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A Strategy for the Late-Stage Divergent Syntheses of Scyphostatin Analogues

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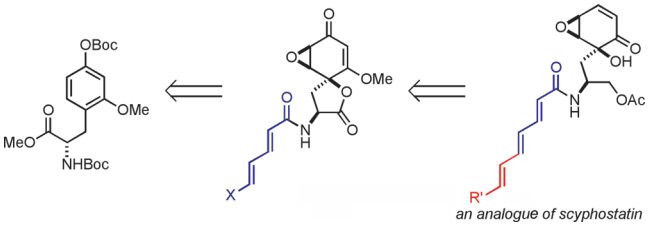

This account details the synthesis of two scyphostatin analogues exhibiting a reactive polar epoxycyclohexenone core and various amide side chains outfitted for late-stage chemical derivatization into the desirable lipophilic tails. Our efforts highlight a key ipso-dearomatization process and provide new insights regarding the incompatibility and orthogonal reactivity of scyphostatin's functional groups. We further showcase the utility of resorcinol derived 2,5-cyclohexadienones as synthetic platforms capable of participating in selective chemical reactivity, and we further demonstrate their potential for rapid elaboration into complex structural motifs.

Introduction

Sphingomyelin (SM) (**1**) is an integral constituent of biological membranes. It is found in bacterial cells, as well as eukaryotic cells, and it is a source of the secondary messenger molecule ceramide.[1] Sphingomyelinases (SMases) are a class of phosphatase enzymes which initiate the degradation of SM to phosphocholine and ceramide (**2**) (Figure 1). Ceramide (**2**) then participates in a myriad of biophysical events including an early definitive step toward cell apoptosis.[2] The SMase family is broadly classified according to the pH where it exhibits optimal activity: acidic, neutral, and basic. Three distinct isoforms of neutral SMases (N-SMases) have been identified, and each contains magnesium in the active site. While no crystal structure has been determined for these isoforms, a structure has been solved for membrane-bound SM isolated from *Bacillus ceureus* (Bc-SMase), and it is thought to be a close homologue of at least one of the N-SMase isoforms that is found in mammalian species.[3] However, it remains unclear as to which mammalian isoform is most involved with ceramide release, and which may be most therapeutically relevant to target with an inhibitor. Inhibition of this target may prevent or lessen the apoptosis that accompanies ischemia and reperfusion injuries caused by stroke and myocardial infarction.

In 1997, Ogita and co-workers isolated scyphostatin (**3**) in the mycelial extract of the fermentation broths from *Dasyscyphus mollisimus* SANK-13892 (Figure 1).[4] They found the compound indefinitely stable as a methanolic solution but unstable as a solid. From a structural standpoint, scyphostatin (**3**) and sphingomyelin (**1**) have many apparent similarities; both are complex amphiphilic molecules. The epoxycyclohexenone core constitutes the polar moiety of scyphostatin (**3**), whereas the zwitterionic ammonium phosphate moiety comprises the polar core of sphingomyelin (**1**). Regarding their lipophilic regions, scyphostatin (**3**) contains a trienoyl 15-carbon tail, which is likely kinked because of the repeating methyl stereochemistry, whereas sphingomyelin

(1) Wiegmann, K.; Schütze, S.; Machleidt, T.; Witte, D.; Krönke, M. *Cell* **1994**, *78*, 1005–1015.
(2) Pushkareva, M.; Obeid, L. M.; Hannun, Y. A. *Immunol. Today* **1995**, *16*, 294–297.
(3) Ago, H.; Oda, M.; Takahashi, M.; Tsuge, H.; Ochi, S.; Katunuma, N.; Miyano, M.; Sakurai, J. *J. Biol. Chem.* **2006**, *281*, 16157–16167.
(4) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871–7872.
(5) Wascholowski, V.; Giannis, A.; Pitsinos, E. N. *ChemMedChem* **2006**, *1*, 718–721.

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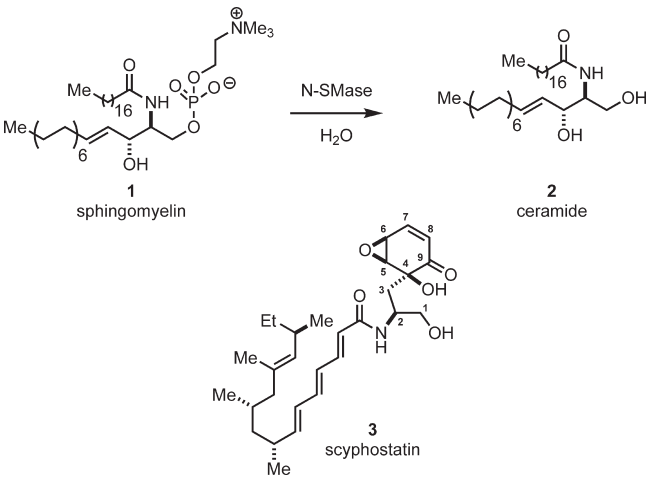


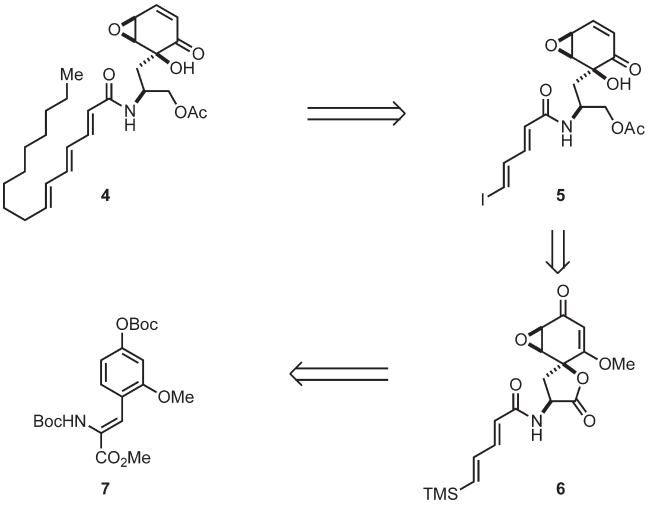
FIGURE 1. Production of ceramide (**2**) and structural similarities to scyphostatin (**3**).

(**1**) contains two achiral hydrocarbon tails, one with 17 and one with 15 hydrocarbon residues. In addition, both molecules express a reactive group three atoms away from their respective amide side chain: the phosphorus of a phosphate in the case of sphingomylein (**1**), and the reactive carbon of an epoxide and carbonyl in the case of scyphostatin (**3**). The subsequent discovery that scyphostatin (**3**) is an effective inhibitor of crude N-SMases at low concentrations (IC_{50} = 1.0 μM) made these structural similarities all the more compelling to study.[4] To date, scyphostatin (**3**) remains the most potent reversible inhibitor of N-SMases. Several efforts aimed at determining the origins of its activity have produced counterintuitive results,[5] indicating an aggregated micellar presentation of scyphostatin (**3**) to the active site. Studies also suggest, however, that the hydrophobic side chain moiety plays a critical role in controlling both the reversibility and selectivity of inhibition. For this reason, a synthetic strategy that enables a rapid and effortless survey of lipophillic tails would be highly desirable.

With an attractive biological profile, scyphostatin (**3**) has been the focus of numerous synthetic efforts, culminating in several total syntheses.[6] Each endeavor is a testament to the difficulties of managing reactive functionalities in close proximity found throughout this natural product and its precursors. We were interested in generating a strategy in which we could manipulate the hydrophobic side chain at a late stage while maintaining the epoxycyclohexenone motif found to be paramount for the biological activity of scyphostatin (**3**).

The *O*-acetate scyphostatin analogue **4** contains all of the reactive motifs that are found in scyphostatin (**3**) (Scheme 1). We envisioned that analogues of this type could be accessed from the properly outfitted dienoylamide **5**, where some

SCHEME 1. Preliminary Synthetic Analysis



functionality on the sorbyl side chain (e.g., iodide) would serve as a flexible handle and participate in cross-coupling processes to rapidly afford various trienoyl amides. Dienoylamide **5** was imagined to be synthetically accessible through the discriminatory introduction of three hydrides to the functionality distributed about the polar core of spirolactone **6** and followed when necessary by the appropriate acid-promoted rearrangement. In addition, large quantities of vinylogous ester **6** could be obtained from the reduction, deprotection, oxidative dearomatization, and subsequent epoxidation of ester **7**.[7]

Results and Discussion

Our studies began with the preparation of new phenolic dearomatization precursors, which we believed would participate in diastereoselective dearomatization reactions (Figure 2, eq 1). From our previous isariotin studies,[7] we knew that an oxygen atom positioned on the R-amine substituent, such as a dienoyl amide fragment, participated in an undesirable *ipso* reaction with the phenoxonium intermediate formed by oxidative dearomatization and led to an undesired six-membered spirocycle. Furthermore, we observed instances where the oxygen atom of the corresponding nitro materials participated in *ipso* cyclization to afford the corresponding five-membered spironitronate derivatives.[8] We therefore sought new amide derivatives in the hope that the residues in these compounds might survive the oxidative dearomatization conditions and then be exchanged later. We favored the Weinreb amide because this functionality had enhanced diastereoselectivity in our past experiences by stiffening the overall scaffold (Figure 2, eq 2).[9]

