Design and Synthesis of a Library of Tetracyclic Hydroazulenoisoindoles

Kay M. Brummond,*[,†] Shuli Mao,[†] Sunita N. Shinde,[§] Paul J. Johnston,[§] and Billy W. Day[†,‡]

Center for Chemical Methodologies & Library Development, Department of Chemistry, Department of Pharmaceutical Sciences, and Department of Pharmacology & Chemical Biology, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received February 13, 2009

Forty-four tetracyclic hydroazulenoisoindoles were synthesized via a tandem cyclopropanation/Cope rearrangement, followed by a Diels−Alder sequence from easily available five-membered cyclic cross-conjugated trienones. These trienones were obtained from two different routes depending upon whether R^1 and R^2 are alkyl or amino acid derived functional groups, via a rhodium(I)-catalyzed cycloisomerization reaction. To increase diversity, four maleimides and two 1,2,4-triazoline-3,5-diones were used as dienophiles in the Diels−Alder step. Several Diels−Alder adducts were further reacted under palladium-catalyzed hydrogenation conditions, leading to a diastereoselective reduction of the trisubstituted double bond. This library has demonstrated rapid access to a variety of structurally complex natural product-like compounds via stereochemical diversity and building block diversity approaches.

Introduction

The drug discovery process relies upon the continuous availability of compounds possessing novel molecular shapes;[1] however, indicators suggest a proliferation of predominantly the most common frameworks.[2] A promising solution is the realization of innovative diversity oriented synthesis (DOS) strategies for the preparation of compound libraries.[3] Inspired by the potential biological impact of an expanded chemical space,[4] we are continuing to expand our DOS strategy where a single compound can be used to access multiple scaffolds using a reagent-based differentiating pathway.[5] An excellent review by Nielsen and Schreiber gives examples demonstrating the power of this build/couple/pair (B/C/P) strategy.[6] Moreover, this strategy has been successfully implemented in a high throughput reaction discovery program designed by Porco and Beeler to isolate new chemotypes.[7] An example of this diverging strategy that we have contributed is shown in Figure 1. Allene-yne **1**, possessing an amino acid tether (P = Bz, Cbz, Boc), can be converted to: methylenecyclopenta[*c*]pyrrol-5(1*H*)-one **2** using molybdenum hexacarbonyl and DMSO, cyclopenta[*c*]pyridin-6(5*H*)-one **3** when reacted with rhodium biscarbonyl chloride dimer in a carbon monoxide atmosphere, vinyl piperidine **4** when reacted with the same rhodium catalyst but in a nitrogen atmosphere, and cyclobutenyl-[*c*]pyridine **5** by simply heating the allene-yne for 15 min at 250 °C.[8]

The reactive functionality imparted by the allene-yne in each of these scaffolds (**2**−**5**, Figure 1) is subsequently being exploited for its diversification potential with the ultimate goal of obtaining novel chemotypes that will function as biological probes. Four representative compounds from libraries that have been synthesized using these scaffolds are shown in Figure 2. Compounds **6**−**8** were realized from their respective cross-conjugated trienes and Diels−Alder reactions, and compound **9** was prepared from the alkylidenecyclopentenone scaffold **2** via a Stetter/Paal−Knorr reaction sequence.[9] To date, this novel class of polyenes has been used in transmissive Diels−Alder reactions, and while these studies have led to an array of functionally and structurally unique compounds, it was envisioned that the double bonds of this triene would be amenable to a rich variety of structural modifications. Interestingly, selective chemical reactions of trienyl-containing compounds are not well documented in the literature.

Results and Discussion

Recently, we reported on a Rh(I)-catalyzed carbocyclization reaction of an allene-*ynone* that affords 2-alkylidene-

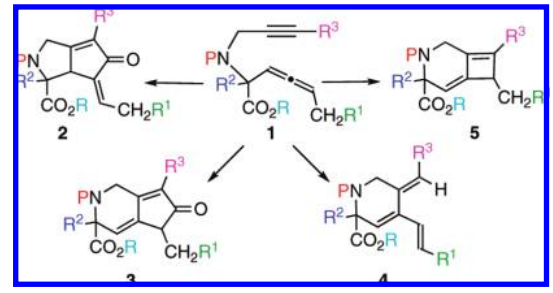


Figure 1. Reagent-based differentiating pathway.

* To whom correspondence should be addressed. E-mail: kbrummon@pitt.edu.
† Center for Chemical Methodologies & Library Development and Department of Chemistry.
§ Department of Pharmacology & Chemical Biology.
‡ Department of Pharmaceutical Sciences.

10.1021/cc900024p CCC: $40.75
Published on Web 04/14/2009

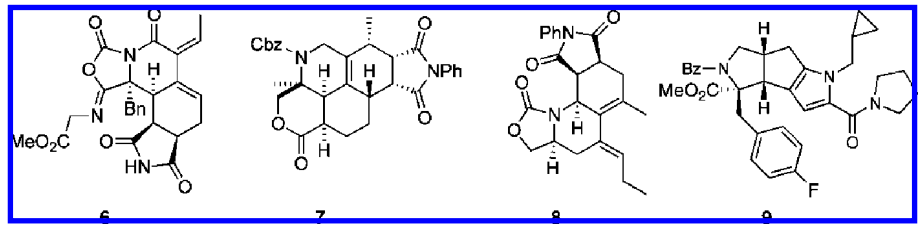
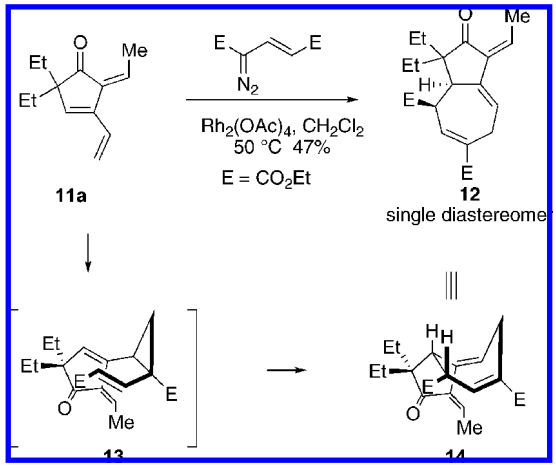
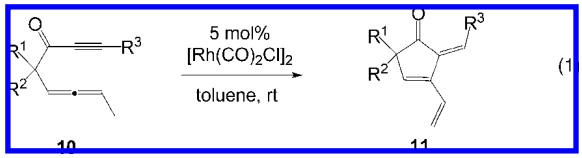


Figure 2. Novel chemotypes from triene and cyclopentenone scaffolds.

