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Heterocyclic α-Alkylidene Cyclopentenones Obtained via a Pauson−Khand Reaction of Amino Acid Derived Allenynes. A Scope and Limitation Study Directed toward the Preparation of a Tricyclic Pyrrole Library

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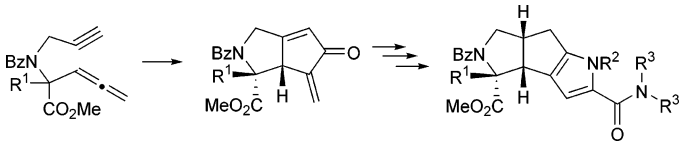

The synthesis of a novel class of tricyclic pyrroles has been accomplished by using a Pauson−Khand/Stetter/Paal−Knorr reaction sequence. Full details of the Pauson−Khand reaction of amino acid tethered allenynes **4a**−**e** and **9a**−**d** are disclosed. The study of this reaction led to the discovery of an unprecedented substituent effect on the diastereoselectivity of the $Mo(CO)_6$ mediated allenic Pauson−Khand reaction. It was found that amino acid tethered allenynes with aromatic side chains afford α-alkylidene cyclopentenones with the opposite diastereoselectivity compared to those with aliphatic side chains. This effect has been attributed to complexation of the metal mediator to the aromatic ring in the substrate. Furthermore, an isomerization of one of the diastereomers of the α-alkylidene cyclopentenones was encountered, leading to eventual decomposition. The stable diastereomers were found to react well in the Stetter reaction leading to 1,4-diketones that were converted to pyrroles. The observation that the first generation of 2-alkyl-substituted pyrroles was unstable led to a second generation of 2-carboxamide pyrroles with sufficient stability for biological tests which are in progress.

Introduction

Diversity oriented synthesis (DOS) constitutes a powerful concept for synthesizing collections of small molecules that will impact research, either as biological tools or pharmacological agents.[1] The DOS approach used most frequently involves sequential reactions whereby substructures are incorporated into scaffolds of growing complexity, thereby creating diversity. An alternative and less common approach involves the construction of a pivotal compound that, when subjected to the appropriate reagents or catalysts, can give new, structurally distinct products. Nature has made extensive use of this latter diversification strategy, for example, by enzyme-catalyzed construction of the various sesquiterpene carbon skeletons of secondary metabolites from one common precursor, farnesyl pyrophosphate. Transition metal catalyzed processes are ideal for these reagent-controlled diversification strategies, since seemingly small changes in the reaction conditions or catalyst can lead to remarkable changes in the bonds formed and broken during the synthetic transformation.

Recently we have communicated our results pertaining to the scope and limitations of converting a common intermediate **A** to three heterocyclic scaffolds **B**, **C**, and **D** by changing only the transition metal catalyst (Scheme 1).[2] In short, 15 common intermediates were synthesized in an effort to establish the effect of the substrate specificity on the course of the transition metal catalyzed reactions. The results were very encouraging with most common intermediates affording good yields of the cross-conjugated triene **B**,[3] 4-alkylidene cyclopentenone **C**,[4] or α-alkylidene cyclopentenone **D**.[5] While the compounds generated thus far are novel and will be tested for biological activity, it is the unique reactivity profile of

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(1) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(2) Brummond, K. M.; Mitasev, B. *Org. Lett*. **2004**, *6*, 2245.

(3) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc*. **2002**, *124*, 15186.

(4) Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J. *Org. Lett.* **2002**, *11*, 1931

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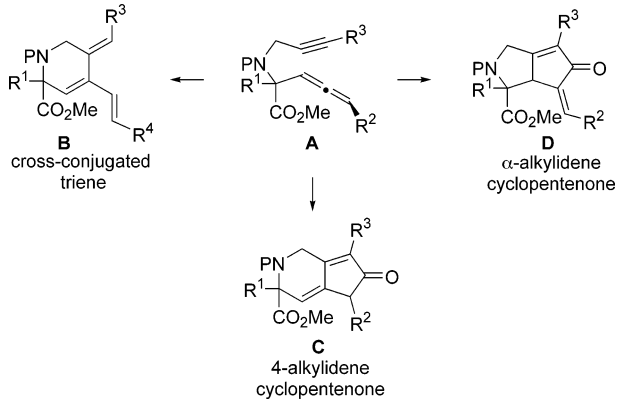
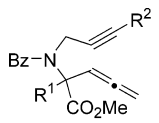
SCHEME 1. Diversification of Allenyne A by Changing Only the Catalyst



each scaffold (cross-conjugated triene, 4-alkylidene cyclopentenone, α-alkylidene cyclopentenone) and its potential to be differentially functionalized that is deemed the most valuable feature of this approach. The subsequent diversification of each scaffold enhances the size and the diversity of the small molecule libraries that can be synthesized, and the approach therefore follows the "libraries from libraries" principle originally introduced by Houghten et al. and used by others.[6]

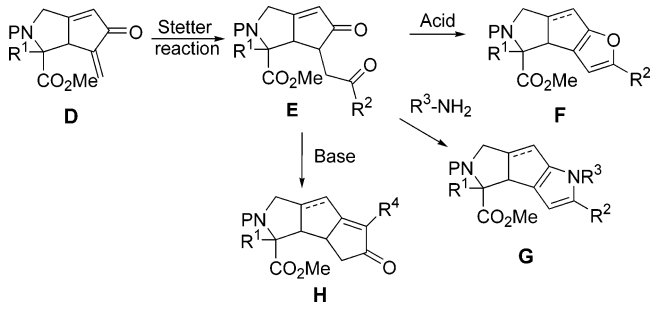
In this report, results obtained during our efforts to diversify scaffold **D**, the α-alkylidene cyclopentenone, are discussed. Moreover, complete details describing the conversion of the common intermediate **A** to α-alkylidene cyclopentenones are presented. The most enticing characteristic of scaffold **D** is the exocyclic double bond of the cross-conjugated enone, which can be used in various Michael-type additions. Specifically, umpolung addition of an aldehyde to **D** via a Stetter[7] reaction would yield a 1,4-diketone moiety **E**. This 1,4-dicarbonyl moiety can be transformed to furan **F** or pyrrole **G** via a Paal–Knorr synthesis or enone **H** depending on the reaction conditions used (Scheme 2). We were motivated to first examine the formation of pyrrole **G** for three reasons: (1) multicomponent processes involving a Stetter/Paal–Knorr reaction sequence have been utilized previously for the synthesis of functionalized pyrroles;[8] (2) an additional diversification site could be easily introduced by the preparation of pyrrole **G** by using a variety of amines (R^3-NH_2); and (3) a plethora of biologically interesting compounds possess pyrroles as part of their



4a R^1 = Bn, R^2 = Me
4b R^1 = Bn, R^2 = H
4c R^1 = Me, R^2 = Me
4d R^1 = Me, R^2 = H
4e R^1 = iBu, R^2 = H

FIGURE 1. Amino acid-derived allenynes **4a–e**.

SCHEME 2. Diversification Potential of 1,4-Dicarbonyl Compounds Derived from D



substructure.[9] Thus, these compounds are likely to be useful as biological probes.