The three-step preparation of the racemic resorsinol derivative **8** from 4-hydroxy-2-methoxybenzaldehyde has been

(6) For total syntheses of scyphostatin, see: (a) Inoue, M.; Yokota, W.; Murugesh, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem.* **2004**, *116*, 4303–4305. *Angew. Chem., Int. Ed.* **2004**, *43*, 4207-4209; (b) Fujioka, H.; Sawama, Y.; Kotoku, N.; Ohnaka, T.; Okitsu, T.; Murata, N.; Kubo, O.; Li, R.; Kita, Y. *Chem.—Eur. J.* **2007**, *13*, 10225–10238. (c) Takagi, R.; Miyanaga, W.; Tojo, K.; Tsuyumine, S.; Ohkata, K. *J. Org. Chem.* **2007**, *72*, 4117–4125. (d) Pitsinos, E. N.; Athinaios, N.; Xu, Z.; Wang, G.; Negishi, E. *Chem. Commun.* **2010**, *46*, 2200–2202. For model studies of the polar core, see: (e) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943–1946. (f) Pitsinos, E. N.; Cruz, A. *Org. Lett.* **2005**, *7*, 2245–2248. (g) Hoye, T. R.; Jeffrey, C. S.; Nelson, D. P. *Org. Lett.* **2010**, *12*, 52–55.

(7) Cha, J. Y.; Huang, Y.; Pettus, T. R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9519–9521.

(8) Marsini, M. A.; Huang, Y.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2007**, *9*, 3229–3232.

(9) (a) Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*, 1535–1538. (b) Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2843–2846. (c) Mejorado, L. H.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2006**, *128*, 15625–15631. (d) Wenderski, T. A.; Huang, S.; Pettus, T. R. R. *J. Org. Chem.* **2009**, *74*, 4104–4109. (e) Wenderski, T. A.; Hoarau, C.; Mejorado, L. H.; Pettus, T. R. R. *Tetrahedron* **2010**, *66*, 5873–5883.

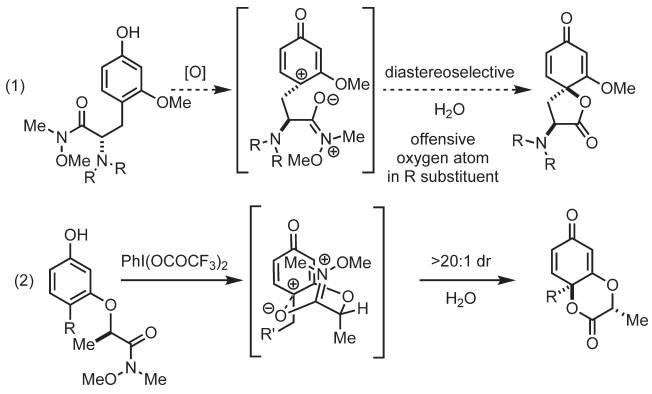
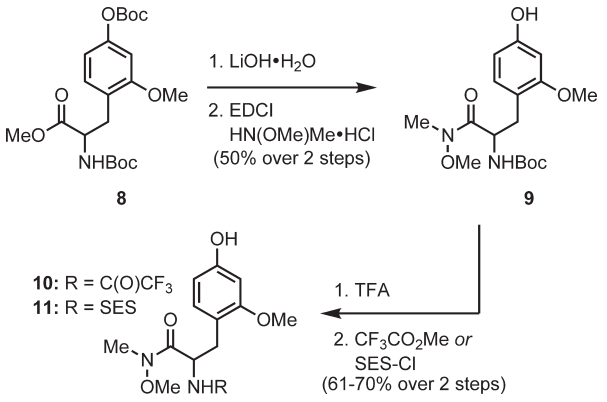


FIGURE 2. Our plan (eq 1) and its predication (eq 2).

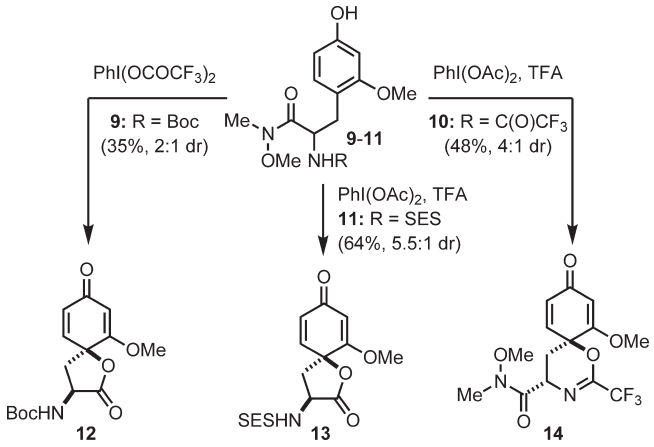
SCHEME 2. Preparation of Substrates for Dearomatization



previously reported.[7] Treatment of this compound with lithium hydroxide induced saponification of both the *O*-Boc and methyl ester residues. The crude acid was next subjected to amide bond formation with *N*,*O*-dimethylhydroxylamine hydrochloride using standard peptide coupling conditions (Scheme 2). The reaction afforded *N*-Boc Weinreb amide **9** in 50% overall yield. In addition to carbamate derivative **9**, we prepared electron-deficient trifluoroacetamide **10** and sulfonamide **11** by acid-mediated *N*-Boc deprotection and reprotection of the free amine using TFA followed by methyl trifluoroacetate or TFA followed by SESCl.[10] We hoped that either residue might render the offending oxygen atom less nucleophilic and thereby dissuade its participation with the intervening phenoxonium intermediate.

We next examined the outcome afforded by exposing phenols **9**−**11** to various hypervalent iodine oxidants (Scheme 3). Subjecting phenolic carbamate **9** to standard oxidative dearomatization conditions produced spirolactone **12** in 35% yield with 2:1 dr. The poor mass recovery indicated to us the incompatibility of the *N*-Boc protecting group with trace amounts of acid and suggested that this may have siphoned some of the material away during the course of the reaction. Attempts to circumvent this issue by oxidation of the trifluoroacetamide derivative **10** provided spirocarbamate **14** in 48% yield with ~3.7:1 dr. This is the result of the favorable participation from the oxygen atom of the trifluoroacetamide carbonyl, as opposed to the oxygen atom of the Weinreb amide carbonyl in the cyclization. On the

SCHEME 3. Preliminary Exploration of Dearomatization



other hand, oxidation of sulfonamide **11** with hypervalent iodine afforded dienone **13** in a very reasonable 64% yield with 5.5:1 dr. Unfortunately, these diastereomers were not easily separable. It is worthy to note that the use of phenyliodine bis(trifluoroacetate) on < 100 mg scale smoothly afforded dearomatized products; however, scaling this reaction up beyond 100 mg resulted in low yields of the desired product. Nevertheless, this reaction could be scaled to > 100 mg utilizing oxidation conditions developed by Ciufolini and co-workers.[11]

It should be noted that Wipf and co-workers have oxidized symmetric *N*-Cbz tyrosine derivatives and that the transformation has been shown to proceed to the respective spirocyclic lactone in useful yields.[12] However, in these tyrosine-based examples, the oxidative dearomatization does not generate a new stereocenter because the starting phenol is symmetric. In the previous case, the dissymmetric resorcinol cores of compounds **9**−**11** lead to two diastereomers; the *anti* diastereomer (**A′**), where the amine and methoxy substituents are on opposite sides of the spirocycle, and the *syn* diastereomer (**A**), where the amine and the methoxy residues are on the same side of the molecule (Figure 3). We had suspected that the *anti* diastereomer would be favored and that the disparity would be reflected in the transition state. We also imagined that the spirocyclic ring junction would provide a conformational lock and prevent undesired intramolecular participation of the amino substituent at C2 with the dienone moiety upon subsequent deprotection.

The diastereoselectivity exhibited during formation of sulfonamide-protected analogue **13** clearly demanded more attention (Scheme 3). We attempted to epoxidize the enone portion of sulfonamide **13**; however, all attempts using standard peroxide sources (H_2O_2, ROOH, etc.) and amine bases were unsuccessful and returned starting material with an enriched enantiomeric ratio. Next, we explored opening the spirolactone with an appropriate nucleophile, so that we might harness the directing power of the freed tertiary hydroxyl group (Scheme 4). We treated sulfonamide **13** with pyrrolidine, which resulted in intermediate amide **17**, although we were not able to spectroscopically identify this compound. Without the spirocycle serving as a conformational

(10) For a review of the SES group as an amine protecting group, see: Ribière, P.; Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2006**, *106*, 2249–2269.

(11) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299–4301.

(12) (a) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195–7203. (b) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576–4577. and references therein.