Scheme 1. Tandem Cyclopropanation/Cope Rearrangement of Trienone



3-vinylcyclopentenones (eq 1).[10] Trienones **11** were designed in an effort to introduce control elements that differentiate the reactivity of each of the double bonds. The carbocyclization reaction was particularly facile (1−2 h, rt) and tolerant of a variety of functionality (R^1 = alkyl, R^2 = alkyl, NHBz, R^3 = 2-pyridyl, aryl, alkyl, H). Moreover, the mild conditions were compatible with the ynone and trienone moieties in **10** and **11**, respectively.



Investigations concerning the selective chemical reaction of double bonds of trienone **11** then followed. After some experimentation, it was found that by using Davies chemistry and reacting trienone **11a** with *E*-diethyl-4-diazo-2-pentenedioate and Rh(II) acetate afforded the hydroazulenone **12** as single diastereomer.[11] This formal [4 + 3] cycloaddition reaction results from the selective cyclopropanation of the vinyl group of trienone **11a** by a rhodium-stabilized carbene affording mainly the *cis*-divinylcyclopropane and a minor amount of the *trans*-divinylcyclopropane (not shown). The *cis*-divinylcyclopropane then undergoes a strain driven Cope rearrangement to afford the seven-membered ring of **12**. Meanwhile, the *trans*-divinylcyclopropane is recovered.

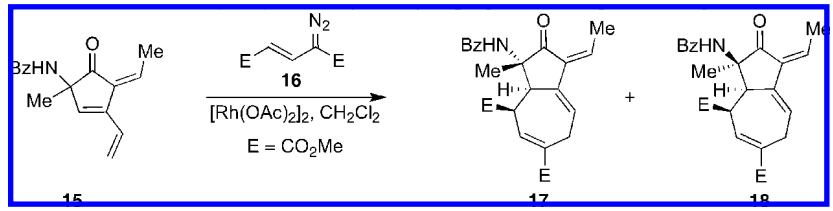
On the basis of the ease in which trienones **11** can be prepared, the stereospecificity of the tandem cyclopropanation/Cope rearrangement, and the novelty of scaffold **12**, we concluded that these compounds would be ideal for the preparation of a library (vide infra). Feasibility studies to determine the compatibility of the benzamide containing trienones to the rhodium-catalyzed cyclopropanation reaction commenced. We chose this series of trienones to optimize the reaction sequence due to the stability of the trienone **15** (white solid, stable on benchtop for months), the additional heteroatom in the rearrangement product and to examine the diastereoselectivity of the tandem process (Scheme 2).

A preliminary screening of solvents showed CH_2Cl_2 to be the solvent of choice because of the solubility of trienone **15**. In addition, it was found that better yields were obtained if trienone **15** and *E*-dimethyl-4-diazo-2-pentenedioate (**16**) were freshly prepared. Initially, the diazo species **16** was used as the limiting reagent; however, the yield was low, presumably because of dimerization of reactive vinylcarbenoid (entries 1 and 2, Table 1). Next, trienone **15** was used as the limiting reagent and 1.2 equiv of **16** were added, but trienone **15** was not completely consumed (entry 3). The addition of an additional 1.2 equiv of **16** gave a low yield of **17** (28%). Because of this, 1.5 equiv of **16** were added at the beginning of the reaction to give a 38% yield of **17** (entry 4) and for the first time diastereomer **18** was obtained in an 11% yield. Increasing the catalyst loading to 10 mol % and the equivalents of **16** to two gave **17** and **18** in 41% and 31% yield, respectively (entry 5). Increasing the scale of the reaction 3-fold had little effect on the yield and diastereomeric ratio of the products (compare entries 5 and 6). Alternatively, 2.5 equiv of **16** gave only a 43% combined yield of **17** and **18** (entry 7). The diastereomers were separated by flash silica gel chromatography and the stereochemistry of each was confirmed later by X-ray analysis (vide infra). The poor diastereoselectivity can be explained by the little steric difference between a methyl and a benzamide group.

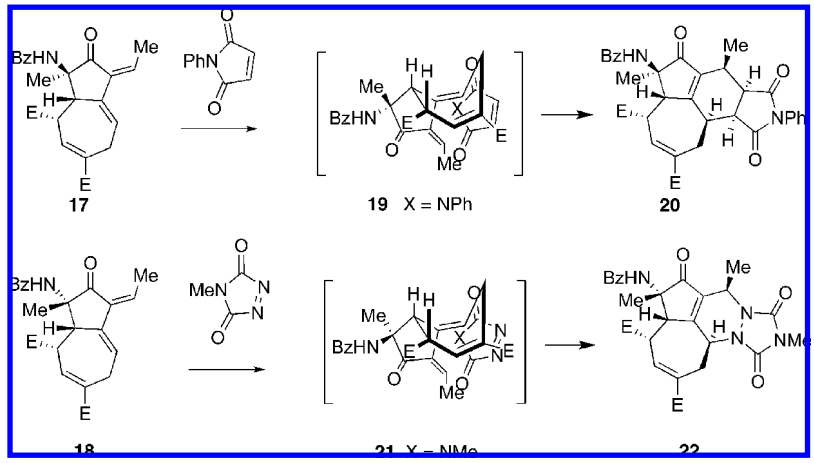
With optimized conditions in hand for the cyclopropanation/Cope rearrangement sequence, we turned to an additional complexity generating reaction. Diastereomer **17** was reacted with *N*-phenylmaleimide to give the Diels−Alder adduct **20** (Scheme 3). In turn, diastereomer **18** was reacted with 4-methyl-1,2,4-triazoline-3,5-dione to give the Diels−Alder adduct **22**. Both **20** and **22** were crystalline solids and X-ray structures were obtained (Figure 3), confirming the stereochemistry of hydroazulenones **17** and **18**, and the endo mode of addition for the dienophile depicted by structures **19** and **21**.

Hydroazulenone **12** was also reacted with 4-phenyl-1,2,4-triazoline-3,5-dione to give the Diels−Alder adduct **23**. For this series of substrates, the trisubstituted double bond was reduced using a palladium-catalyzed hydrogenation. The stereochemistry of compound **24** was confirmed by X-ray analysis (Scheme 4).