Results and Discussion

We therefore set out to examine the scope and limitations of this diversification strategy for the preparation of a collection of pyrroles. Initially, allenynes of three different amino acids were prepared (Figure 1): one containing an aromatic residue in the side chain (phenylalanine **4a** and **4b**) and two containing an aliphatic side chain (alanine **4c** and **4d** and leucine **4e**). Alanine- and phenylalanine-derived allenynes were prepared either with a terminal alkyne (**4b**, **4d**) or a methyl-substituted alkyne (**4a**, **4c**). The syntheses of all compounds but **4e** have been reported previously, and **4e** was synthesized in an analogous manner.[2]

Pauson–Khand Reaction. With these allenynes in hand, we next examined the Pauson–Khand reaction to effect formation of the α-alkylidene cyclopentenones. We were interested in both the regioselectivity and diastereoselectivity of this transformation under the standard $Mo(CO)_6$ conditions used by our group for effecting allenic Pauson–Khand reactions. When phenylalanine-derived allenynes were submitted to the standard Pauson–Khand conditions, the reaction proceeded in high yield to give a mixture of products whose composition could be easily determined by integration of the olefinic resonances in the ^{1}H NMR spectrum of the crude reaction

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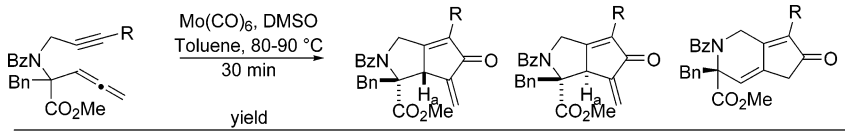
TABLE 1. Pauson−Khand Reaction of Phenylalanine-Derived Allenynes 4a and 4b

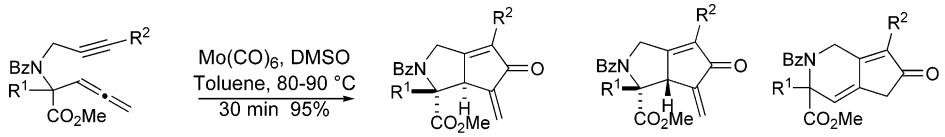


	yield			
4a R = Me	79%	**5a** 58%	**6a** 9%	**7a** 12%
4b R = H	94%	**5b** 57%	**6b** 19%	**7b** 15%

[a] (**5a**+**6a**):**7a** = 5.7 : 1, **5a** : **6a** = 6.4 : 1 (**5b**+**6b**):**7b** = 5 : 1, **5b** : **6b** = 3 : 1

[a] Ratios determined by integration of the olefinic resonances in the ^{1}H NMR spectrum.

TABLE 2. Pauson−Khand Reaction of Alanine- and Leucine-Derived Allenynes



4c R^1 = Me, R^2 = Me	**5c** 81%	**6c** 8%	**7c** 6%
4d R^1 = Me, R^2 = H	**5d** 82%	**6d** 7%	**7d** 6%
4e R^1 = iBu, R^2 = H	**5e** 74%	**6e** 14%	**7e** 7%

[a] (**5c**+**6c**) : **7c**=14 : 1, **5c** : **6c**=10 : 1; (**5d**+**6d**) : **7d**=14 : 1, **5d** : **6d**=11 : 1; (**5e**+**6e**) : **7e**=12 : 1, **5e** : **6e**=5.3 : 1

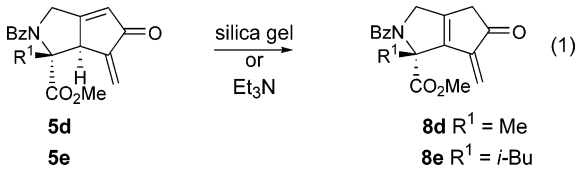
[a] Ratios determined by integration of the olefinic resonances in the ^{1}H NMR spectra.

mixture. In both reactions, the major diastereomers **5a** and **5b** could be easily separated by column chromatography from the remaining two components (the minor diastereomers **6a** and **6b** and the [6−5] products **7a** and **7b**, respectively) that coeluted.

The relative configuration of the major diastereomer **5b** was determined by X-ray crystallography, showing the benzyl group and H_a to reside in a syn orientation. On the basis of an X-ray crystal structure of compound **15** (vide infra) this is also the configuration of the major diastereomer in the reaction of **4a**.

Next, we examined the Pauson−Khand reaction of the three allenynes possessing aliphatic side chains. A dramatic increase in the regioselectivity was observed showing a preference for reaction at the internal double bond (12−14:1 versus 5−6:1; compare Tables 1 and 2). Moreover, the diastereoselectivities were substantially higher especially for substrates **4c** and **4d** (compared to **4a** and **4b**).

When the products from the Pauson−Khand reaction of **4d** and **4e** were applied to silica gel, a new compound was isolated and determined to be **8d** and **8e** based on ^{1}H NMR, ^{13}C NMR, dept, and MS (eq 1). Further studies revealed that **8d** and **8e** resulted from isomerization of **5d** and **5e**, respectively.[10] Unfortunately, compounds **8d** and **8e** were unstable and decomposed upon storage in solution.



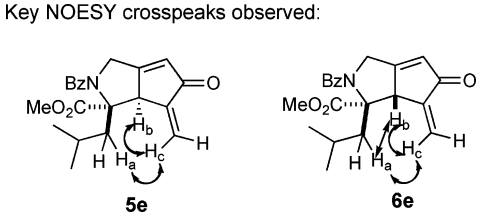
5d
5e

8d R^1 = Me
8e R^1 = *i*-Bu

(1)

Since the phenylalanine-derived Pauson−Khand product **5b** (Table 1) did not isomerize under basic or silica gel conditions, we became suspicious that the aryl- and alkyl-derived substrates may be affording opposite diastereoselectivity. NOESY study of the two diastereomers in the leucine case (**5e** and **6e**) revealed this to be true (Scheme 3). The major diastereomer (**5e**) of this reaction is the one where the ester functionality and the ring fusion hydrogen H_b are on the same side of the ring.