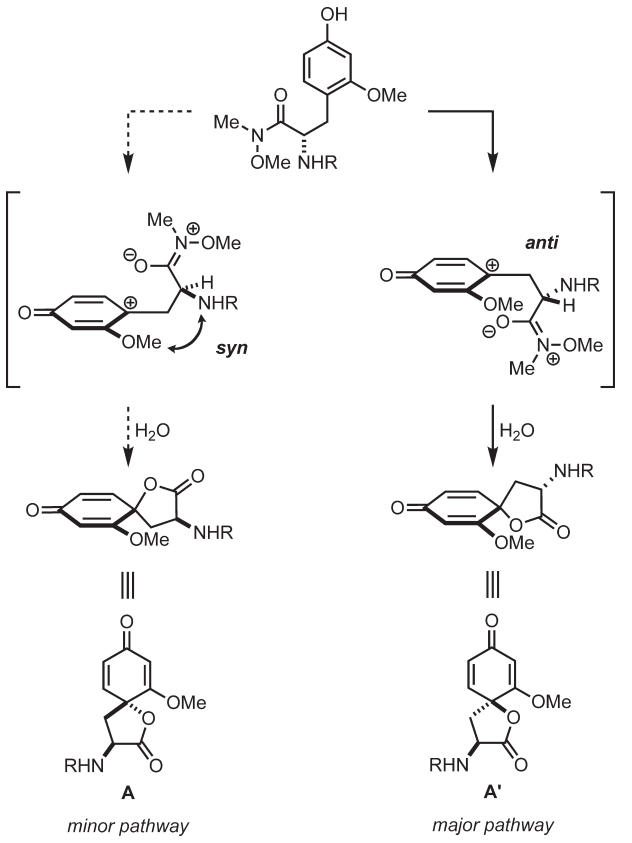


FIGURE 3. Diastereoselectivity due to steric hindrance.

lock, however, the hydroindole **18** emerged in 67% yield as a single diastereomer. The emergence of a single diastereomer was thought to proceed via epimerization of the amine stereocenter under the basic conditions upon formation of bicycle **18**. In an attempt to avoid this amine cyclization, we subjected sulfonamide **13** to further protection by acylation with sorbyl chloride, **19**, and DMAP. Remarkably, the 5.5:1 dr of sulfonamide **13** appeared irrelevant, because dienone **15**, in which the amine functionality was now bis-protected, emerged in an 80% yield as a single diastereomer. Interestingly, upon acylation of the 5.5:1 diastereomeric mixture of dienone **13** with sorbyl chloride, we were able to initially observe both acylated diastereomers by TLC. However, the enhanced acidity of the amine stereocenter proton of dienone **15** was prone to epimerization with DMAP and cleanly converged the initial diastereomeric mixture of acylated products to a single diastereomer. All attempts to open the lactone in **15** with various nucleophiles such as pyrrolidine failed and simply returned the starting material, even after prolonged reaction times. To overcome this new obstacle, we sought to decrease the steric bulk surrounding the nitrogen atom by deprotection of the SES group with various fluoride reagents. However, we observed coumarin **16** in 88% yield upon treatment of sulfonamide **15** with cesium fluoride.

(13) (a) Kozlowski, M. C.; Bartlett, P. A. *J. Org. Chem.* **1996**, *61*, 7681–7696. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031–5041. (c) Parker, K. A.; Mindt, T. L. *Org. Lett.* **2002**, *4*, 4265–4268. (d) Declerck, V.; Ribière, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372–8381. (e) Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2002**, 2308–2316.

SCHEME 4. Explorations of Dienone Reactivity

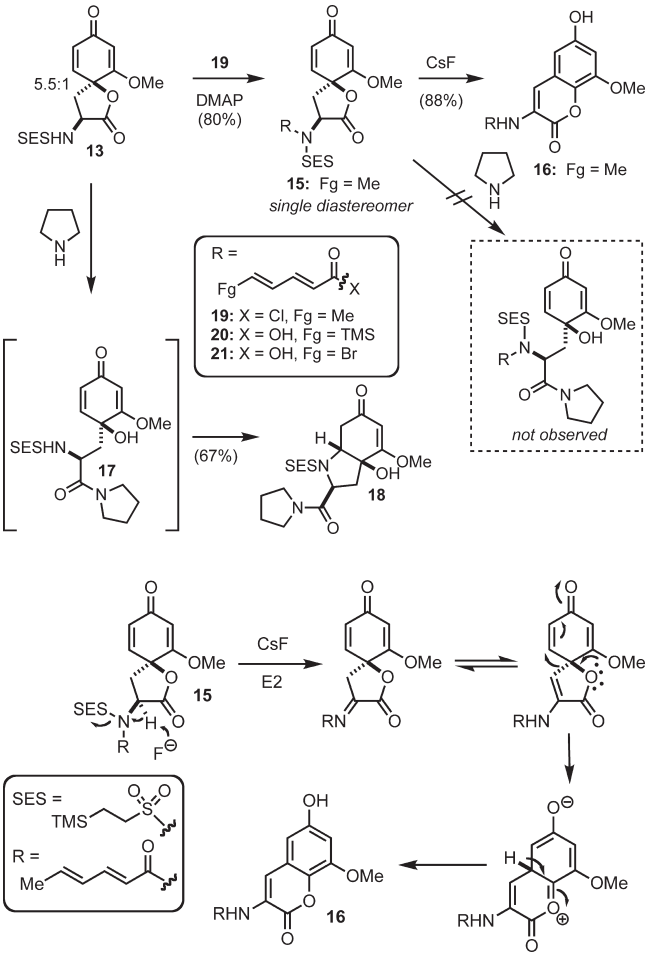


FIGURE 4. Plausible mechanism for coumarin formation.

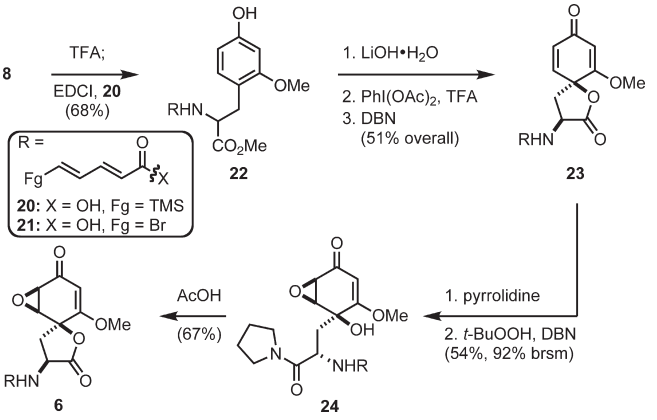
While the specifics of this transformation, which surprisingly occurs under basic conditions, remain elusive, Barlett has suggested that the SES residue on sulfonamide can be cleaved by E2 elimination.[13] From this imine intermediate, we suspected that tautomerization and dienone−phenol rearrangement would produce observed coumarin **16** (Figure 4).

On the basis of these many observations, we now realized the extent to which the nature of the substituents on the amino group drastically affected our ability to functionalize the dienone core. Moreover, while the sulfonamide substitution provided fairly good diastereoselection from the oxidative dearomatization procedure with Weinreb amide derivatives, it was proving to be a liability in subsequent reactions. We therefore decided to investigate the dearomatization of acid derivatives, as this was expected to be more tolerant of various amine derivatives. While the diastereoselection was expected to be poor, this problem appeared resolvable.

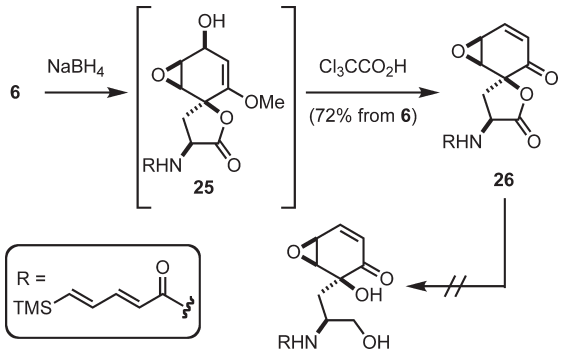
We returned to the bis-Boc material **8** (Scheme 5). Its treatment with TFA resulted in cleavage of both the *N*-Boc and *O*-Boc residues. The coupling of this crude material with TMS dienoyl acid **20**[14] using EDCI afforded dienoyl amide derivative **22** in 68% yield. The ester functionality within this

(14) Abarbri, M.; Parrain, J.-L.; Duchêne, A.; Thibonnet, J. *Synthesis* **2006**, *17*, 2951–2970.