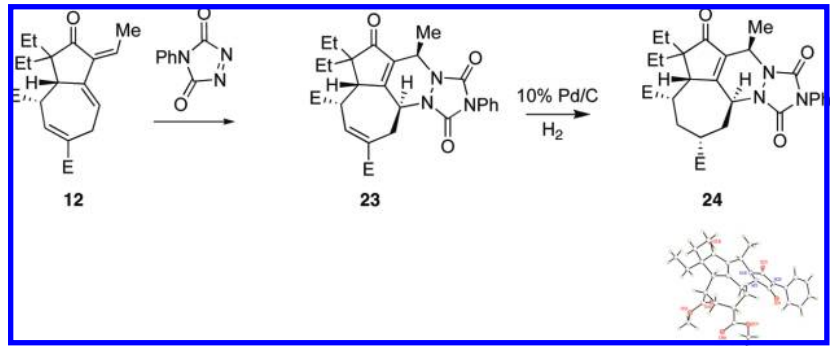
Scheme 2. $[Rh(OAc)_2]_2$-Catalyzed Cyclopropanation/Cope Rearrangement



Scheme 3. Diels−Alder Reaction of Hydroazulenones **17** and **18**



Scheme 4. Stereochemistry Determination via Hydrogenation Product **24**



Library Design-Phase 1 Chemical Considerations. Based on the scope and limitations of the studies above, a library of tetracyclic hydroazulenoisoindoles was designed incorporating both stereochemical and building block diversity. In series 2, two diastereomers were generated from the cyclopropanation/Cope rearrangement reaction, so each of them were reacted separately to give two conformationally different molecules. Building block diversity was achieved by first installing three substituents in the cross-conjugated trienone. The design of the substituents was based on the successful formation of trienones that we published recently.[10] In series 1, $R^1 = R^2$ and lipophilic groups such as methyl, ethyl, and cyclohexyl groups were chosen. In series 2, R^1 and R^2 are amino acid derived groups, that is, R^1 = methyl or isobutyl group and R^2 = a benzamide. In this case, nitrogen was introduced into the system as a polar and hydrogen bond donor functionality. In both cases, a quaternary carbon center was introduced to avoid any potential isomerization of the allene-ynones, the precursor of the trienones. Substitutents for R^3 included an alkyl (methyl or *n*-butyl), a phenyl, a simple hydrogen, a methoxy methyl, and a 2-pyridyl group. Thus, a variety of both lipophilic and polar groups were introduced at this stage. Building block diversity was further introduced in the Diels−Alder step by using six symmetrical dienophiles to avoid the formation of regioisomers. These dienophiles included commercially available *N*-phenylmaleimide as an aromatic representative, *N*-methylmaleimide as a small alkyl group representative and maleimide itself as a representative of a hydrogen bond donor. In addition, a synthetic *N*-acetate maleimide was used because of its electron-withdrawing and polar character. Moreover, two 1,2,4-triazoline-3,5-diones were included since the incorporation of two more nitrogens would make final compounds more drug-like. Another aspect worth

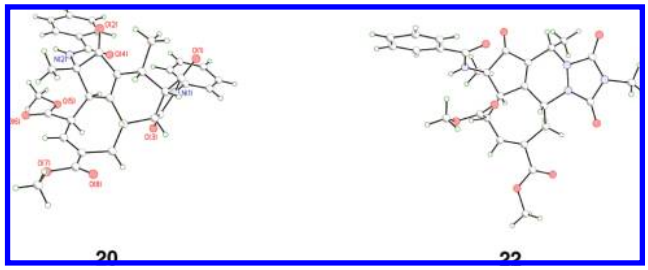
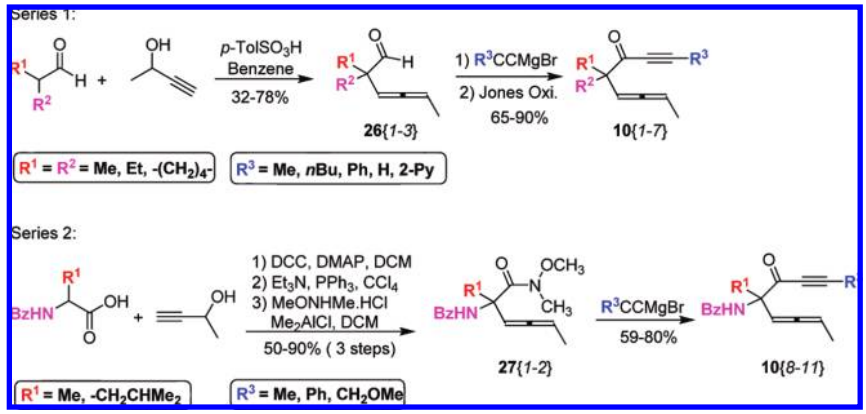
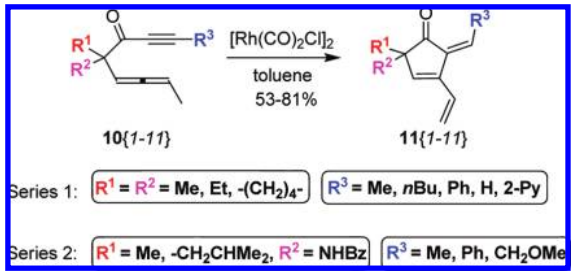


Figure 3. X-ray structures of Diels−Alder adducts **20** and **22**.

Scheme 5. Synthesis of Allene-ynones **10**{*1*−*11*}



Scheme 6. Synthesis of Trienones **11**{*1*−*11*}



mentioning is that the [6-5] fused ring moiety is more rigid than those obtained by using maleimide as dienophiles.

Finally, an additional diversity was introduced by reducing the trisubstituted double bonds of the Diels−Alder adduct, which resulted in a more flexible seven-membered ring scaffold and the removal of the Michael acceptor. We have used a similar strategy in the library syntheses.[12]

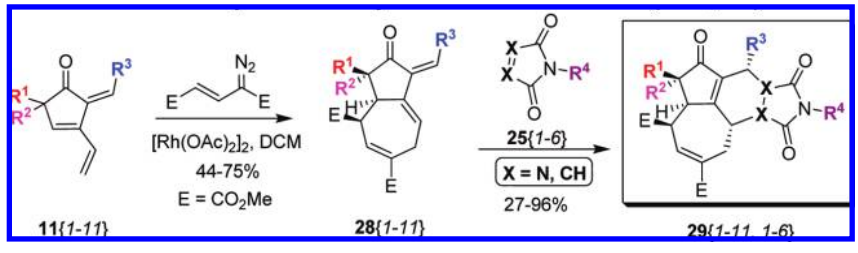
Physicochemical Profiling. Three-dimensional models of forty-four compounds were built and minimized using the MM2 force field in Macro Model 8.6. The physiochemical properties of the library members were predicted computationally using QikProp 2.1,[13] and selected data are shown in Table 2. Important physicochemical properties like molecular weight, number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA), number of rotatable bonds, and logP were used to predict the drug-likeness of the compounds. We were pleased to find all the properties fit within the range of the drug-likeness properties[14] and only the average HBD was low (0.2).