SCHEME 3. Stereochemical Assignment of the Pauson−Khand Products from Table 2



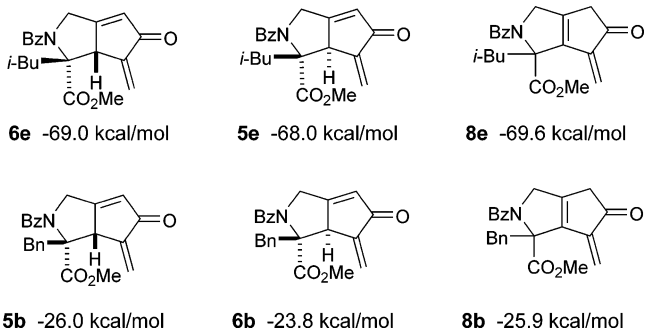
5e **6e**

Similar observations were made in the alanine case **5d**, so it is predicted based upon these examples that all aliphatic amino acids will give product **5** as the major diastereomer and **6** as the minor diastereomer.[11] The facile isomerization of diastereomers **5d**, **5e** and **6b** may result from the methyl ester carbonyl functionality serving as an internal Lewis base assisting in the deprotonation of the ring fusion proton. Compounds **5c** and **6c**, where R^2 = Me, did not isomerize under any of these conditions. In the case of **5c** and **6c** the double bond is already tetrasubstituted, which may account for this

(10) Isomerization of the enones was prevented by using 1% acetic acid in the eluting solvent during column chromatography on silica gel. In this way pure enones were obtained and then re-adsorbed onto silica gel. Diastereomers **5d** and **5e** isomerized completely within 1 h and diastereomers **6d** and **6e** did not isomerize. Exposure of **5d**, **6d**, **5e**, and **6e** to triethylamine led to rapid isomerization of **5d** and **5e**, but negligible isomerization of **6d** and **6e**. For similar base-promoted isomerizations see: Areces, P.; Duran, A. M.; Plumet, J.; Hursthouse, M. B.; Light, M. E. *J. Org. Chem.* **2002**, *67*, 3506.

(11) Another substrate derived from norvaline (R^1 = *n*-Bu) was shown to give the same diastereoselectivity as alanine and leucine (communication from Stefan Fischer, Curran group).

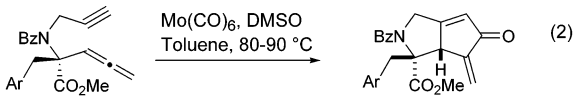
SCHEME 4. Ab Initio Energy Calculations of the α-Methylene Cyclopentenones



observation. The phenylalanine-derived cyclopentenones **5a** and **6a** did not isomerize.

Ab initio calculations were performed to compare the energy differences between the diastereomeric α-methylene cyclopentenones and the new dienones **8**. It was found that the transformations of both **5e** to **8e** and **6b** to **8b** are energetically favorable. However, when comparing the energies of **6e** to **8e** and **5b** to **8b**, these are nearly isoenergetic (Scheme 4).[12] These calculations are consistent with the observed results.

To determine whether the diastereoselectivity of the Pauson−Khand reaction could be increased, other aromatic amino acid-derived substrates were synthesized bearing a *p*-OMe-phenyl, *p*-F-phenyl, 2-thienyl, and 3-*N*-Boc-indolyl moieties. These aromatic groups were chosen to provide an electron-donating group, an electron-withdrawing group, and two heterocyclic aromatic groups, respectively (**9a**−**d**).



9a	**10a** Ar = *p*-OMe-Ph 42% dr = 2.3 : 1[a]
9b	**10b** Ar = *p*-F-Ph 40% dr = 2 : 1[b]
9c	**10c** Ar = 2-thienyl 39% dr = 2 : 1[a]
9d	**10d** Ar = 3-*N*-Boc-indolyl 45%, dr = 2.7 : 1[c]

[a] yield of mixture 95%; [b] yield of mixture 76%, yield of major diastereomer determined by NMR; [c] yield of mixture 77%, yield of major diastereomer determined by NMR.

Interestingly, the Pauson−Khand reaction of all four substrates (**9a**−**d**) gave nearly the same diastereomeric ratios as the phenylalanine case (**4b**) (eq 2). Again, isomerization of the major diastereomers was not observed, whereas the minor diastereomers isomerized upon standing neat at room temperature.

Thus, for the aromatic amino acids the opposite isomers are favored for the Pauson−Khand reaction, giving diastereomeric ratios in the range of 2−3:1 compared to the aliphatic amino acids which give dr values of 1:5−11. We speculate that this interesting reversal in diastereoselectivity can be attributed to complexation of the aromatic ring from the side chain with the transition

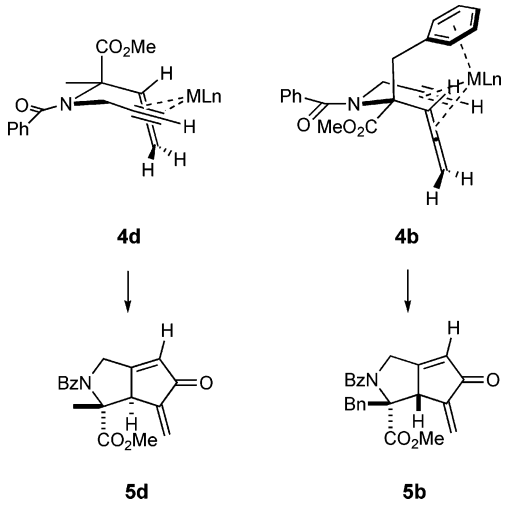
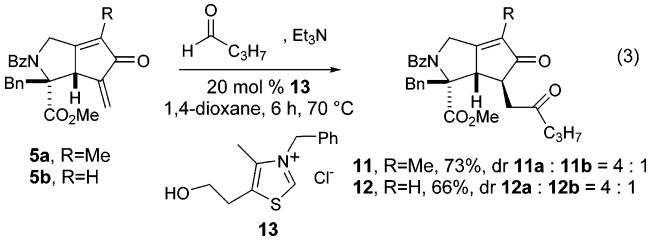


FIGURE 2. Arene complexation model explaining the diastereoselectivity in the Pauson−Khand reaction.

metal as shown in **4b**, Figure 2. Whereas in the case of the aliphatic side chain, the aliphatic group resides preferentially in the pseudoequatorial position (**4d**, Figure 2).

Stetter Reaction. Next, conversion of the α-methylene cyclopentenones to 1,4-dicarbonyl compounds was examined by using a Stetter reaction protocol reported by Tius.[13] Diversifications were performed only with phenylalanine-derived α-methylene cyclopentenones **5a** and **5b** since the major diastereomers **5d** and **5e** (from the alanine- and leucine-derived substrates, respectively) isomerized under basic conditions needed for the Stetter reaction.[14] Exposure of **5a** to butyraldehyde, Et_3N, and thiazolium salt **13** in 1,4-dioxane for 6 h at 70 °C resulted in the Stetter product **11** in 73% yield as a 4:1 mixture of diastereomers (eq 3).[15] The relative configuration of **11a** was subsequently assigned by X-ray crystallography of the reduced product (**15**, eq 5). The major diastereomer is depicted in eq 3. Cyclopentenone **5b** was also submitted to the same reaction conditions to give a 66% yield of product **12** with the same diastereoselectivity.



A single attempt to convert **11a** to a pyrrole by using a Paal−Knorr protocol was unsuccessful (eq 4).[16] The reversibility of the pyrrole forming reaction and the

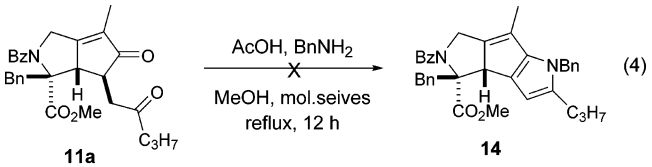
(12) Calculations were performed with MacSpartan Pro 1.0.4. First, a conformational search with MMFF94 calculation was performed, followed by a geometry optimization with a semiempirical program RHF/AM1.