SCHEME 5. Dearomatization of Acid Derivatives



SCHEME 6. First Foray toward Reduction

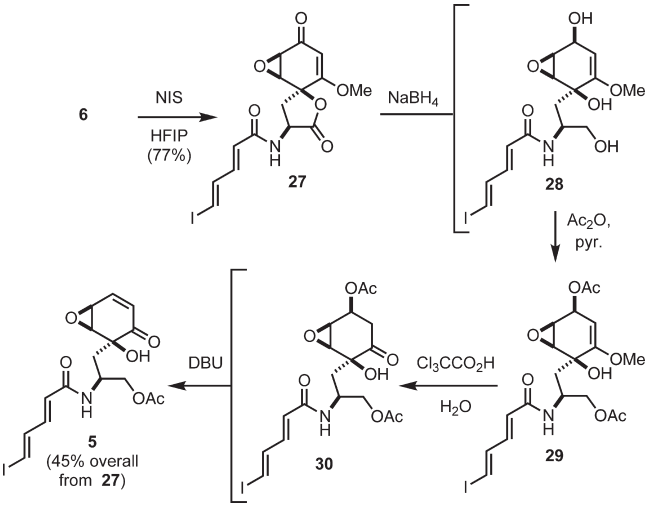


compound underwent saponification upon treatment with lithium hydroxide. Exposure of the crude acid to $PhI(OAc)_2$ and TFA followed by treatment of the resulting 1:1 mixture of diastereomers emerging from workup with DBN smoothly provided spirocyclic lactone **23** as a 6:1 mixture of diastereomers with a 51% yield of the major isomer after purification. Resubjection of the undesired diastereomer to DBN resulted in equilibration to a 6:1 mixture again favoring lactone **23**.

With a less sterically encumbered amine substituent, the lactone in **23** easily underwent addition of pyrrolidine. Subsequent treatment with *t*-BuOOH and DBN afforded epoxide **24** in 54% yield (92% brsm). Relactonization of **24** in the presence of acetic acid gave the desired epoxylactone **6** in 67% yield. Remarkably, it was this lactonization process that ultimately determined our choice of the TMS dienoyl amide derived from **20**, as opposed to corresponding bromide analogue derived from **21**. The latter (**24**: Fg = Br) inexplicably failed to undergo relactonization under acidic conditions. This decision, however, now mandated another step in our plan as the TMS residue would have to be exchanged later for a more reactive functional group to ensure the success of the vinyl coupling reaction.

We next investigated the introduction of a single hydride to lactone **6** (Scheme 6). Treatment of this lactone with aqueous $NaBH_4$ resulted in 1,2-reduction of the dienone carbonyl from the α-face to afford the unstable *syn*-epoxy alcohol **25**.[15] While we were unable to fully establish the

SCHEME 7. Second Reduction Sequence



stereochemistry of the hydride addition, we were extremely gratified to find that treatment of the crude alcohol with trichloroacetic acid revealed the desired epoxycyclohexenone **26** with a 72% yield over two steps. Unfortunately, all further attempts to reduce the lactone portion of compound **26** to the primary alcohol as found in scyphostatin (**3**) proved unsuccessful.

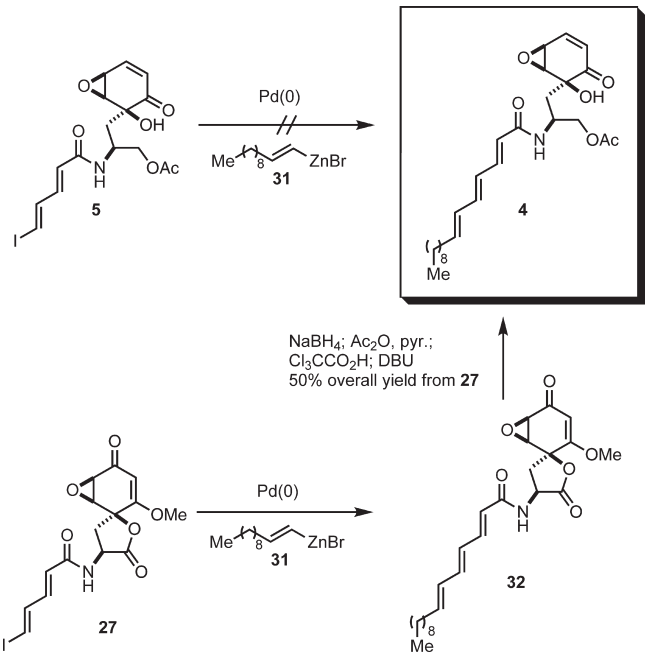
In light of these findings, we decided to investigate the sequential introduction of three hydrides prior to the rearrangement and full disclosure of the enone core (Scheme 7). We had previously demonstrated the successful introduction of two hydrides and rearrangement during our synthesis of the isariotins.[7] Because the rearrangement would require the subsequent use of a strong acid, however, we felt it prudent to perform the exchange of the acid-labile vinyl TMS residue for the iodide substituent now rather than later. Exposure of lactone **6** to the conditions developed by Zakarian and coworkers cleanly afforded iodide **27** in 77% yield.[16] Further treatment of this material with $NaBH_4$ at 0 °C, followed by warming to rt, produced intermediate triol **28**. We believe that this transformation proceeded by the sequential reduction of the vinylogous ester, the lactone and finally the hemiketal. Because of its polarity, the triol was not isolated nor subjected to aqueous workup. Instead it was immediately bis-acetylated with acetic anhydride and pyridine. Concentration of this crude reaction mixture, followed by sequential treatment with aqueous trichloroacetic acid then DBU, provided vinyl iodide **5** in a 45% overall yield from **27** via the intermediacy of **28**, **29**, and **30** as evident by ^1H NMR spectroscopy.

We were now determined to find a suitable set of conditions that would enable cross-coupling of organometallic species **31** with vinyl iodide **5**. This would generate an analogue of the chiral lipophilic tail found in scyphostatin (**3**) (Scheme 8). All attempts to expose iodide **5** to ligandless, phosphine-based (PPh_3, dtbpf, dppf, dppe, etc.), neutral (dba), and NHC-based (PEPSI) palladium mediated cross-coupling conditions led to the immediate destruction of the starting material. We then considered vinyl iodide **27** which

(15) Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A., Jr. *Org. Lett.* **2001**, *3*, 1649–1652.

(16) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727–1730.

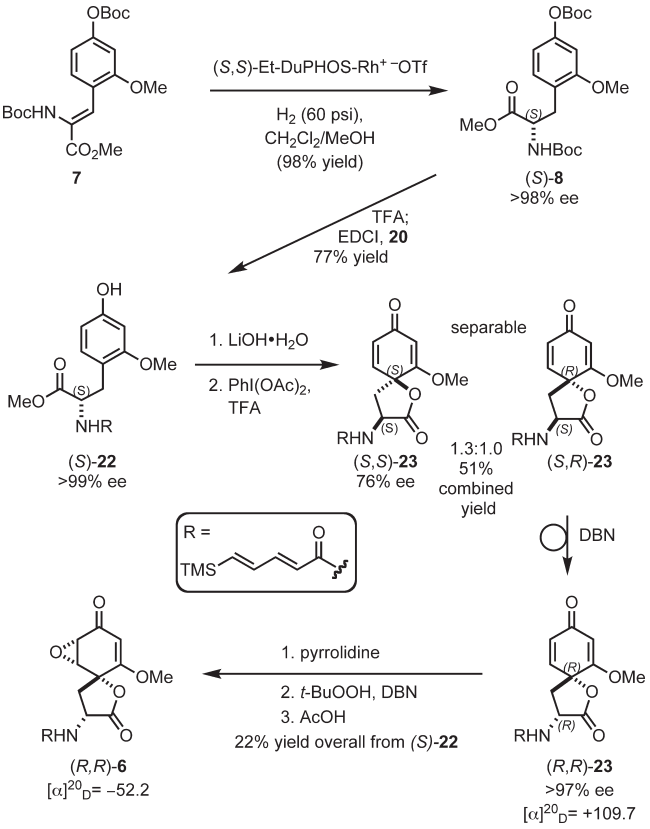
SCHEME 8. Failed Cross-Coupling and a Workaround Solution



seemed more tolerant of coupling reactions. Fortunately, we found that when catalyzed by Pd(0), vinyl iodide **27** smoothly engaged with vinyl zinc species **31**, as prepared from (*E*)-1-iodoundec-1-ene,[17] and the reaction afforded trienoyl amide **32** in 75% yield.[18] Sequential treatment of the carbonyls in compound **32** to the same regimen of hydride, acetic anhydride, acid, and then base as previously applied to **27** gave acetate **4** in 50% yield from **27**. Incidentally, an analogue of acetate **4** has been reported to successfully undergo deprotection when treated with lipase PS.[6a] Therefore, we had successfully accomplished our goal of identifying a new material for the late stage elaboration into scyphostatin analogues displaying various lipophilic tails. However, these efforts would only result in racemic derivatives of **4**. We therefore turned our attention to adapting the prior strategy so that we might also enable enantioselective access.