Library Synthesis. According to the reported procedure,[10] allene-ynones were obtained in three steps for series 1 via Claisen rearrangement, Grignard addition, and Jones oxidation, or in four steps for series 2 via DCC coupling, oxazolidinone formation, Weinreb amide formation and Grignard addition. In series 1, the Claisen rearrangement was amenable to large scale reactions. For example, 14 g of the allenic aldehyde (R^1 and R^2 are methyl group) was obtained in 39% yield after vacuum distillation. The yield was low due to the volatility of isobutyraldehyde. For other substrates, where either R^1 and R^2 was an ethyl group or a cyclohexyl group, the Claisen rearrangement yield was 78% and 75%, respectively. In series 2, DCC coupling was carried out on large scale to give 14 g of the propargylic ester (R^1 = Me) in 74% yield. In series 1, Grignard addition was quite facile and the reaction was complete within 5 h; however, in series 2, freshly prepared Grignard reagent was required to avoid low yield, and even so the reaction took a long time (24 h).

The synthesis of five-membered cross-conjugated trienones followed the same protocol as published before.[10] Typically, the allenic alkynones were dissolved in toluene (for series 1) or suspended in toluene (for series 2), then treated with 5% $[Rh(CO)_2Cl]_2$ at rt. At the end of the reaction, the solution appeared yellow or orange. The reaction was stopped after disappearance of the allenic alkynone starting material. The cross-conjugated trienones were obtained in 53−81% yield after quick silica gel flash chromatography by first removing toluene using hexane followed by a more polar solvent system (e.g., 3:1 hexane/EtOAc) (Scheme 6). This reaction was scaled up to 2 g and still gave a good yield (78%, R^1 = Me, R^2 = NHBz). Altogether, eleven trienones were synthesized and used in the subsequent transformations.

Next, the eleven trienones **11**{*1*−*11*} were subjected to the cyclopropanation/Cope rearrangement reaction under optimized reaction conditions (Table 1, entries 5 and 6). Eight trienones were transformed to the [5-7] fused hexahydroazulenes successfully in 44−75% yield (Scheme 7). Two trienones (Figure 4, **11**{*6*} and **11**{*10*}) gave, however, very

Scheme 7. Synthesis of Hydroazulenoisoindoles **29**{*1*−*11*,*1*−*6*}



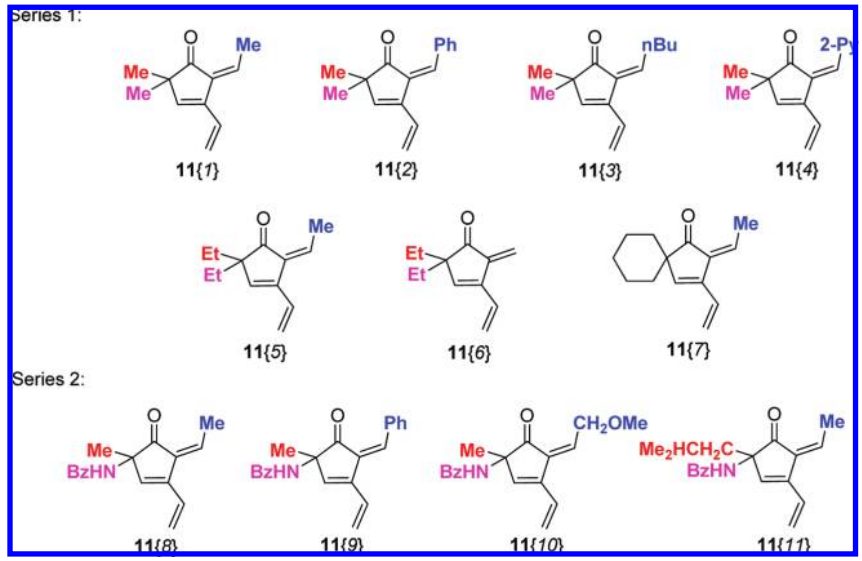


Figure 4. Trienone building blocks.

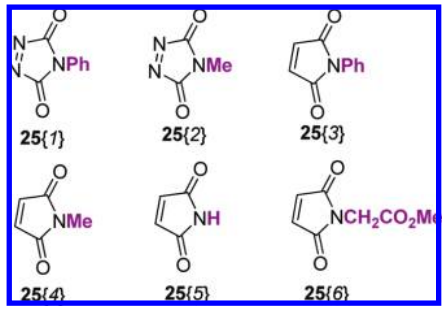


Figure 5. Dienophile building blocks in the Diels−Alder reaction.

Table 1. Optimization of $[Rh(OAc)_2]_2$ Catalyzed Cyclopropanation/Cope Rearrangement[a]

entry	scale (mg of **15**)	**15** (equiv)	**16** (equiv)	$[Rh(OAc)_2]_2$ (mol%)	**17** (yield)	**18** (yield)
1	58	1.2	1.0	5	30%	ND
2	65	1.5	1.0	5	26%	ND
3	53	1.0	1.2 + 1.2	5	28%	ND
4	110	1.0	1.5	5	38%	11%
5	100	1.0	2.0	10	41%	31%
6	320	1.0	2.0	10	44%	31%
7	50	1.0	2.5	15	23%	20%

[a] For all entries, the concentration of **15** is 0.1 M, CH_2Cl_2 was degassed, and a CH_2Cl_2 solution of **16** was added via syringe pump to a mixture of **15** and $[Rh(OAc)_2]_2$ under argon.

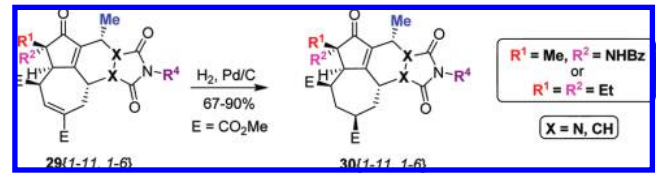
low yields of the hexahydroazulene products. In these cases, complex mixtures were obtained and, even after the final Diels−Alder step, the product was not clean (purity <90% by LC/MS/ELSD). In addition, one trienone (Figure 4, **11**{*4*}) failed to give any desired product. The probable reason is that the basic nitrogen coordinates with rhodium, making the catalyst inactive.