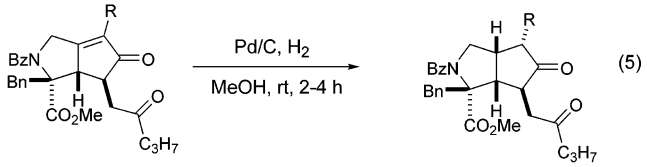
(13) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509.

(14) Treatment of **5e** and **5d** to the Stetter reaction conditions resulted mainly in decomposition and very low yields of 1,4-diketone.

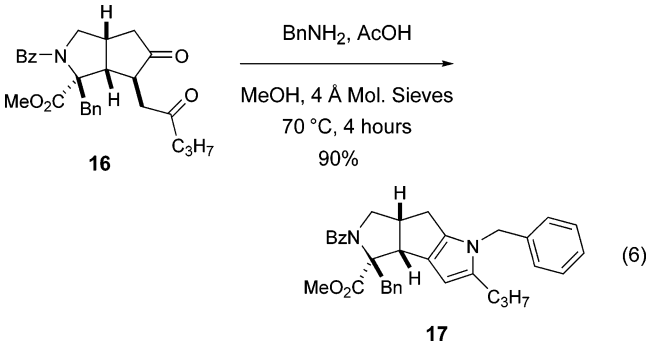
(15) This ratio was confirmed to be kinetic by an experiment where a 3:1.7 mixture of starting material and minor diastereomer **11b** was submitted to the reaction conditions. The observed diastereomeric ratio after the reaction was approximately 1:1. The ratio expected based on a complete conversion of the starting material to products and no decomposition would also be 1:1.

strained nature of product **14** was deemed problematic, so reduction of the double bond in **11a** was effected to alleviate strain. Reduction of cyclopentenones **11a** and **12a** gave single diastereomers of cyclopentanones **15** and **16** (eq 5). The structure and relative stereochemistry of **15** was confirmed by X-ray crystallography.



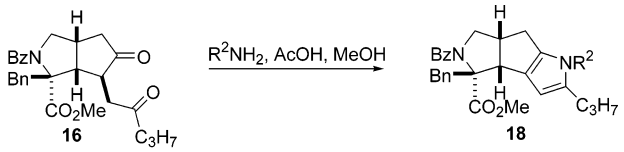


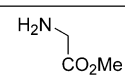
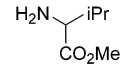
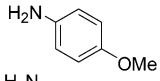
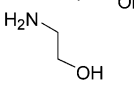
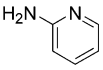
The success of this reduction was highly dependent on the purity of the starting enone; presumably sulfur-containing impurities from the Stetter reaction can poison the palladium catalyst. When **16** was treated with benzylamine and AcOH in methanol in the presence of molecular sieves at 70 °C, it afforded tricyclic *N*-benzyl pyrrole **17** in 90% yield (eq 6).



Other amines were tested in this pyrrole-forming reaction to determine its scope, and the results are shown in Table 3. We first attempted the reaction with an amino acid derivative, since incorporation of a second amino acid would be an interesting diversification feature. The soluble glycine-methyl ester hydrochloride participated in the reaction and gave pyrrole **18a** in 70% yield (Table 3, entry 1) but the more sterically hindered valine methyl ester failed to participate under the same reaction conditions (Table 3, entry 2). Next the aromatic amine anisidine was used (Table 3, entry 3) and the reaction proceeded to give **18c** in 85% yield. Similarly, ethanolamine gave **18d** in 76% yield (Table 3, entry 4). Finally, 2-aminopyridine gave none of the desired product (Table 3, entry 5). Based upon this small sampling of amines, aliphatic amines of type H_2N-CH_2-R are the best substrates for the pyrrole formation since substitution next to the amine results in complete recovery of the starting material. Of the two aromatic amines tested, electron-rich *p*-anisidine was an excellent substrate for the pyrrole formation and 2-aminopyridine was unreactive, which can be attributed to the presence of a second basic nitrogen in the molecule proximal to the reactive primary amine.

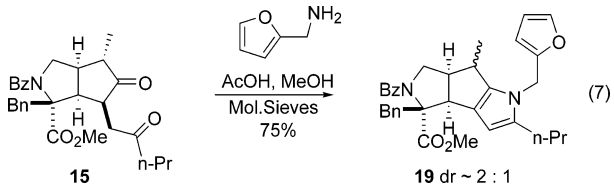
TABLE 3. Preparation of Tricyclic Pyrroles from 16



Entry	Amine	Temp.	Time(h)	Product	Yield (%)
1		70 °C	4	**18a**	70[a]
2		70 °C	4	**18b**	No reaction[a]
3		60 °C	2	**18c**	85[a]
4		70 °C	1	**18d**	76[b]
5		70 °C	4	**18e**	No reaction[a]

[a] R^2NH_2 (5 equiv), AcOH (5 equiv). [b] R^2NH_2 (10 equiv), AcOH (8 equiv).

Reaction of a single diastereomer of the methyl-substituted diketone **15** with furfurylamine gave pyrrole **19** in 75% yield, unfortunately as a mixture of two diastereomers in 2:1 ratio (eq 7). The diastereomers resulted from epimerization of the stereocenter bearing the methyl group.



Based upon these exploratory studies, a protocol was developed to form a small library of pyrroles from a single diastereomer of 1,4-diketone **20**. Heating **20** to 140 °C in toluene, in the presence of amine and excess acetic acid, afforded the desired pyrroles (Table 4). Upon completion of the reaction, the excess amine was scavenged from the reaction mixture with polymer-bound sulfonic acid resin,[17] and the crude reaction mixtures were purified by semi-preparative HPLC. As expected all compounds were obtained as mixtures of diastereomers due to epimerization of the methyl-bearing stereocenter.

(16) **11a** was treated with AcOH (excess) and 3 equiv of benzylamine in refluxing methanol in the presence of molecular sieves. After 12 h, the reaction afforded a mixture of unidentifiable compounds with mostly recovered starting material (eq 4).

(17) Resin was purchased from Novabiochem. Smith, R. A.; Bhargava, A.; Browe, C.; Chen, J.; Dumas, J.; Hatoum-Mokdad, H.; Romero, R. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2951.