The rhodium-catalyzed enantioselective reduction of *Z*-configured material **7** proceeded smoothly under the conditions outlined by Han and co-workers in the presence of Burk's Et-DuPHOS ligand to afford ester (*S*)-**8** in 98% yield and >98% ee (Scheme 9).[19,20] We then attached the sorbyl side chain, using **20** as before, and obtained (*S*)-**22** in 77% yield and >99% ee. With this optically active substrate, we were now poised to explore the stereochemical consequences of our dearomatization protocol. In the context of the earlier synthesis of racemic **4**, we had observed basic conditions causing epimerization of the amine stereocenter. However, the process by which this event occurred remained unclear to us. We hoped that perhaps this was an S_N2' process resulting

SCHEME 9. Enantioselective Access



in the opening and closing of the lactone ring on the cyclohexadienone catalyzed by base, as opposed to the more conventional notion of deprotonation and reprotonation. If the former idea were true, then the undesired (*S*,*R*) diastereomer might be converted into its (*S*,*S*) enantiomer. Otherwise, we would then be forced to separate the two diastereomers, epimerize the undesired isomer, and carry each enantiomer forward separately.

Ester (*S*)-**22** was hydrolyzed, as before, and subjected to oxidative dearomatization to afford a 51% yield of a 1.35:1 mixture of diastereomers. The major diastereomer (*S*,*S*)-**23** was produced in 76% ee. Treatment of the minor diastereomer (*S*,*R*)-**23** with DBN afforded (*R*,*R*)-**23** in 85% yield and >97% ee. The erosion of enantioselectivity within the desired (*S*,*S*)-**23** was attributed to classical epimerization during the course of the dearomatization. Nevertheless, both enantiomers of **23** were separately carried forward to their respective enantiomers of the late stage coupling partner **6** as outlined earlier.

Conclusion

In summary, a strategy for the generation of non-natural scyphostatin analogues has been implemented along with access to enantiomerically enriched cyclohexadienones. From our studies of the oxidative dearomatization of non-natural tyrosine analogues, we found it best to utilize a carboxylic acid cyclization component due to the inability of sulfonamide-based cyclohexadienones to be utilized in our epoxidation protocol. In addition, we successfully identified the requisite timing of introducing the trienoyl motif with

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vinylogous ester **5** as well as the necessary sequence of reduction and revelation of the polar epoxycyclohexenone core found in scyphostatin (**3**). With our nonracemic tyrosine analogues, we elucidated a probable pathway that leads to the generation of enantiomerically pure cyclohexadienones and secured the ability to advance these materials forward in an epoxidation protocol without compromising the stereochemical integrity of the core.

Experimental Section

General Procedures. In reactions where water was not present as a solvent, reagent, or byproduct, all glass vessels were flame-dried. A slight positive pressure of dry nitrogen was maintained via rubber septum seal during the course of the reaction. Atmospheric (1 atm) hydrogenations were carried out using hydrogen-filled balloons. Reagents were purchased from commercial vendors and used as received unless otherwise stated. Tetrahydrofuran (THF) and toluene ($PhCH_3$) were distilled from sodium and benzophenone. Methanol (MeOH) was distilled from $Mg(OMe)_2$. Dichloromethane (CH_2Cl_2) and triethylamine (NEt_3) were distilled from CaH_2. *N*,*N*-Dimethylformamide (DMF) was distilled from $CaSO_4$ under reduced pressure (15 mmHg). Pyrrolidine was distilled from sodium at atmospheric pressure. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) was distilled under reduced pressure (1 mmHg). Trifluoroacetic acid (TFA) was fractionally distilled. Reactions were monitored by analytical thin-layer chromatography on hard layer silica gel-60F-250. Visualization was effected by ultraviolet light (254 nm), followed by staining (Seebach or permanganate). Removal of solvents was typically accomplished using a rotary evaporator. If the product was not volatile (bp >300 °C), remaining trace solvents were removed at a pressure of approximately 0.03 mmHg. Silica gel (60, particle size 0.043−0.063 mm) was used for flash column chromatography. NMR spectra were recorded on either a 400 or 500 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations (or combinations thereof) are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad, app = apparent). High-resolution mass spectra (HRMS) were recorded by electrospray ionization/time-of-flight experiments. Melting points are uncorrected.

***tert*-Butyl 3-(4-Hydroxy-2-methoxyphenyl)-1-(methoxy(methyl)-amino)-1-oxopropan-2-ylcarbamate (9).** To a solution of ester **8** (1320 mg, 3.10 mmol, 1.0 equiv) in 1:1 THF/H_2O (16 mL) was added $LiOH \cdot H_2O$ (450 mg, 11 mmol, 3.5 equiv). The mixture was stirred at rt for 14 h and then acidified with 1 M HCl to pH 1. The aqueous mixture was extracted with EtOAc (4 × 25 mL), and the combined organic extracts were washed with brine (1 × 50 mL) and dried over Na_2SO_4. The organic extracts were then filtered through a small pad of SiO_2 while eluting with EtOAc and concentrated in vacuo to give an oil that was sufficiently pure for use in the next step. To a solution of a portion of the crude acid prepared above (322 mg, 1.03 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added $HN(OMe)Me \cdot HCl$ (202 mg, 2.07 mmol, 2.01 equiv), NEt_3 (0.720 mL, 5.17 mmol, 5.02 equiv), and then $EDCI \cdot HCl$ (397 mg, 2.07 mmol, 2.01 equiv). The solution was allowed to stir at rt for 16 h and then diluted with EtOAc. The organic solution was washed with satd $NaHCO_3$ (3 × 20 mL), satd NH_4Cl (3 × 20 mL), H_2O (2 × 20 mL), and brine (1 × 20 mL). The solution was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (45% → 70% EtOAc/Hex) to give Weinreb amide **9** (183 mg, 50% from **8**) as a white solid: mp 200−203 °C; R_f = 0.26 (60h% EtOAc/Hex); IR (neat) ν_{max} 3360, 3271, 2972, 2926, 2851, 1686, 1651, 1616, 1597, 1539, 1512, 1470, 1429, 1391, 1368, 1346, 1290, 1246, 1192, 1161, 1125, 1038, 997, 856; *this compound exhibited rotomers in the NMR spectra obtained; ^{1}H NMR (500 MHz; DMSO-d_6) δ 9.23 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.79 (s, 1H), 6.33 (s, 1H), 6.21 (d, J = 7.5 Hz, 1H), 4.61 (td, J = 0.8, 0.6 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.03 (s, 3H), 2.77−2.75 (m, 1H), 2.51 (t, J = 12.0 Hz, 1H), 1.29−1.24 (m, 9H); ^{13}C NMR (125 MHz; DMSO-d_6) δ 173.2, 158.3, 157.4, 155.3, 131.4, 115.5, 106.3, 98.7, 77.9, 61.0, 55.1, 50.5, 31.9, 31.2, 28.2; HRMS (ESI/TOF) calcd for $C_{17}H_{26}N_2O_6Na$ $[M + Na]^+$ 377.1689, found 377.1687.

3-(4-Hydroxy-2-methoxyphenyl)-*N*-methoxy-*N*-methyl-2-(2,2,2-trifluoroacetamido)propanamide (10). To a suspension of Weinreb amide **9** (213 mg, 0.601 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added TFA (460 μL, 6.0 mmol, 10. equiv). After 4 h, the solution was concentrated in vacuo. The crude residue was redissolved in MeOH (6 mL) and to this was added NEt_3 (420 μL, 3.0 mmol, 5.0 equiv) and methyl trifluoroacetate (120 μL, 1.2 mmol, 2.0 equiv). The solution was allowed to stir at rt for 4 h and then concentrated in vacuo. The crude residue was purified by flash chromatography (45% → 70% EtOAc/Hex) to give **10** (147 mg, 70%) as a white solid: mp 170−172 °C; R_f = 0.53 (60% EtOAc/Hex); IR (neat) ν_{max} 3426, 3227, 3084, 2944, 1709, 1642, 1613, 1566, 1512, 1462, 1356, 1290, 1223, 1208, 1190, 1148, 1037, 986, 957, 882, 829, 704, 629; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.83 (d, J = 7.0 Hz, 1H, −NH), 7.01 (s, 1H, −OH), 6.79 (d, J = 8.1 Hz, 1H), 6.26 (d, J = 8.0 Hz, 1H), 6.17 (s, 1H), 5.11 (m, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.25 (s, 3H), 3.07 (m, 2H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 170.6, 158.3, 157.5, 131.8, 117.1, 114.8, 107.6, 99.2, 62.0, 55.2, 52.0, 32.5, 31.4, 29.9; HRMS (ESI/TOF) calcd for $C_{14}H_{17}N_2O_5F_3Na$ $[M + Na]^+$ 373.0987, found 373.0975.