Finally, hexahydroazulenes were subjected to the Diels−Alder reaction. When 1,2,4-triazoline-3,5-diones were used as dienophiles, the reaction was done as follows: 1.0 equiv of hexahydroazulene was dissolved in CH_2Cl_2, and after it was cooled to 0 °C, 1.1 equiv of 1,2,4-triazoline-3,5-dione dissolved in CH_2Cl_2 was added to the diene solution dropwise. The reaction was typically run at 0 °C for 4 h with these very reactive dienophiles. In the case of maleimides as dienophiles, however, the reaction was usually run

Table 2. Predicted Physiochemical Properties for 44 Library Members (Calculated with QikProp 2.1)

property	average value	range for 95% drug-likeness
MW [g/mol]	546	130−725
Volume [Å^3]	1566	500−2000
SASA [Å^2]	804	300−1000
HBD	0.2	0−6
HBA	10.6	2−20
logP	3.7	−2−6
logS	−5.8	−6−0.5
Rotatable Bonds	4.3	0−15
Caco-Perm [nm/sec]	164	25 poor, 500 great

Scheme 8. Palladium-Catalyzed Hydrogenation



at rt for 12 h until most of the starting material was consumed. Attempts to run the reaction at higher temperature (e.g., oil-bath heating, toluene at 90 °C) gave two diastereomers and an unidentified impurity that was difficult to separate, even though the hexahydroazulenes were consumed. Therefore, lower temperature was used to ensure one major diastereomer was obtained and purification was easy. In addition, CH_2Cl_2 was used to dissolve the hexahydroazulenes completely. After the reaction was deemed complete, the solvents were removed and the crude mixture was purified on an ISCO Companion automated chromatography system.

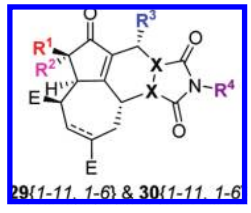
Five hydroazulenoisoindoles were further examined for selective reduction. We tried to use DIBAL-H to reduce the ester to hydroxymethyl group to make the compound more polar and more natural-product-like (e.g., phorbol and ingenol have a hydroxylmethyl functionality); however, DIBAL-H gave an unstable allylic alcohol that resulted from the reduction of the enone ketone. Use of $NaBH_4$ gave a mixture of four compounds. To our delight, in reactions with 10% Pd/C in THF for 24 h at rt (Scheme 8), only the α,β-unsaturated double bond of the methyl ester was reduced and the enone double bond remained intact. In addition, the

Table 3. Yields (Purities) (in %) for the Diels−Alder Adducts and Hydrogenation Products

R^1	R^2	R^3	R^4	X	**29**{*1−11,1−6*}	**30**{*1−11,1−6*}
Me	Me	Me	Ph	N	55(90)	
Me	Me	Me	Me	N	42(100)	
Me	Me	Me	Ph	CH	40(90)	
Me	Me	*n*Bu	Ph	N	62(96)	
Me	Me	*n*Bu	Me	N	50(100)	
Me	Me	Ph	Ph	CH	52(100)	
Me	Me	Ph	Ph	CH	50(100)	
Me	Me	Ph	Me	CH	59(100)	
Et	Et	Me	Ph	N	92(100)	88(100)
Et	Et	Me	Me	N	93(100)	90(100)
Et	Et	Me	Ph	CH	85(<90)	81(100)
Et	Et	Me	CH_2CO_2Me	CH	44(100)	
Et	Et	Me	Me	CH	66(<90)	84(100)
Et	Et	Me	Et	CH	30(99)	
Et	Et	Me	Bn	CH	36(100)	
Et	Et	Me	NH	CH	59(98)	
$-(CH_2)_4-$		Me	Ph	N	70(100)	
$-(CH_2)_4-$		Me	Me	N	84(100)	
$-(CH_2)_4-$		Me	CH_2CO_2Me	CH	61(100)	
Me	NHBz	Me	Ph	N	70(100)	67(100)
Me	NHBz	Me	Me	N	77(100)	
Me	NHBz	Me	Ph	CH	80(98)	
Me	NHBz	Me	Me	CH	76(100)	
Me	NHBz	Me	H	CH	65(100)	
Me	NHBz	Me	CH_2CO_2Me	CH	50(100)	
Me	NHBz	Me	Bn	CH	77(100)	
Me	NHBz	Ph	Ph	N	93(100)	
Me	NHBz	Ph	Me	CH	92(100)	
Me	NHBz	Ph	Ph	CH	85(100)	
Me	NHBz	Ph	H	CH	96(100)	
NHBz	Me	Me	Ph	N	54(100)	
NHBz	Me	Me	Me	N	51(100)	
NHBz	Me	Me	Me	CH	54(100)	
NHBz	Me	Me	H	CH	60(100)	
NHBz	Me	Me	CH_2CO_2Me	CH	56(100)	
$-CH_2CH(Me)_2$	NHBz	Me	Ph	N	50(94)	
$-CH_2CH(Me)_2$	NHBz	Me	Me	N	37(100)	
$-CH_2CH(Me)_2$	NHBz	Me	CH_2CO_2Me	CH	27(100)	
NHBz	$-CH_2CH(Me)_2$	Me	Ph	N	63(100)	
NHBz	$-CH_2CH(Me)_2$	Me	Me	N	76(100)	

reduction was diastereoselective, resulting in two cis methyl esters. We postulate that the hydrogen comes from the sterically less hindered face, away from the free methyl ester.

Purity Analysis. The purity of all compounds was analyzed by LC/MS/ELSD. Forty-four compounds had purities of >90% and the average purity was 98.7%. The isolated yields from the Diels−Alder reaction and the hydrogenation reaction, together with the final compound purity, are listed in Table 3.



Biological Evaluations. Aliquots of these 44 compounds were given to a variety of researchers involved with the NIH-funded Centers for Methodologies and Library Development or in the Molecular Libraries Screening Center Network for biological testing. Results of these evaluations, some of which are still ongoing, can be accessed in Pubchem (http://pubchem.ncbi.nlm.nih.gov), where all of the 44 structures are deposited. In-house, we examined the library in a cell-based phenotypic screen for inhibitors of agonist-induced nuclear localization of glucocorticoid receptor (GR). Details of the screen will be reported elsewhere (Zhu et al., submitted; Johnston et al., in preparation). In brief, the assay utilized mouse mammary 3617.4 adenocarcinoma cells stably expressing green fluorescent protein of GR (GFP-GR) under control of a "tetracycline-off" inducible system.[15] Cells at 2500/well were aliquoted into 384-well plates, allowed to attach for 48 h in the absence of tetracycline, treated for 1 h with the library members or vehicle (DMSO), then for 0.5 h with 1 μM dexamethasone, the GR agonist. Cells were simultaneously fixed and stained with Hoechst 33342 in paraformaldehyde to define nuclei, and ≥100 cells in each well were examined with an ArrayScan V^{TI} automated fluorescence imaging system (Cellomics, Inc.) in the blue (Hoechst/nuclei) and green (GFP-GR) channels. Each cell was scored for nuclear accumulation of GFP-GR. Of the 44 compounds, two (**29**{*1,1*} and **30**{*5,3*}) were found to inhibit nuclear accumulation of GFP-GR at IC50s of 12 and 25 μM, respectively.