SCHEME 5. Addition of Glyoxylamides to 5b and Reduction of the Double Bond

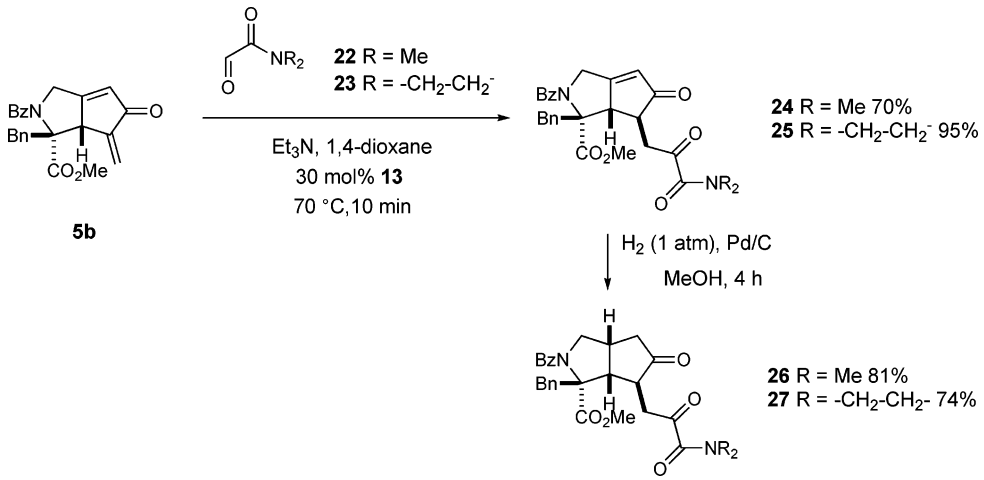
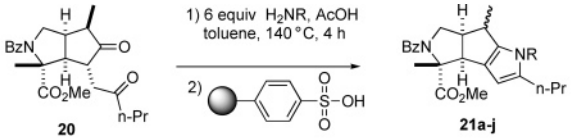
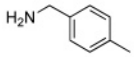
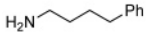
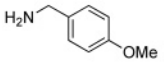
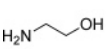
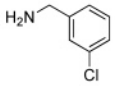
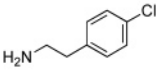
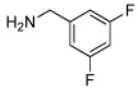
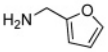


TABLE 4. Preparation of a Collection of Pyrroles from 20 with Use of an Amine Scavenger Protocol

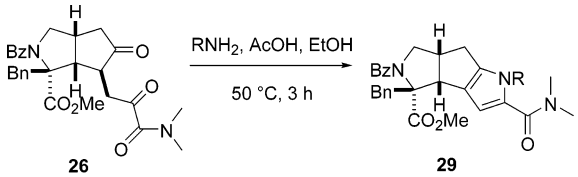


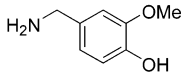
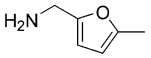
amine	product	yield	amine	product	yield
	**21a**	76%		**21g**	87%
	**21b**	72%		**21h**	77%
	**21c**	81%			
	**21d**	63%		**21i**	64%
	**21e**	85%		**21j**	63%
	**21f**	69%			

Unfortunately, compounds **18a**,**c**,**d** and **21a**−**j** decomposed when stored neat or open to the atmosphere, rendering them undesirable for biological assays. Stabilizing the pyrrole moiety with an acyl substituent had potential since this group could be introduced via the Stetter reaction by 1,4-addition of a glyoxylamide.[18] Two glyoxylamides, dimethylamine (**22**) and pyrrolidine (**23**), were prepared.[19] These highly electrophilic aldehydes both participated in the Stetter reaction under the same conditions affording the products in 10 min as single diastereomers (Scheme 5). After Stetter's original report in 1987, there are no examples in the literature utilizing this 1,4-addition of glyoxylamides. This reaction is a viable entry into the α-keto-amide moiety that is both synthetically useful[20] and present in biologically active molecules.[21]

Next, the double bonds of enones **24** and **25** were reduced giving **26** and **27** in 81% and 74% yield, respectively. A slightly modified protocol for pyrrole formation was developed with use of 3 equiv of the amine, excess acetic acid, and EtOH as solvent. Heating at 50 °C for 2−3 h generally gave complete conversion to pyrroles **28**, which were isolated following an acidic workup and short column chromatography purification (Table 5). To our knowledge, the resulting pyrrole-2-carboxamide moiety has not been previously synthesized directly via a Paal−Knorr synthesis.[22]

Two pyrroles were also prepared from diketone **26** by using the same conditions (eq 8).

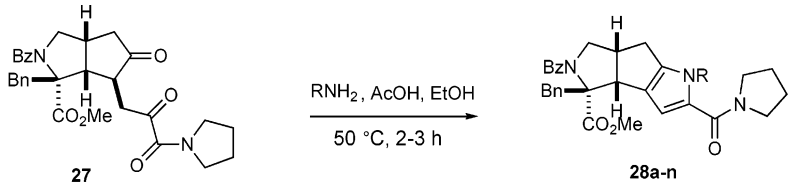


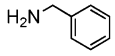
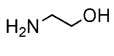
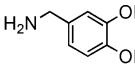
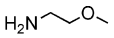
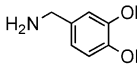
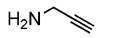
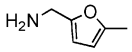
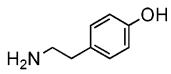
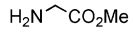
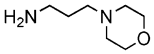
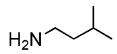
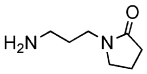
amine	product	yield
	**29a**	36%
	**29b**	70%

The most suitable aliphatic amines for the Paal−Knorr reaction do not have branching at the position α to the amine since cyclohexylamine failed to give any product. When 2,2,2-trifluoroethylamine and isobutylamine were used, the reaction rate was significantly retarded, and in both cases the reaction failed to go to completion.

(18) Stetter, H.; Skobel, H. *Chem. Ber*. **1987**, *120*, 643.
(19) Suzuki, M.; Kimura, Y.; Terashima, S. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 3559.
(20) (a) Aoyama, H.; Hasegawa, T.; Watanabe, M.; Shiraishi, H.; Omote, Y. *J. Org. Chem*. **1978**, *43*, 419. (b) Hashizume, D.; Kogo, H.; Sekine, A.; Ohashi, Y.; Miyamoto, H.; Toda, F. *J. Chem. Soc., Perkin Trans. 2* **1996**, 61. (c) Youn, S. W.; Kim, Y. H.; Hwang, J.-W.; Do, Y. *Chem. Commun*. **2001**, 996.
(21) (a) Wada, C. K.; Frey, R. R.; Ji, Z.; Curtin, M. L.; Garland, R. B.; Holms, J. H.; Li, J.; Pease, L. J.; Guo, J.; Glaser, K. B.; Marcotte, P. A.; Richardson, P. L.; Murphy, S. S.; Bouska, J. J.; Tapang, P.; Magoc, T. J.; Albert, D. H.; Davidsen, S. K.; Michaelides, M. R. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3331. (b) Wasserman, H. H.; Petersen, A. K.; Xia, M. *Tetrahedron* **2003**, *59*, 6771. (c) Otto, H. H.; Schirmeister, T. *Chem. Rev*. **1997**, *97*, 133. (d) Han, W.; Hu, Z.; Jiang, X.; Decicco, C. P. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 711.
(22) (a) Meth-Cohn, O.; Wang, M.-X. *Tetrahedron Lett*. **1995**, *36*, 9561. (b) Jousseaume, B.; Kwon, H.; Verlhac, J.-B.; Denat, F.; Dubac, J. *Synlett* **1993**, 117. (c) Martyn, D. C.; Vernall, A. J.; Clark, B. M.; Abell, A. D. *Org. Biomol. Chem*. **2003**, *1*, 2103.