3-(4-Hydroxy-2-methoxyphenyl)-*N*-methoxy-*N*-methyl-2-(2-(trimethylsilyl)ethylsulfonamido)propanamide (11). To a suspension of Weinreb amide **9** (686 mg, 1.94 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added TFA (1.5 mL, 20. mmol, 10. equiv). The solution was allowed to stir for 4 h and concentrated in vacuo. The resulting crude residue was redissolved in DMF (8 mL) and to this was added pyridine (390 μL, 4.8 mmol, 2.5 equiv) and SESCl (427 mg, 2.13 mmol, 1.10 equiv). The solution was stirred for 6 h, at which time, the solution was diluted with EtOAc (30 mL) and brine (30 mL). The organic layer was washed with brine (2 × 30 mL), satd NH_4Cl (3 × 20 mL), H_2O (3 × 20 mL), and brine (1 × 30 mL). The solution was then dried over Na_2SO_4 and concentrated in vacuo. The crude residue was azeotroped with heptane (3 × 30 mL) and then purified by flash chromatography (35% → 60% EtOAc/Hex) to give **11** as a white solid (494 mg, 61% from **9**): mp 120−122 °C; R_f = 0.30 (50% EtOAc/Hex); IR (neat) ν_{max} 3270, 2951, 1651, 1616, 1599, 1512, 1470, 1435, 1389, 1317, 1296, 1250, 1196, 1165, 1140, 1082, 1036, 988, 955, 895, 860, 839, 737, 698; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.93 (d, J = 8.0 Hz, 1H), 6.36 (d, J = 2.1 Hz, 1H), 6.32 (dd, J = 8.0, 2.2 Hz, 1H), 6.20 (s, O*H*), 5.18 (d, J = 9.7 Hz, N*H*), 4.73 (m, 1H), 3.77 (s, 6H), 3.22 (s, 3H), 2.95 (dd, J = 13.6, 4.6 Hz, 1H), 2.83 (dd, J = 13.5, 8.7 Hz, 1H), 2.62 (m, 2H), 0.84 (m, 2H), −0.04 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 172.9, 158.9, 156.9, 132.3, 116.1, 107.1, 99.2, 61.9, 55.6, 53.7, 50.1, 33.7, 32.5, 10.2, −1.9; HRMS (ESI/TOF) calcd for $C_{17}H_{30}N_2O_6SSiNa$ $[M + Na]^+$ 441.1492, found 441.1489.

***tert*-Butyl (3*S*,5*S*)-6-Methoxy-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-ylcarbamate (12).** To a solution of Weinreb amide **9** (33 mg, 0.090 mmol, 1.0 equiv) in CH_2Cl_2 (9 mL) at 0 °C was added in one portion $PhI(OCOCF_3)_2$ (100 mg, 0.232 mmol, 2.6 equiv). After the mixture was stirred for 15 min, satd $NaHCO_3$ (10 mL) was added followed by EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (1 × 20 mL) and dried over Na_2SO_4. The organic layer was then filtered through a small pad of SiO_2 eluting with EtOAc and concentrated in vacuo. The crude residue was purified by flash chromatography (45% → 65% EtOAc/Hex) to give **12** as a white solid (10 mg, 35%): mp 178−180 °C; R_f = 0.35 (60%

EtOAc/Hex); IR (neat) ν_{max} 3351, 2924, 2851, 1794, 1705, 1669, 1636, 1608, 1516, 1456, 1375, 1316, 1281, 1254, 1227, 1200, 1159, 1123, 1022, 987, 953, 856, 737, 631; ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.70 (d, J = 9.7 Hz, 1H), 6.23 (d, J = 9.8 Hz, 1H), 5.55 (s, 1H), 5.25 (m, 1H), 4.66 (m, 1H), 3.80 (s, 3H), 2.79 (t, J = 11.3 Hz, 1H), 2.44 (t, J = 11.7 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 186.1, 174.5, 172.4, 171.3, 155.4, 142.6, 129.3, 101.9, 81.3, 56.6, 50.7, 38.6, 28.5; HRMS (ESI/TOF) calcd for $C_{15}H_{19}NO_6Na$ $[M + Na]^+$ 332.1110, found 332.1104.

(6*S*)-*N*,7-Dimethoxy-*N*-methyl-9-oxo-2-(trifluoromethyl)-1-oxa-3-azaspiro[5.5]undeca-2,7,10-triene-4-carboxamide (14). To a solution of $PhI(OAc)_2$ (29 mg, 0.090 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) at rt was added TFA (10. μL, 0.13 mmol, 2.2 equiv). After being stirred for 30 min, the solution was cannulated over to a solution of **10** (21 mg, 0.060 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL). After being stirred for 10 min, the mixture was quenched with SiO_2 and solid $NaHCO_3$ and then filtered through a small pad of SiO_2, eluting with EtOAc. The solution was then concentrated in vacuo. The crude oil was purified by flash chromatography (45% → 70% EtOAc/Hex) to give **14** as an oil (10 mg, 48%, 4:1 dr). *Values for the major diastereomer are listed: R_f = 0.36 (5% MeOH/CH_2Cl_2); IR (neat) ν_{max} 2942, 2853, 1701, 1670, 1638, 1605, 1458, 1437, 1364, 1341, 1298, 1225, 1215, 1154, 1094, 1065, 991, 964, 901, 855, 766; ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.59 (d, J = 10.0 Hz, 1H), 6.24 (dd, J = 9.9, 1.6 Hz, 1H), 5.56 (d, J = 1.6 Hz, 1H), 4.97 (br s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.25 (s, 3H), 2.39 (t, J = 14.4 Hz, 1H), 2.09 (dd, J = 14.6, 5.3 Hz, 1H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 185.7, 172.3, 142.9, 139.3, 129.6, 129.2, 103.1, 101.9, 73.4, 62.1, 56.7, 49.7, 32.7, 30.5; HRMS (ESI/TOF) calcd for $C_{14}H_{15}N_2O_5F_3Na$ $[M + Na]^+$ 371.0831, found 371.0814.

***N*-((3*S*,5*S*)-6-Methoxy-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)-2-(trimethylsilyl)ethanesulfonamide (13).** To a solution of $PhI(OAc)_2$ (2.4 g, 7.5 mmol, 1.5 equiv) in CH_2Cl_2 (150 mL) at rt was added TFA (0.86 mL, 11.2 mmol, 2.2 equiv). After being stirred for 30 min, the solution was cannulated over to a solution of **11** (2.1 g, 5.0 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL). After being stirred for 10 min, the mixture was quenched with SiO_2 (5 g) and filtered through a small pad of SiO_2, eluting with EtOAc. The solution was then concentrated in vacuo. The crude oil was purified by flash chromatography (45% → 70% EtOAc/Hex) to give **13** as an oil (1.2 g, 64%, 5.5:1 dr): R_f = 0.28 (50% EtOAc/Hex); IR (neat) ν_{max} 3271, 2953, 2922, 2851, 1792, 1669, 1634, 1607, 1456, 1377, 1337, 1227, 1196, 1171, 1136, 1074, 1018, 990, 964, 858, 842, 797, 758, 739, 698, 629; *values for the major diastereomer are listed; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.58 (d, J = 9.8 Hz, 1H), 6.27 (d, J = 9.9 Hz, 1H), 5.58 (s, 1H), 5.32 (d, J = 7.9 Hz, N*H*), 4.79 (ddd, J = 10.7, 9.3, 7.5 Hz, 1H), 3.83 (s, 3H), 3.17 (m, 2H), 2.94 (dd, J = 15.5, 7.5 Hz, 1H), 2.37 (dd, J = 15.8, 8.6 Hz, 1H), 1.12 (m, 2H), 0.09 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 185.9, 174.3, 170.7, 141.9, 129.8, 102.1, 76.5, 56.9, 52.7, 51.4, 40.0, 10.7, −1.8; HRMS (ESI/TOF) calcd for $C_{15}H_{23}NO_6SiSNa$ $[M + Na]^+$ 396.0913, found 396.0907.

(2*S*,3a*S*,7a*R*)-3a-Hydroxy-4-methoxy-2-(pyrrolidine-1-carbonyl)-1-(2-(trimethylsilyl)ethylsulfonyl)-3,3a,7,7a-tetrahydro-1*H*-indol-6(2*H*)-one (18). To a solution of dienone **13** (20 mg, 0.05 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) at 0 °C was added pyrrolidine (10. μL, 0.12 mmol, 2 equiv). The yellow solution was allowed to stir for 2 h at rt and then diluted with EtOAc (10 mL) and satd NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (1 × 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (0% → 15% MeOH/CH_2Cl_2) to provide **18** (15 mg, 67%) as an oil: R_f = 0.5 (20% acetone/CH_2Cl_2); IR (neat) ν_{max} 3194, 3094, 2953, 2924, 2851, 1728, 1661, 1622, 1615, 1456, 1424, 1339, 1289, 1251, 1250, 1229, 1211, 1167, 1148, 1132, 1094, 1046, 1036, 978, 860, 843, 741, 702; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.79 (s, 1H), 5.42 (s, 1H), 4.92 (d, J = 9.1, 1H), 4.33 (dd, J = 11.4, 6.3, 1H), 3.90 (dt, J = 9.7, 6.7, 1H), 3.79 (s, 1H), 3.49 (m, 1H), 3.26 (dd, J = 16.8, 6.3, 1H), 3.00 (m, 1H), 2.60 (dd, J = 13.9, 9.9, 1H), 2.38 (m, 1H), 2.03 (m, 1H), 1.93 (m, 1H), 1.09 (m, 1H), 0.04 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 194.4, 174.1, 170.6, 103.1, 77.8, 69.1, 58.3, 57.0, 49.8, 47.5, 47.1, 44.4, 39.5, 26.3, 24.3, 10.3, −1.8; HRMS (ESI/TOF) calcd for $C_{19}H_{32}N_2O_6SiSNa$ $[M + Na]^+$ 467.1648, found 467.1629.