Conclusion

A library synthesis of relatively complex tetracyclic hydroazulenoisoindoles was achieved in six or seven steps for each final compound from commercially available starting

materials. The key transformations involved in the synthesis were (1) a rhodium(I)-catalyzed cycloisomerization reaction to assemble a five membered cross-conjugated trienone, (2) a rhodium(II)-catalyzed tandem cyclopropanation/Cope rearrangement reaction to form a [5-7] fused hydroazulene, and (3) a Diels−Alder reaction to obtain a [5-7-6-5] fused hydroazulenoisoindole. To maximize structural diversity, stereochemical diversity and building block diversity approaches were employed. The library members included up to six points of diversity and the substitutents included lipophilic groups, such as aliphatic or phenyl moieties, and polar groups, such as benzamide. Altogether, 44 compounds were obtained in amounts of 5−50 mg with an average purity of 98.7% by LC/MS/ELSD. True to the hope that a complex scaffold accompanied by substituents that comprise drug-like properties, two of the 44 compounds showed biological activity in a cellular system (a 4.5% hit rate).

Experimental Section

General. All air and moisture sensitive reactions were performed under an argon atmosphere. THF was purified by distillation from Na/benzophenone. Toluene was purified by passage through dry Al_2O_3. Other solvents or reagents were used without further purification. NMR spectra were recorded in $CDCl_3$ (298K) at 300.1 (^{1}H) or 75.5 (^{13}C) using a Bruker Avance 300 with Topspin software. Chemical shifts (δ) are reported in parts per million (ppm). Chloroform-*d* was used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), coupling constants, and integration. IR spectra were obtained on a Nicolet AVATAR 360 FTIR ESP spectrometer. EI mass spectrometry was performed on a Micromass Autospec high resolution mass spectrometer. Melting points were obtained using a heating rate of 2 °C/min on a MelTemp melting point apparatus with digital temperature reading and are reported uncorrected.

Compounds were analyzed by reverse-phase HPLC (Alltech Prevail C-18, 100 × 4.6 mm, 1 mL/min, CH_3CN, H_2O, and 0.1% TFA) with UV (210, 220, and 254 nm), ELS (nebulizer 45 °C, evaporator 45 °C, N_2 flow 1.25 SLM), and MS detection using a ThermoFinnigan Surveyor LC and LCQ Advantage MS system (ESI, positive ion detection mode).

(1*Z*,3*aR*,4*R*,5*E*,8*E*)-Dimethyl-3,3-diethyl-1-ethylidene-2-oxo-1,2,3,3*a*,4,7-hexahydroazulene-4,6-dicarboxylate (28{*5*}). General Procedure A. A 25 mL three-neck flask was charged with $Rh(OAc)_2$ (39 mg, 0.088 mmol), followed by the addition of trienone **11**{*5*} (0.34 g, 1.8 mmol, dissolved in 10 mL degassed CH_2Cl_2). This was placed into a preheated oil bath (53 °C) and a CH_2Cl_2 (degassed) solution of dimethyl 4-diazo-2-pentenedioate (0.36 g, 2.0 mmol) was added slowly via syringe pump. After the addition was complete, the oil bath was removed, and the crude product was purified by silica gel flash chromatography to give **28**{*5*} (0.28 g, 45%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.07 (d, J = 4.8 Hz, 1H), 6.85 (q, J = 7.5 Hz, 1H), 6.07 (bs, 1H), 3.70 (s, 3H), 3.49 (bs, 3H), 3.42−3.19 (m, 3H), 2.94 (bs, 1H), 2.17 (d, J = 7.5 Hz, 1H), 1.97−1.90 (m, 1H), 1.46−1.27 (m, 3H), 0.86 (t, J = 6.9 Hz, 3H), 0.69 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 208.1, 170.8, 168.1, 141.2, 137.8, 134.6, 131.6, 130.5, 117.1, 53.7, 52.3, 51.8, 47.6, 44.2, 29.8, 27.0, 18.7, 14.3, 8.5, 8.2; IR (thin film) ν 3445, 2966, 2876, 1732, 1716, 1642, 1438 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 346 ([$M^{+\bullet}$], 22), 285 (30), 257 (34), 68 (84), 53 (100); HRMS (EI) calcd for $C_{20}H_{26}O_5$ *m*/*z* ($M^{+\bullet}$) 346.1780, found 346.1778.

(1*Z*,3*S*,3*aR*,4*R*,5*E*,8*E*)-Dimethyl-3-benzamido-1-ethylidene-3-methyl-2-oxo-1,2,3,3*a*,4,7-hexahydroazulene-4,6-dicarboxylate (17). Following General Procedure A, $Rh(OAc)_2$ (17 mg, 0.038 mmol), trienone **11**{*8*} (0.11 g, 0.41 mmol) and dimethyl 4-diazo-2-pentenedioate (90 mg, 0.49 mmol) gave **17** (65 mg, 38%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 7.2 Hz, 2H), 7.53−7.40 (m, 3H), 7.32 (d, J = 6.9 Hz, 1H), 6.49 (q, J = 7.5 Hz, 1H), 6.17 (bs, 2H), 4.40 (bs, 1H), 4.19 (t, J = 6.8 Hz, 1H), 3.77 (s, 3H), 3.74−3.69 (m, 1H), 3.33−3.25 (m, 3H), 3.06 (bs, 1H), 2.26 (d, J = 7.5 Hz, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 200.5, 172.9, 166.5, 165.9, 137.8, 136.8, 135.3, 133.6, 133.1, 132.1, 128.7, 127.2, 120.2, 65.6, 52.3, 52.2, 43.3, 42.8, 31.2, 23.1, 19.3, 15.2; IR (thin film) ν 3379, 2982, 1731, 1646, 1580, 1525, 1487 cm^{-1}.