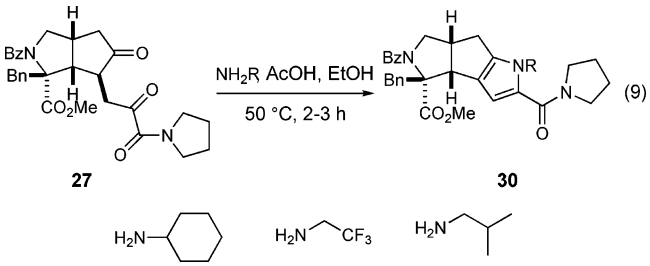
TABLE 5. Preparation of a Small Library of Acyl Pyrroles from 27[a]



amine	product	yield	amine	product	yield
	**28a**	80%		**28h**	80%
	**28b**	88%		**28i**	93%
	**28c**	72%		**28j**	89%
	**28d**	85%		**28k**	69%
	**28e**	63%		**28l**	79%
	**28f**	39%		**28m**	95%
	**28g**	81%	NH_3	**28n**	64%

[a] Conditions: R-NH_2 (3 equiv), AcOH (excess).

Increased heating drives the reaction further but results in the formation of impurities (eq 9).



To determine whether the newly formed acyl pyrroles **28a**−**n** are more stable than the alkyl pyrroles as postulated, we performed an NMR experiment where an alkyl and acyl pyrrole of benzylamine were placed in an NMR tube together with a standard (*p*-phthalic acid ethyl ester) in d_6-DMSO. The sample was kept at room temperature in a sealed NMR tube. Monitoring of the ^{1}H NMR of the sample over a period of 60 days revealed that the alkyl pyrrole had been reduced to half of its initial amount, whereas the acyl pyrrole remained virtually unchanged.

Conclusions

We have developed a concise route to novel tricyclic pyrroles using a Pauson−Khand, Stetter, Paal−Knorr reaction sequence. The final compounds are obtained as single diastereomers by chromatographic separation of the diastereomeric Pauson−Khand adducts. Three diversification elements (amino acid, aldehyde, amine) were easily incorporated into the reaction sequence. Interestingly, the amino acid diversification element led to an unprecedented substituent effect on the diastereoselectivity of the Pauson−Khand reaction. Glyoxylamides participate in the Stetter reaction with α-methylene cyclopentenones to provide α-keto amides stereoselectively, which are converted into pyrrole-2-carboxamides. This reaction sequence provides a direct route to a novel class of pyrroles. Finally, the protocols used to synthesize these pyrroles are currently in the hands of the staff within the University of Pittsburgh Chemical Methodologies and Library Development Center (UPCMLD). The robustness of the chemistry is highlighted by the Center's preparation of 179 unique acyl pyrroles (∼20 mg each) in less than 10 weeks.[23] The compounds are currently being evaluated for biological activity.

Experimental Section

$Mo(CO)_6$-Mediated Pauson−Khand Reaction (General Procedure D). To a solution of the allenyne (0.3 mmol) in toluene (3 mL) in a 10-mL round-bottomed flask was added DMSO (1.5−3.0 mmol)[24] followed by $Mo(CO)_6$ (0.37 mmol) at room temperature under N_2 atmosphere. The flask was equipped with a reflux condenser and heated slowly to 80−90 °C in an oil bath. Stirring was continued at this temperature until TLC analysis showed the absence of starting material. Upon completion of the reaction, the volume of the mixture

(23) Werner, S.; Coleman, C. M.; Fodor, M. D.; Iyer, P. S.; Mitasev, B.; Twining, L. A.; Brummond, K. M. Manuscript in preparation.
(24) See individual compounds for details.

was reduced to 1 mL under vacuum and the brown liquid mixture directly applied to a silica gel column pretreated with a solvent system hexanes−EtOAc 20:1 v/v (1% AcOH) and purified with gradient elution (hexanes−EtOAc 20:1 to 1:1 v/v (1% AcOH)). Product ratios were determined by integration of the olefinic peaks in the ^{1}H NMR taken after complete removal of all volatiles from a small reaction sample.

Pauson−Khand Reaction of 4b. General procedure D was followed for the molybdenum-mediated allenic Pauson−Khand reaction with 2-(benzoylprop-2-ynylamino)-2-benzylhexa-3,4-dienoic acid methyl ester **4b** (360 mg, 1.0 mmol), DMSO (355 μL, 5.0 mmol), and $Mo(CO)_6$ (330 mg, 1.25 mmol). The reaction was heated to 90 °C for 20 min and the crude mixture was purified by flash chromatography (gradient elution, hexanes−EtOAc, 19:1 to 1:1, v/v (1% AcOH)). The yield of crude mixture was 365 mg (94%) consisting of **5b** (57%), **6b** (19%), and **7b** (15%). Due to isomerization of **6b** to **8b**, only **8b** was characterized.

2-Benzoyl-1-benzyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[*c*]pyrrole-1-carboxylic acid methyl ester (5b): 224 mg, 57%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.27 (m, 10H), 6.19 (s, 1H), 6.07 (s, 1H), 5.63 (s, 1H), 4.24 (1/2 AB, J = 14.9 Hz, 1H), 4.23 (1/2 AB, J = 14.2 Hz, 1H), 4.03 (1/2 AB, J = 15.0 Hz, 1H), 3.98 (s, 1H), 3.62 (s, 3H), 3.39 (1/2 AB, J = 14.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 170.9, 170.2, 170.1, 140.6, 135.7, 135.5, 131.1, 128.6, 128.5, 127.3, 126.2, 118.0, 70.8, 52.3, 51.5, 50.9, 37.7; IR (thin film) 3027, 1741, 1710, 1641, 1383 cm^{-1}; MS *m/z* (%) 387 (15), 328 (10), 282 (22), 105 (100); EI-HRMS calcd for $C_{24}H_{21}NO_4$ *m/z* [M$^+$] 387.1471, found 387.1470.

2-Benzoyl-3-benzyl-6-oxo-2,3,5,6-tetrahydro-1*H*-[2]pyrindine-3-carboxylic acid methyl ester (7b): 58 mg, 15%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.41 (m, 3H), 7.34−7.27 (m, 5H), 7.21−7.17 (m, 2H), 5.90 (s, 1H), 5.70 (s, 1H), 4.39 (1/2 AB, J = 18.1 Hz, 1H), 4.15 (1/2 AB, J = 13.8 Hz, 1H), 3.81 (s, 3H), 3.38 (1/2 AB, J = 13.8 Hz, 1H), 3.05 (s, 2H), 3.01 (1/2 AB, J = 18.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 171.3, 171.1, 161.1, 135.8, 135.4, 135.2, 130.3, 129.9, 128.7, 128.3, 127.4, 127.2, 126.3, 123.5, 65.9, 53.0, 45.1, 39.6, 37.7; IR (thin film) 2950, 1740, 1710, 1643, 1391 cm^{-1}; MS *m/z* (%) 387 (47), 356 (15), 328 (12), 296 (30), 105 (100); EI-HRMS calcd for $C_{24}H_{21}NO_4$ *m/z* [M$^+$] 387.1471, found 387.1489.

