trifluoroethyl)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1e).** The product was isolated as described above in 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, J = 7.8, 1.6 Hz, 1H), 7.74 (dd, J = 7.8, 1.2 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 6.80−6.73 (m, 2H), 6.68 (s, 1H), 5.98 (AB, 2H), 4.90 (t, J = 6.8 Hz, 1H), 4.05−3.87 (m, 2H), 3.86 (d, J = 11.2 Hz, 1H), 3.76−3.67 (m, 3H), 3.23−3.20 (m, 1H), 2.50−2.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 153.7, 148.0, 147.9, 137.9, 136.2, 135.2,

131.0, 130.2, 128.7, 127.6, 122.9 (q, J_{CF} = 277.5 Hz), 121.9, 108.3, 101.5, 77.7, 64.0, 56.8, 54.2, 44.8, 41.2, 40.2. HR-FABMS: *m/z* calcd for MH^+ ($C_{23}H_{19}Cl_2F_3N_3O_6S$) 592.0324, found 592.0281.

(4*R,5*S**,5a*R**,8a*S**)-7-((1-Methyl-1*H*-pyrrol-2-yl)methyl)-5-phenyl-2-propyl-4-(thiophen-2-yl)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1f).** The product was isolated as described above in 15% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.28 (m, 3H), 7.18 (d, J = 4.8 Hz, 1H), 7.02 (dd, J = 7.2, 3.6 Hz, 2H), 6.85 (dd, J = 5.2, 3.6 Hz, 1H), 6.74 (t, J = 2.0 Hz, 1H), 6.63 (dd, J = 4.0, 1.2 Hz, 1H), 6.16−6.13 (m, 2H), 5.65 (d, J = 7.6 Hz, 1H), 4.29 (t, J = 7.6 Hz, 1H), 3.84 (s, 3H), 3.78 (AB quartet, 2H), 3.60−3.34 (m, 3H), 3.35 (d, J = 10.4 Hz, 1H), 3.07 (d, J = 9.6 Hz, 1H), 2.93 (d, J = 10.4 Hz, 1H), 2.88 (dd, J = 9.6, 5.6 Hz, 1H), 1.77−1.68 (m,2H), 1.03 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ176.1, 157.8, 137.3, 137.2, 129.1, 128.8, 128.4, 127.3, 126.2, 125.2, 122.8, 122.8, 108.9, 106.5, 76.6, 65.0, 64.7, 58.5, 57.1, 51.0, 48.3, 41.2, 34.2, 21.6, 11.7. HR-FABMS: *m/z* calcd for MNa^+ ($C_{27}H_{30}N_4NaO_2S$) 497.1987, found 497.1995.

(4*R,5*R**,5a*R**,8a*S**)-5-Ethyl-2-(3-methylbutyl)-7-(2-nitrobenzenesulfonyl)-4-phenylhexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1g).** the product was isolated as described above in 34% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.2 Hz, 1H), 8.03−7.69 (m, 3H), 7.40−7.26 (m, 5H), 4.46 (d, J = 11.6 Hz, 1H), 3.93−3.82 (m, 2H), 3.66 (d, J = 11.2 Hz, 1H), 3.51−3.34 (m, 3H), 3.23−3.19 (m, 1H), 2.52−2.43 (m, 1H), 1.49−1.21 (m, 5H), 0.94−0.87 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 156.1, 148.8, 134.5, 132.7, 131.9, 131.3, 129.8, 129.6, 129.1, 128.4, 124.5, 76.5, 69.0. 58.5, 50.5, 48.8, 46.7, 38.2, 36.8, 26.3, 22.8, 22.6, 20.5, 12.8. HR-FABMS: *m/z* calcd for MH^+ ($C_{27}H_{33}N_4O_6S$) 541.2122, found 541.2144.

(4*R,5*S**,5a*R**,8a*S**)-5-Ethyl-2-phenyl-7-(thiophene-2-sulfonyl)-4-(4-(trifluoromethyl)phenyl)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1h).** The product was isolated as described above in 19% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (dd, J = 4.8, 1.2 Hz, 2H), 7.67 (dd, J = 4.4, 1.6 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.42−7.38 (m, 2H), 7.35−7.33 (m, 1H), 7.23−7.17 (m, 3H), 5.13 (d, J = 7.6 Hz, 1H), 3.87 (d, J = 11.2 Hz, 1H), 3.71 (dd, J = 18.0, 10.4 Hz, 2H), 3.47 (dd, J = 10.0, 4.8 Hz, 1H), 2.91−2.82 (m, 2H), 1.34−1.25 (m, 1H), 0.98−0.90 (m, 1H), 0.80 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 155.2, 139.8, 135.0, 133.2, 133.0, 131.1, 130.8 (q, J_{CF} = 32.6 Hz), 129.3, 128.6, 128.2, 128.0, 125.8 (J_{CF} = 3.8 Hz), 125.6, 125.2, 122.7, 77.4, 76.2, 66.7, 57.3, 51.9, 51.5, 49.1, 22.5, 12.6. HR-FABMS: *m/z* calcd for MH^+ ($C_{27}H_{25}F_3N_3O_4S_2$) 576.1239, found 576.1253.