(1*Z*,3*R*,3*aR*,4*R*,5*E*,8*E*)-Dimethyl-3-benzamido-1-ethylidene-3-methyl-2-oxo-1,2,3,3*a*,4,7-hexahydroazulene-4,6-dicarboxylate (18). Following General Procedure A, $Rh(OAc)_2$ (17 mg, 0.038 mmol), trienone **11**{*8*} (0.11 g, 0.41 mmol) and dimethyl 4-diazo-2-pentenedioate (90 mg, 0.49 mmol) gave **18** (37 mg, 22%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.80 (dd, J = 9.0 Hz, 2H), 7.57−7.42 (m, 3H), 7.02 (dd, J = 9.0, 2.7 Hz, 1H), 6.93 (bs, 1H), 6.63 (q, J = 7.8 Hz, 1H), 6.31 (bs, 1H), 3.75 (s, 3H), 3.53 (s, 3H), 3.51−3.28 (m, 4H), 2.34 (d, J = 7.8 Hz, 3H), 1.59 (s, 3H).

(4*R*,4*aR*,5*S*,7*S*,12*aR*,*E*)-Dimethyl-5-benzamido-5,7-dimethyl-6,9,11-trioxo-10-phenyl-1,4,4*a*,5,6,7,9,10,11,12*a*-decahydroazuleno[8,1-*cd*][1,2,4]triazolo[1,2-*a*]pyridazine-2,4-dicarboxylate (29{*8*,*1*}). General Procedure B. A threaded culture tube was charged with a DCM solution (1 mL) of **28**{*8*} (44 mg, 0.103 mmol) under argon. This was cooled to 0 °C, and 5 min later, a DCM solution of 4-phenyl-4*H*-1,2,4-triazole-3,5-dione **25**{*1*} (22 mg, 0.123 mmol) was added dropwise. The yellow solution changed to orange solution after the addition finished. After the mixture was stirred for 6 h, solvents were removed in vacuo, and the crude mixture was purified by an ISCO Companion chromatography system (4 g SiO_2 cartridge, hexane/EtOAc; 3:1 to 1:1) to give **29**{*8*,*1*} (43 mg, 70%). ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 3.6 Hz, 2H), 7.56−7.38 (m, 8H), 7.29 (dd, J = 4.2, 1.5 Hz, 0.09H)*, 7.26 (dd, J = 5.1, 1.5 Hz, 1H), 6.51 (bs, 0.09H)*, 6.49 (bs, 1H), 5.18 (dd, J = 6.0, 0.6 Hz, 1H), 5.05 (tq, J = 3.3, 0.9 Hz, 1H), 4.63 (dd, J = 17.4, 1.5 Hz, 1H), 4.56 (b d, J = 4.2 Hz, 0.08H)*, 4.41 (bs, 0.08H)*, 4.38 (td, J = 3.9, 0.9 Hz, 1H), 3.95 (d, J = 0.9 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.76 (tt, J = 7.4, 1.2 Hz, 1H), 2.66 (tt, J = 7.4, 0.9 Hz, 0.11H)*, 1.56 (d, J = 3.3 Hz, 3H), 1.50 (d, J = 0.3 Hz, 0.09H)*, 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.1, 171.9, 167.6, 167.2, 166.5, 155.3, 150.4, 137.6, 133.2 (2 C), 133.1, 131.1, 129.4, 128.9, 128.5, 127.3, 125.8, 63.9, 59.0, 53.0, 48.6, 47.6, 44.4, 18.6, 16.4; IR (thin film) ν 2924, 2854,

1718, 1652 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 1197 ([2 M + H]$^+$, 8), 621 ([M + Na]$^+$, 20), 599 ([M + H]$^+$, 100), 478 (80), 446 (24); HRMS (ESI) *m/z* calcd for $C_{32}H_{31}N_4O_8$ [M + H]$^+$ 599.2142, found 599.2137. [The asterisk (*) denotes other diastereomer.]

(4*R*,4*aR*,5*R*,7*R*,7*aS*,10*aR*,10*bS*,*E*)-Dimethyl 5-benzamido-5,7-dimethyl-6,8,10-trioxo-9-phenyl-1,4,4*a*,5,6,7,7*a*,8,9,10,10*a*,10*b*-dodecahydroazuleno[8,1-*ef*]isoindole-2,4-dicarboxylate (29{*8*,*3*}). General Procedure C. A threaded culture tube was charged with a DCM solution (0.7 mL) of **28**{*8*} (30 mg, 0.071 mmol) under argon, followed by *N*-phenylmaleimide **25**{*3*} (18 mg, 0.11 mmol) at rt. After the mixture was stirred for 12 h, solvents were removed in vacuo, and the crude mixture was purified by an ISCO Companion chromatography system to give **29**{*8*,*3*} (26 mg, 62%). ^{1}H NMR ($CDCl_3$) δ 7.77 (dd, J = 8.1, 0.6 Hz, 2H), 7.57−7.21 (m, 9H), 6.69 (bs, 1H), 4.15 (dd, J = 9.3, 4.2 Hz, 1H), 3.79 (d, J = 0.6 Hz, 3H), 3.41 (d, J = 0.6 Hz, 3H), 3.59−3.27 (m, 4H), 3.15 (dd, J = 8.9, 2.4 Hz, 1H), 3.04 (d, J = 11.1 Hz, 1H), 2.62 (dd, J = 15.0, 13.1 Hz, 1H), 1.59 (s, 3H), 1.53 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 204.5, 177.2 (2 C), 170.4, 168.1, 167.6, 167.3, 137.9, 136.5, 135.7, 134.1, 132.2, 131.8, 129.4, 128.9, 127.1, 126.6, 126.3, 63.8, 53.3, 52.9, 52.1, 46.1, 45.3, 43.1, 37.5, 32.4, 27.2, 25.1, 21.3; IR (thin film) ν 2918, 2849, 1715, 1651 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 619 ([M + Na]$^+$, 12), 597 ([M + H]$^+$, 100), 565 (14), 475 (25), 444 (16); HRMS (ESI) *m/z* calcd for $C_{34}H_{33}N_2O_8$ [M + H]$^+$ 597.2237, found 597.2236.