(2*E*,4*E*)-*N*-(6-Methoxy-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)-*N*-(2-(trimethylsilyl)ethylsulfonyl)hexa-2,4-dienamide (15). To a solution of **13** (92 mg, 0.25 mmol, 1.0 equiv) in DCM were added sorbyl chloride (0.061 mL, 0.50 mmol, 2.0 equiv) and DMAP (153 mg, 1.25 mmol, 5.0 equiv) at rt. The resulting solution was allowed to stir for 16 h, at which time the volatile material was removed in vacuo. The crude residue was purified by flash chromatography (5% → 35% EtOAc/CH_2Cl_2) to provide **15** (94 mg, 80%) as an oil: R_f = 0.37 (35% EtOAc/Hex); IR (neat) ν_{max} 2953, 2924, 2851, 1792, 1670, 1634, 1609, 1601, 1458, 1356, 1314, 1250, 1227, 1196, 1167, 1154, 1123, 1076, 1036, 1003, 928, 899, 856, 793, 758, 739, 696, 621; *this compound exhibited rotomers in the NMR spectra which broadened several peaks, designated by **; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.44 (m, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 13.3 Hz, 1H), 6.30 (m, 2H), 6.21 (dd, J = 9.9, 1.5 Hz, 1H), 5.55 (d, J = 1.4 Hz, 1H), 5.20 (br s, 1H), 3.82 (s, 3H), 3.40 (m, 1H), 2.72 (m, 1H), 2.57 (m, 1H), 1.90 (d, J = 4.9 Hz, 3H), 1.18 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 186.2, 172.6, 171.1, 166.2, 149.3, 143.2, 142.4, 130.2, 128.9, 117.3, 101.9, 76.7, 56.7, 56.1, 53.2, 35.7, 19.2, 10.1, −1.8; HRMS (ESI/TOF) calcd for $C_{21}H_{29}NO_{7}$-SiSNa $[M + Na]^+$ 490.1332, found 490.1322.

(2*E*,4*E*)-*N*-(6-Hydroxy-8-methoxy-2-oxo-2*H*-chromen-3-yl)-hexa-2,4-dienamide (16). To a stirred solution of **15** (30 mg, 0.06 mmol, 1.0 equiv) in DMF (2.0 mL) at rt was added in one portion CsF (98 mg, 0.65 mmol, 10 equiv) and then H_2O (0.2 mL). The resulting solution was stirred for 6 h and then diluted with EtOAc (15 mL). The organic solution was washed with brine (5 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography with NEt_3 doped SiO_2 (15% → 55% EtOAc/Hex) to give **16** as an oil (16 mg, 88%). *Note: this compound is both light (ambient and UV) and acid sensitive: R_f = 0.24 (35% EtOAc/Hex); IR (neat) ν_{max} 3322, 3270, 3131, 3028, 2942, 2849, 1778, 1688, 1663, 1636, 1607, 1530, 1456, 1379, 1343, 1300, 1229, 1157, 1132, 1103, 1067, 1032, 995, 910, 856, 779, 731, 648; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.79 (s, 1H), 7.35 (m, 1H), 7.17 (s, 1H), 6.33 (m, 2H), 6.24 (m, 2H), 5.95 (d, J = 14.8, 1H), 5.68 (d, J = 1.2, 1H), 3.73 (s, 3H), 1.89 (d, J = 4.6, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 186.0, 169.5, 167.6, 165.0, 145.2, 141.3, 139.1, 130.6, 129.6, 127.8, 127.2, 126.1, 119.3, 103.7, 56.6, 19.0; HRMS (ESI/TOF) calcd for $C_{16}H_{15}NNaO_5$ $[M + Na]^+$ 324.0848, found 324.0842.

(*S*)-Methyl 3-(4-Hydroxy-2-methoxyphenyl)-2-((2*E*,4*E*)-5-(trimethylsilyl)penta-2,4-dienamido)propanoate (22). To a solution of **8** (2.8 g, 6.6 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) was added TFA (20 mL). The solution was stirred at rt for 24 h and concentrated in vacuo using a water aspirator. The crude residue was azeotroped with hexanes (3 × 50 mL) and placed under high vacuum (0.03 mmHg) for 3 h. The resulting crude trifluoroacetate salt was redissolved in DMF (7 mL), and to this was added a solution of acid **20** (1.46 g, 8.56 mmol, 1.3 equiv) in DMF (7 mL), EDCI (1.64 g, 8.57 mmol, 1.3 equiv), and then NEt_3 (4.6 mL, 33 mmol, 5.0 equiv). The resulting solution was stirred for 16 h at rt and then partitioned between EtOAc (50 mL) and brine (50 mL). The layers were separated, and the organic layer was washed with brine (3 × 25 mL), satd NH_4Cl (3 × 25 mL), satd $NaHCO_3$ (3 × 25 mL), H_2O (2 × 25 mL), and brine (1 × 50 mL). The solution was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (30% → 45% EtOAc/Hex) to give **22** (1.69 g, 68%) as a white solid: mp 202−204 °C; R_f = 0.41 (50% EtOAc/Hex); IR (neat) ν_{max} 3295, 2953, 1744, 1732, 1657, 1651, 1615, 1582, 1557, 1537, 1512, 1470, 1454, 1435, 1366, 1348,

1337, 1279, 1248, 1198, 1177, 1161, 1127, 1036, 1007, 957, 862, 837, 774, 748, 737, 718, 694, 633; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.12 (dd, J = 15.1, 10.5 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.56 (dd, J = 18.3, 10.5 Hz, 1H), 6.32 (m, 3 overlapping signals, N*H* and 3H), 5.92 (br s, O*H*), 5.81 (d, J = 15.0 Hz, 1H), 4.81 (q, J = 6.6 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.07 (m, 2H), 0.11 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 172.6, 165.9, 158.6, 156.7, 144.1, 143.4, 141.3, 131.8, 123.6, 116.2, 107.4, 99.2, 55.7, 53.6, 52.5, 32.1, −1.3; HRMS (ESI/TOF) calcd for $C_{19}H_{27}NO_5SiNa$ $[M + Na]^+$ 400.1556, found 400.1543. Chiral HPLC analysis indicated an enantiomeric excess of 99.0% (Chiracel OD-H column; flow: 1.0 mL/min; 8% IPA/Hex; 275 nm; minor enantiomer (*R*)-**22**, t_R = 27.6 min; major enantiomer (*S*)-**22**, t_R = 49.1 min; $[\alpha]^{20}$ +2.5 (*c* 0.98, $CHCl_3$)). This material was prepared optically pure utilizing (*S*)-**8**, which was prepared from the asymmetric reduction of (*Z*)-**7**: A Parr flask was charged with a degassed solution of (*Z*)-**7** (1.0 g, 2.4 mmol, 1.0 equiv) in 1:1 CH_2Cl_2/MeOH (12 mL) and to this was added [((*S*,*S*)-Et-DuPhos)Rh(COD)]OTf (17 mg, 0.024 mmol, 0.01 equiv). The resulting solution was saturated with H_2 and then shaken under an H_2 atmosphere at 60 psi for 6 days. The solution was purged with N_2 for 10 min and then filtered through a pad of Celite and concentrated in vacuo to give analytically pure (*S*)-**8** (1.0 g, ca. 98%, 98.1% ee) that matched the spectral data for the racemic compound. HRMS (ESI/TOF) calcd for $C_{21}H_{31}NO_8Na$ $[M + Na]^+$ 448.1947, found 448.1937. Chiral HPLC analysis indicated an enantiomeric excess of 98.1% (Chiracel OD-H column; flow: 1.0 mL/min; 8% IPA/Hex; 275 nm; minor enantiomer (*R*)-**8**, t_R = 7.8 min; major enantiomer (*S*)-**8**, t_R = 9.1 min; $[\alpha]^{20}$ +16.2 (*c* 1.0, $CHCl_3$)).