2-Benzoyl-1-benzyl-6-methylene-5-oxo-1,2,3,4,5,6-hexahydrocyclopenta[*c*]pyrrole-1-carboxylic acid methyl ester (8b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.35 (m, 5H), 7.27−7.25 (m, 3H), 7.11−7.08 (m, 2H), 5.94 (s, 1H), 5.58 (s, 1H), 4.08 (d, J = 15.7 Hz, 1H), 4.04 (d, J = 13.8 Hz, 1H), 3.84 (s, 3H), 3.56−3.52 (m, 2H), 2.85 (d, J = 22.5 Hz, 1H), 2.70 (d, J = 22.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 170.1, 169.2, 145.2, 142.5, 138.5, 136.2, 136.1, 130.1, 128.5, 127.9, 127.0, 126.4, 112.6, 74.3, 55.1, 52.9, 38.4, 36.2; IR (thin film) 2950, 1743, 1631, 1405, 1253 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{21}NO_4Na$ *m/z* [M + 23$^+$] 410.1368, found 410.1375.

Preparation of Compounds 11, 12, 24, and 25 (General Procedure E for the Stetter Reaction). To a solution of cyclopentenone (0.3 mmol) in 1,4-dioxane (2 mL) was added Et_3N (0.9 mmol), aldehyde (1.5 mmol), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (0.06 mmol). The reaction vessel was sealed with a rubber septum and heated to 70 °C (6 h for compounds **11** and **12**; 10 min for compounds **24** and **25**). The reaction mixture was then poured into water (50 mL), and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. Purification procedure for compounds **11** and **12**: Hexanes (5 mL) was added and a white precipitate formed. The precipitate was collected by decantation and purified by flash chromatography (gradient elution; hexanes−EtOAc, 9:1 to 2:1, v/v) to afford the major diastereomer. The minor diastereomer remained in the decanted liquid, which could be purified by flash chromatography. Purification procedure for compounds **24** and **25**: The crude yellow oil was purified by flash chromatography (gradient elution, hexanes−EtOAc 3:1 to 0:1 v/v) to afford the product as a single diastereomer (NMR).

2-Benzoyl-1-benzyl-4-methyl-5-oxo-6-(2-oxopentyl)-1,-2,3,5,6,6a-hexahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Methyl Ester (11). **11** was prepared by following general procedure E with **5a** (163 mg, 0.403 mmol), Et_3N (42 μL, 0.30 mmol), butyraldehyde (184 μL, 2.03 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (22 mg, 0.080 mmol), and 1,4-dioxane (2 mL). Isolated: **11a** (121 mg, 63%) and **11b** (19 mg, 10%). **11a** (major diastereomer, eluting slower, hexanes−EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.44 (m, 5H), 7.33−7.27 (m, 3H), 7.17−7.14 (m, 2H), 4.17 (d, J = 15.0 Hz, 1H), 4.10 (d, J = 14.2 Hz, 1H), 3.99 (d, J = 15.1 Hz, 1H), 3.75 (s, 3H), 3.44−3.39 (m, 1H), 3.28 (d, J = 14.2 Hz, 1H), 3.03 (dd, J = 18.4, 5.1 Hz, 1H), 2.86 (dd, J = 18.4, 3.9 Hz, 1H), 2.50 (t, J = 7.2 Hz, 2H), 2.13 (dd, J = 8.5, 4.1 Hz, 1H), 1.66 (sex, J = 7.4 Hz, 2H), 1.62 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 207.8, 171.6, 171.3, 166.0, 136.1, 136.0, 131.8, 131.2, 131.0, 128.6, 128.4, 128.3, 127.4, 127.2, 71.7, 52.4, 51.7, 50.8, 45.4, 44.5, 40.9, 37.7, 17.1, 13.7, 8.8; IR (thin film) 2953, 1740, 1719, 1687, 1638, 1390 cm^{-1}; MS *m/z* (%) 473 (7), 441 (8), 414 (17), 382 (20), 350 (18), 105 (100); EI HRMS calcd for $C_{29}H_{31}NO_5$ *m/z* [M$^+$] 473.2202, found 473.2181. **11b** (minor diastereomer, eluting faster, hexanes−EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.29 (m, 10H), 4.21 (d, J = 14.8, 1H), 4.03−3.94 (m, 2H), 3.71 (s, 3H), 3.68 (br s, 1H), 3.34−3.27 (m, 1H or ddd, J = 10.8, 7.0, 3.4), 3.11 (d, J = 14.1 Hz, 1H), 2.91 (dd, J = 19.2, 3.5 Hz, 1H), 2.52 (t, J = 7.4 Hz, 2H), 2.43 (dd, J = 19.2, 11.3 Hz, 1H), 1.73 (sex, J = 7.4 Hz, 2H), 1.62 (s, 3H), 1.00 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 208.9, 172.6, 171.6, 168.2, 136.5, 135.8, 131.6, 131.4, 131.2, 128.7, 128.2, 127.6, 127.0, 69.7, 52.4, 50.7, 49.0, 44.1, 42.0, 39.4, 36.3, 17.2, 13.8, 8.5.

2-Benzoyl-1-benzyl-6-(2,3-dioxo-3-pyrrolidin-1-yl-propyl)-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Methyl Ester (25). **25** was prepared by following general procedure E with **5b** (840 mg, 2.17 mmol), Et_3N (905 μL, 6.51 mmol), oxo-pyrrolidin-1-yl-acetaldehyde (1.38 g, 11.8 mmol), and 1,4-dioxane (20 mL). **25**: yield 1.17 g, >95%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.42 (m, 5H), 7.36−7.29 (m, 3H), 7.23−7.20 (m, 2H), 5.91 (s, 1H), 4.27 (d, J = 15.7 Hz, 1H), 4.17 (d, J = 14.3 Hz, 1H), 4.07 (d, J = 15.7 Hz, 1H), 3.82 (s, 3H), 3.66 (t, J = 6.4 Hz, 2H), 3.58 (t, J = 6.4 Hz, 2H), 3.52−3.44 (m, 2H), 3.33 (dd, J = 18.7, 5.3 Hz, 1H), 3.23 (d, J = 14.3 Hz, 1H), 2.47 (q, J = 4.7 Hz, 1H), 1.99−1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 198.2, 174.1, 171.2, 161.9, 135.6, 131.2, 131.0, 128.6, 128.4, 127.2, 123.4, 71.5, 53.2, 52.6, 51.7, 47.3, 46.4, 46.0, 37.6, 37.1, 26.3, 23.6; IR (thin film) 2952, 1716, 1638, 11447, 1384 cm^{-1}; MS *m/z* (%) 514 (13), 455 (6), 416 (17), 105 (100); EI-HRMS calcd for $C_{30}H_{30}N_2O_6$ *m/z* [M$^+$] 514.2104, found 514.2115.