(4*R*,4*aR*,5*S*,7*S*,7*aS*,10*aR*,10*bS*,*E*)-Dimethyl-5-benzamido-5-methyl-6,8,10-trioxo-7,9-diphenyl-1,4,4*a*,5,6,7,7*a*,8,9,10,10*a*,10*b*-dodecahydroazuleno[8,1-*ef*]isoindole-2,4-dicarboxylate (20). Following General Procedure C, **28**{*9*} (10 mg, 0.019 mmol) and *N*-phenylmaleimide **25**{*3*} (11 mg, 0.064 mmol) afforded **20** (11 mg, 85%) as a white solid. mp 239.1−242.6 °C; ^{1}H NMR ($CDCl_3$) δ 7.67 (dd, J = 7.2, 1.5 Hz, 2H), 7.48 (d, J = 7.2 Hz, 1H), 7.42−7.37 (m, 2H), 7.31−7.27 (m, 6H), 7.22−7.19 (m, 2H), 7.16−7.13 (m, 2H), 6.40 (bs, 1H), 6.31−6.27 (m, 2H), 4.83 (d, J = 8.4 Hz, 1H), 4.40 (d, J = 8.1 Hz, 1H), 3.99−3.92 (m, 2H), 3.85−3.73 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.59 (dd, J = 9.5, 7.9 Hz, 1H), 3.36−3.24 (m, 1H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 203.6, 175.2, 174.8, 173.8, 172.5, 168.0, 167.8, 137.1, 136.9, 136.7, 133.7, 133.1, 132.2, 131.1, 129.7, 129.0, 128.8, 128.4, 128.2, 127.2, 126.3, 63.0, 53.0, 52.7, 51.6, 45.3, 45.1, 42.0, 37.3, 36.2, 29.9, 28.9, 18.3; IR (thin film) ν 2924, 2853, 1716, 1651 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 681 ([M + Na]$^+$, 29), 659 ([M + H]$^+$, 100), 538 (64), 506 (92); HRMS (ESI) *m/z* calcd for $C_{39}H_{34}N_2O_8$ [M + H]$^+$ 659.2393, found 659.2395.

(4*R*,4*aR*,7*S*,12*aR*,*E*)-Dimethyl-5,5-diethyl-7-methyl-6,9,11-trioxo-10-phenyl-1,4,4*a*,5,6,7,9,10,11,12*a*-decahydroazuleno[8,1-*cd*][1,2,4]triazolo[1,2-*a*]pyridazine-2,4-dicarboxylate (23). Following General Procedure B, **28**{*5*} (80 mg, 0.23 mmol) and 4-methyl-4*H*-1,2,4-triazole-3,5-dione **25**{*1*} (49 mg, 0.28 mmol) afforded **23** (114 mg, 95%). ^{1}H NMR ($CDCl_3$) δ 7.53−7.35 (m, 5H), 7.21 (dd, J = 7.8, 2.7 Hz, 1H), 5.17 (d, J = 11.4 Hz, 1H), 4.95 (q, J = 6.3 Hz, 1H), 4.66 (dd, J = 17.4, 2.7 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.76 (bs, 1H), 3.28 (bs, 1H), 2.71−2.60 (m, 1H), 1.76−1.35 (m, 4H), 1.42 (d, J = 6.6 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.8, 171.5, 167.3, 166.5, 155.4, 150.3, 137.9, 134.8, 133.4, 131.1, 129.3, 128.5, 125.8, 59.2, 54.6, 53.2, 53.0, 48.6, 47.6, 45.4, 30.0, 25.9, 23.3, 16.4, 8.7, 7.9; IR (thin film) ν 2953, 2881, 1776, 1716, 1665 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 1043 ([2 M + H]$^+$, 18), 544 ([M + Na]$^+$, 50), 522 ([M + H]$^+$, 100), 490 (25), 462 (23); HRMS (ESI) *m/z* calcd for $C_{28}H_{31}N_3O_7Na$ [M + Na]$^+$ 544.2060, found 544.2062.

(2*S*,4*R*,4*aR*,7*S*,12*aR*)-Dimethyl-5,5-diethyl-7-methyl-6,9,11-trioxo-10-phenyl-1,2,3,4,4*a*,5,6,7,9,10,11,12*a*-dodecahydroazuleno[8,1-*cd*][1,2,4]triazolo[1,2-*a*]pyridazine-2,4-dicarboxylate (24). General Procedure D. A 5 mL round bottomed flask charged with **23** (35 mg, 0.067 mmol) was dissolved in THF (0.7 mL) under argon to give a colorless solution. This was treated with 10% Pd/C (8 mg, 0.0075 mmol). The crude mixture was evacuated twice and a H_2 balloon was placed on the top of the septum. After 17 h, the crude mixture was filtered through Celite and concentrated in vacuo to afford **24** (31 mg, 88%) as a white solid. Mp 90.9−94.1 °C; ^{1}H NMR ($CDCl_3$) δ 7.55−7.34 (m, 5H), 5.27 (d, J = 12.6 Hz, 1H), 4.88 (q, J = 6.1 Hz, 1H), 4.25 (dd, J = 14.1, 4.8 Hz, 1H), 3.67 (s, 6H), 3.19 (bs, 1H), 3.05−2.96 (m, 3H), 2.04 (dt, J = 12.1, 2.1 Hz, 1H), 1.91 (td, J = 14.7, 5.0 Hz, 1H), 1.65 (q, J = 7.5 Hz, 2H), 1.48−1.28 (m, 2H), 1.38 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.2, 174.7, 173.0, 168.0, 155.2, 150.8, 134.4, 131.3, 129.2, 128.2, 125.7, 59.5, 55.6, 52.5, 52.4, 51.8, 47.6, 41.9, 40.5, 34.7, 29.3, 25.1, 24.0, 16.2, 9.1, 7.9; IR (thin film) ν 2952, 2880, 1775, 1717 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 1069 ([2 M + Na]$^+$, 11), 546 ([M + Na]$^+$, 58), 524 ([M + H]$^+$, 82), 492 (100); HRMS (ESI) *m/z* calcd for $C_{28}H_{33}N_3O_7Na$ [M + Na]$^+$ 546.2216, found 546.2214.

Acknowledgment. We gratefully acknowledge financial support from NIH (P50-GM067082 and R21-NS057026). We thank Mrs. Stephanie Nicolay for LC-MS/UV/ELSD analyses and Dr. Steven Geib for X-ray analysis. We also thank Dr. Daitao Chen for providing some intermediates and Mr. David Turner for providing building block **25**{*6*}. We would like to acknowledge Professor Peter Wipf and Dr. Stefan Werner for stimulating discussions.

Supporting Information Available. Experimental procedures and spectroscopic data for compounds **10**{*1*}, **10**{*2*}, **10**{*3*}, **10**{*4*}, **10**{*5*}, **10**{*6*}, **10**{*7*}, **10**{*8*}, **10**{*9*}, **10**{*11*}, **11**{*1*}, **11**{*2*}, **11**{*3*}, **11**{*4*}, **11**{*5*}, **11**{*6*}, **11**{*7*}, **11**{*8*}, **11**{*9*}, **11**{*10*}, **11**{*11*}, **29**{*7*,*2*}, **29**{*11*,*2*}, and **29**{*9*,*4*} and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC900024P