(4*R,5*S**,5a*R**,8a*S**)-5-Ethyl-2-isopropyl-4-(4-styrylphenyl)-7-((thiophen-2-yl)methyl)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1i).** The product was isolated as described above in 16% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.25−7.28 (m, 2H), 7.07 (s, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.96−6.94 (m, 2H), 4.99 (d, J = 7.6 Hz, 1H), 4.13 (hep, J = 6.8 Hz, 1H), 3.91 (br s, 2H), 3.27 (d, J = 10.0 Hz, 1H), 3.04−3.01 (m, 2H), 2.77−2.74 (m, 2H), 2.68−2.65 (m, 1H), 1.32−1.25 (m, 6H), 1.23−1.02 (m, 2H), 0.79 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 158.3, 142.5, 137.3, 137.0, 136.7, 129.1, 128.8, 128.5, 128.2, 127.8, 126.7, 126.6, 126.5, 125.2, 125.1, 67.7, 65.1, 57.8, 53.8, 52.0, 49.6, 44.4, 30.1, 23.2, 20.1, 19.6, 12.9. HR-FABMS: *m/z* calcd for MH^+ ($C_{32}H_{36}N_3O_2S$) 526.2529, found 526.2538.

(4*R,5*R**,5a*R**,8a*S**)-2-Cyclopropyl-5-ethyl-4-(furan-2-yl)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1j).** The product was isolated as described above in 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (t, J = 1.2 Hz, 1H), 6.42 (d, J = 1.2 Hz, 2H), 4.35 (d, J = 11.6 Hz, 1H), 3.39 (d, J = 11.6 Hz, 1H), 3.24−3.18 (m, 1H), 3.06−2.99 (m, 3H), 2.59−2.51 (m, 2H), 1.99 (br s, 1H), 1.46−1.28 (m, 2H), 0.92−0.82 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 157.3, 147.4, 142.9, 110.8, 110.6, 61.2, 59.2, 49.4, 48.8, 48.4, 22.1, 20.7, 12.7, 5.48, 5.45. HR-FABMS: *m/z* calcd for MH^+ ($C_{17}H_{22}N_3O_3$) 316.1662, found 316.1658.

(4*R,5*R**,5a*R**,8a*S**)-7-Acetyl-2-cyclopropyl-5-ethyl-4-(furan-2-yl)hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1k).** The product was isolated as a 2:1 mixture of isomers (amide bond rotamers) in 25% yield as described above. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 1.2 Hz, 1H), 6.44−6.42 (m, 2H), 4.32 (d, J = 10.8 Hz, 0.33H), 4.28 (d, J = 11.6 Hz, 0.67H), 4.00−3.84 (m, 2H), 3.76−3.64 (m, 2H), 3.32−3.22 (m, 1H), 2.61−2.51 (m, 2H), 2.13 (s, 1H), 2.10 (s, 2H), 1.47−1.26 (m, 2H), 0.96−0.84 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 174.2, 168.7, 157.4, 146.8, 143.2, 111.3, 110.8, 61.7, 57.8, 48.9, 47.2, 45.4, 22.7, 22.5, 20.8, 12.6, 5.6, 5.5; (minor isomer) 174.7, 168.7, 157.0, 147.0, 143.1, 111.2, 110.8, 61.2, 55.5, 48.8, 46.9, 45.0, 22.6, 22.3, 21.2, 12.7, 5.6, 5.5. HR-FABMS: *m/z* calcd for MH^+ ($C_{19}H_{24}N_3O_4$) 358.1768, found 358.1765.

(4*R,5*R**,5a*R**,8a*S**)-5-Ethyl-7-(furan-2-ylcarbonyl)-2-(3-methylbutyl)-4-phenylhexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-dione (1l).** The product was isolated as a thermally equilibrating mixture of isomers (amide bond rotamers) in 32% yield as described above. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.54 (m, 1H), 7.39−7.36 (m, 3H), 7.29−7.27 (m, 2H), 7.18 (d, J = 3.2 Hz, 1H), 6.55−6.53 (m, 1H), 4.47−4.30 (br, 2H), 4.26 (d, J = 11.2 Hz, 1H), 3.84 (br, 1H), 3.51−3.38 (m, 2H), 3.33 (br, 1H), 2.50−2.44 (m, 1H), 1.54−1.36 (m, 6H), 0.94−0.89 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 157.5, 156.8, 147.8, 144.6, 132.9, 129.4, 129.0, 128.3, 117.4, 111.8, 68.6, 57.5, 53.7, 50.7, 46.5, 44.2, 38.1, 36.7, 26.2, 22.7, 22.5, 20.8, 12.7. HR-FABMS: *m/z* calcd for MH^+ ($C_{26}H_{32}N_3O_4$) 450.2395, found 450.2393.

Supporting Information Available: ^{1}H NMR spectra for compounds **1a**−**l** and **10a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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