Preparation of Compounds 15, 16, 26, and 27 (General Procedure F for Reduction of Enones). To a solution of the enone (2.0 mmol) in methanol (50 mL) was added Pd (10 wt % on activated carbon) (170 mg) at room temperature. The reaction was carried out in a low-pressure catalytic hydrogenation apparatus in a Pyrex centrifuge bottle. The bottle was connected to a low-pressure hydrogen tank and alternatively evacuated and filled with hydrogen three times. Hydrogen was then admitted into the system until pressure reached the designated level (1−3 atm) and the bottle was shaken for 4 h. The bottle was then evacuated and air admitted. The mixture was then filtered on a Büchner funnel through a plug of Celite, and the clear liquid was concentrated in vacuo. Purification by flash chromatography (gradient elution, hexanes−EtOAc 3:1 to 1:3 v/v) afforded the desired compound.

2-Benzoyl-1-benzyl-6-(2,3-dioxo-3-pyrrolidin-1-yl-propyl)-5-oxo-octahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Methyl Ester (27). **27** was prepared by following general procedure F with **25** (1.17 g, 2.27 mmol), Pd (10 wt % on activated carbon) (200 mg), H_2 (1 atm). **27**: yield 841 mg,

74%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.24 (m, 10H), 4.18 (d, J = 13.8 Hz, 1H), 3.86 (s, 3H), 3.65 (t, J = 6.7, 2H), 3.53 (t, J = 6.7 Hz, 2H), 3.30−3.17 (m, 3H), 3.11−3.08 (m, 2H), 2.89−2.87 (m, 2H), 2.22 (dd, J = 19.3, 8.5 Hz, 1H), 2.08−1.80 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.6, 198.1, 171.5, 169.6, 161.9, 136.9, 136.7, 130.6, 129.9, 128.5, 127.1, 126.3, 72.8, 55.4, 52.7, 52.1, 47.3, 46.5, 45.6, 39.3, 38.7, 36.1, 26.3, 23.6; IR (thin film) 2950, 1737, 1636, 1404 cm^{-1}; MS *m/z* (%) 516 (8), 485 (7), 457 (36), 425 (51), 105 (100); EI-HRMS calcd for $C_{30}H_{32}N_2O_6$ *m/z* [M$^+$] 516.2260, found 516.2255.

Preparation of Compounds 17, 18, and 19 (General Procedure G). To a solution of 1,4-dione (0.03 mmol) in methanol (0.6 mL) was added amine (0.15−0.3 mmol), AcOH (0.15−0.3 mmol), and 4 Å molecular sieves (30 mg) activated by flame drying under vacuum. The reaction mixture was stirred at 70 °C for 1 to 4 h. Upon completion, the reaction mixture was diluted with EtOAc (50 mL) and washed with 1 M HCl (2 × 20 mL). The organic layer was then dried over $MgSO_4$, and the solvents were removed in vacuo. The crude material was purified by flash chromatography (gradient elution; hexanes−EtOAc, 19:1 to 3:1, v/v) to afford the desired pyrrole.

5-Benzoyl-1,4-dibenzyl-2-propyl-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diaza-cyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17). 17 was prepared by following general procedure G with **16** (10 mg, 0.021 mmol), benzylamine (23 μL, 0.21 mmol), AcOH (12 μL, 0.21 mmol), and methanol (0.5 mL). **17**: yield 10 mg, 90%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.22 (m, 13H), 6.87 (d, J = 7.0 Hz, 2H), 5.70 (s, 1H), 4.85 (s, 2H), 4.24 (d, J = 13.6 Hz, 1H), 3.91 (d, J = 7.2 Hz, 1H), 3.71 (s, 3H), 3.37 (d, J = 13.6 Hz, 1H), 3.36−3.30 (m, 1H), 3.20−3.14 (m, 1H), 2.39 (t, J = 7.6 Hz, 2H), 2.39−2.31 (m, 1H), 2.22 (quin, J = 7.6 Hz, 1H), 2.01 (d, J = 14.5 Hz, 1H), 1.55 (sex, J = 7.6 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 169.9, 138.5, 138.0, 137.6, 137.5, 134.9, 131.2, 129.6, 128.7, 128.4, 128.2, 127.3, 126.7, 126.4, 126.1, 122.4, 73.1, 56.8, 52.9, 52.1, 48.3, 45.5, 39.4, 29.1, 28.8, 22.4, 14.1; IR (thin film) 2950, 1734, 1642, 1402 cm^{-1}; MS *m/z* (%) 532 (24), 441 (16), 250 (20), 105 (100); EI-HRMS calcd for $C_{35}H_{36}N_2O_3$ *m/z* [M$^+$] 532.2726, found 532.2724.

Preparation of Compounds 28a−n (General Procedure I). To a solution of the 1,4-dione (0.07 mmol, 1 equiv) in EtOH (0.9 mL) in a test tube was added amine (0.21 mmol, 3 equiv) followed by glacial acetic acid (90 μL) at room temperature. The test tube was then heated to 50 °C in an oil bath for 2 h when the reaction was complete (as observed by TLC). The light yellow solution was then diluted with EtOAc (20 mL) and poured into 1 M HCl (30 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the organic layers were then combined and washed again with 1 M HCl (20 mL). After drying over $MgSO_4$ and removal of the solvent in vacuo, the pale yellow residue was purified by flash chromatography (gradient elution, hexanes−EtOAc, v/v) to afford the pyrrole in high yields and purity (NMR).

5-Benzoyl-4-benzyl-1-(3-methylbutyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diaza-cyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (28m). **28m** was prepared by following general procedure I with **27** (35 mg, 0.068 mmol), 3-methylbutylamine (21 μL, 0.20 mmol), and AcOH (90 μL). **28m**: yield 36 mg, 95%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.27 (m, 10H), 4.23 (d, J = 13.5 Hz, 1H), 4.17−4.10 (m, 1H), 3.98−3.85 (m, 2H), 3.74−3.55 (m, 7H), 3.40 (d, J = 13.7 Hz, 1H), 3.37−3.30 (m, 1H), 3.21−3.15 (m, 1H), 2.53 (dd, J = 15.1, 6.9 Hz, 1H), 2.36−2.25 (m, 1H), 2.21 (d, J = 16.1 Hz, 1H), 2.01−1.85 (m, 4H), 1.50−1.45 (m, 3H), 0.85 (d, J = 5.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 169.7, 162.0, 140.3, 137.6, 137.1, 130.9, 130.6, 129.5, 129.2, 128.5, 128.3, 128.1, 126.7, 126.2, 122.1, 72.9, 56.3, 52.0, 45.4, 45.2, 40.3, 39.2, 28.5, 25.7, 22.5, 22.4; IR (thin film) 2951, 1735, 1639, 1611, 1446, 1399 cm^{-1}; MS *m/z* (%) 567 (32), 476 (41), 405 (24), 301 (61), 91 (100); EI-HRMS calcd for $C_{35}H_{41}N_3O_4$ *m/z* [M$^+$] 567.3097, found 567.3114.

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Supporting Information Available: Compounds **4a−d** have been prepared previously in our laboratories[2] and the corresponding procedures and characterization for compounds **4e** and **9a−d** prepared in an analogous manner from the corresponding amino acids are given; the Pauson−Khand reactions of **4a**, **4b**, **4c**, and **4d** have been reported previously[2] and the procedures for the preparation and characterization data (not including spectra) for compounds **21a−j** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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