(2*E*,4*E*)-*N*-(6-Methoxy-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)-5-(trimethylsilyl)penta-2,4-dienamide (23). To a solution of **22** (988 mg, 2.62 mmol, 1.0 equiv) in 1:1 THF/H_2O (13 mL) was added $LiOH \cdot H_2O$ (549 mg, 13.1 mmol, 5.00 equiv). The mixture was refluxed for 1 h, cooled to rt, and then acidified with 1 M HCl to pH 1. The aqueous mixture was extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude residue was suspended in CH_2Cl_2 (25 mL), and to this was cannulated over a solution prepared by the addition of TFA (451 μL, 5.89 mmol, 2.25 equiv) to $PhI(OAc)_2$ (1.26 g, 3.91 mmol, 1.49 equiv) in CH_2Cl_2 (25 mL) at rt. The resulting mixture was stirred for 15 min, and to this was added solid $NaHCO_3$ (2 g) and then SiO_2 (5 g). The resulting slurry was filtered through a small pad of SiO_2 and eluted with EtOAc. The solution was then concentrated in vacuo. The resulting crude residue was redissolved in CH_2Cl_2 (26 mL) and treated with DBN (643 μL, 5.20 mmol, 1.98 equiv). After 15 min, the solution was partitioned between EtOAc (100 mL) and satd NH_4Cl (50 mL). The layers were separated and the organic extract was washed with sat. NH_4Cl (2 × 20 mL), H_2O (2 × 20 mL), and brine (1 × 50 mL). The solution was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (40% → 65% EtOAc/Hex) to give (*S*,*S*)-**23** (483 mg, 51% from **22**) as an oil and (*S*,*R*)-**23** as an oil (81 mg): R_f = 0.17 (50% EtOAc/Hex); IR (neat) ν_{max} 3302, 3053, 2955, 2899, 2853, 1794, 1670, 1609, 1578, 1528, 1458, 1375, 1348, 1314, 1263, 1248, 1227, 1198, 1182, 1123, 1100, 1074, 1011, 988, 945, 909, 862, 841, 810, 733, 696, 631; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.20 (dd, J = 15.0, 10.4 Hz, 1H), 6.83 (d, J = 6.9 Hz, 1H), 6.78 (d, J = 9.9 Hz, 1H), 6.57 (dd, J = 18.0, 10.5 Hz, 1H), 6.36 (m, 2 overlapping signals, N*H* and 1H), 6.21 (dd, J = 9.9, 1.6 Hz, 1H), 5.91 (d, J = 15.1 Hz, 1H), 5.56 (d, J = 1.6 Hz, 1H), 4.85 (td, J = 9.9, 6.9 Hz, 1H), 3.80 (s, 3H), 2.80 (dd, J = 13.3, 9.7 Hz, 1H), 2.49 (dd, J = 13.3, 10.3 Hz, 1H), 0.11 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 186.2, 174.8, 171.3, 166.7, 145.5, 144.7, 142.5, 141.0, 129.2, 122.3, 101.9, 76.8, 56.7, 50.1, 37.9, −1.4; HRMS (ESI/TOF) calcd for $C_{18}H_{23}NO_5SiNa$ $[M + Na]^+$ 384.1243, found 384.1245. Optically pure material was obtained by utilizing (*S*)-**22** as a starting material. The same procedure was followed, except epimerization was performed on each individual diastereomer obtained from the dearomatization. Chiral HPLC analysis indicated an enantiomeric excess of 76.6% for (*S*,*S*)-**23** (Chiracel OD-H column; flow: 1.0 mL/min; 15% IPA/Hex; 250 nm; minor enantiomer (*R*,*R*)-**23**, t_R = 19.3 min; major enantiomer (*S*,*S*)-**23**, t_R = 35.5 min; $[\alpha]^{20}$ −87 (*c* 0.47, $CHCl_3$)). (*R*,*R*)-**23** was prepared by using the following procedure: To a solution of (*S*,*R*)-**23** (194 mg, 0.537 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added DBN (125 μL, 1.01 mmol, 1.88 equiv). After 15 min, the solution was partitioned between EtOAc (20 mL) and satd NH_4Cl (20 mL). The layers were separated, and the organic extract was washed with satd NH_4Cl (2 × 20 mL), H_2O (2 × 20 mL), and brine (1 × 50 mL). The solution was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (40% → 65% EtOAc/Hex) to give (*R*,*R*)-**23** as an oil (165 mg, 85% from (*S*,*R*)-**23**) and recovered (*S*,*R*)-**23** (25 mg). Chiral HPLC analysis indicated an enantiomeric excess of 97.5% for (*R*,*R*)-**23** (Chiracel OD-H column; flow: 1.0 mL/min; 15% IPA/Hex; 250 nm; major enantiomer (*R*,*R*)-**23**, t_R = 21.4 min; minor enantiomer (*S*,*S*)-**23**, t_R = 35.5 min; $[\alpha]^{20}$ +109.7 (*c* 0.5, $CHCl_3$)). (*S*,*R*)-**23** could be prepared optically active by utilizing (*S*)-**22** in the hydrolysis/dearomatization protocol described, and then separating the diastereomers resulting from the dearomatization via column chromatography.

(2*E*,4*E*)-*N*-((3*S*,5*R*)-6-Methoxy-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)-5-(trimethylsilyl)penta-2,4-dienamide ((*S*,*R*)-23): R_f = 0.26 (50% EtOAc/Hex); IR (neat) ν_{max} 3293, 2953, 2853, 1792, 1667, 1609, 1578, 1537, 1453, 1377, 1352, 1316, 1277, 1248, 1229, 1182, 1109, 1072, 1009, 943, 862, 839, 741, 723, 696, 648, 627; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.21 (dd, J = 15.0, 10.5, 1H), 6.73 (d, J = 10.0, 1H), 6.59 (dd, J = 18.3, 10.4, 1H), 6.52 (d, J = 6.4, 1H), 6.35 (d, J = 18.3, 1H), 6.25 (dd, J = 10.0, 1.0, 1H), 5.92 (d, J = 15.0, 1H), 5.64 (s, 1H), 5.12 (q, J = 8.3, 1H), 3.81 (s, 1H), 2.82 (dd, J = 13.3, 9.6, 1H), 2.57 (dd, J = 13.2, 10.5, 1H), 0.11 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 185.7, 174.0, 169.2, 166.6, 145.5, 144.7, 141.0, 140.5, 129.1, 122.3, 103.5, 77.3, 56.7, 49.0, 38.0, −1.4; HRMS (ESI/TOF) calcd for $C_{18}H_{23}NO_5SiNa$ $[M + Na]^+$ 384.1243, found 384.1233.

(2*E*,4*E*)-*N*-((*S*)-3-((1*S*,2*S*,6*R*)-2-Hydroxy-3-methoxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-2-yl)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)-5-(trimethylsilyl)penta-2,4-dienamide (24). To a solution of **23** (94 mg, 0.26 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added pyrrolidine (33 μL, 0.40 mmol, 1.5 equiv) at rt. After 14 h, the reaction mixture was diluted with EtOAc (25 mL) and washed with satd NH_4Cl (3 × 10 mL), H_2O (3 × 10 mL), and brine (1 × 20 mL). The solution was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude enone−amide was redissolved in $CHCl_3$ (5 mL), and *t*-BuOOH (5.5 M in decane, 472 μL, 2.6 mmol, 10 equiv) and DBN (29 μL, 0.23 mmol, 0.88 equiv) were added at rt. After 6 h, the reaction mixture was partitioned between EtOAc (20 mL) and satd $Na_2S_2O_3$ (20 mL) and stirred for 1 h. The layers were separated, and the organic layer was washed with H_2O (3 × 10 mL) and brine (1 × 20 mL). The solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10% → 35% acetone/CH_2Cl_2) to give **24** as an oil (63 mg, 54% from **23**) and recovered pyrrolidine amide **SI-24** as an oil (43 mg): R_f = 0.43 (40% acetone/CH_2Cl_2); IR (neat) ν_{max} 3281, 3061, 2953, 2880, 1661, 1615, 1549, 1539, 1454, 1339, 1279, 1248, 1225, 1175, 1128, 1117, 1086, 1040, 1009, 991, 914, 855, 839, 777, 725, 694, 666; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.16 (dd, J = 14.9, 10.3 Hz, 1H), 6.83 (br d, J = 9.0 Hz, N*H*), 6.55 (dd, J = 18.2, 10.5 Hz, 1H), 6.31 (d, J = 18.3 Hz, 1H), 5.86 (d, J = 15.0 Hz, 1H), 5.21 (d, J = 1.9 Hz, 1H), 5.04 (td, J = 8.5, 5.5 Hz, 1H), 4.05 (br s, O*H*), 3.66 (m, 3 overlapping signals, OCH_3 and 2H), 3.45 (m, 2 overlapping signals, 4H), 2.36 (dd, J = 14.5, 5.2 Hz, 1H), 2.14 (dd, J = 14.5, 7.9 Hz, 1H), 1.98 (quintet, J = 6.5 Hz, 2H), 1.89 (quintet, J = 6.7 Hz, 2H), 0.11 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 192.7, 172.2, 169.9, 166.0, 144.7, 144.1, 141.3, 123.3, 98.2, 71.7, 57.3, 56.8, 54.4, 47.1, 46.75, 46.56, 41.3, 26.2, 24.3, −1.4; HRMS

(ESI/TOF) calcd for $C_{22}H_{32}N_2O_6SiNa$ $[M + Na]^+$ 471.1927, found 471.1937. (*S,S*)-**24**: $[\alpha]^{20}$ +108.2 (*c* 1.11, $CHCl_3$). (*R,R*)-**24**: $[\alpha]^{20}$ −111.1 (*c* 0.41, $CHCl_3$).

(2*E*,4*E*)-*N*-((*S*)-3-((*S*)-1-Hydroxy-2-methoxy-4-oxocyclohexa-2,5-dienyl)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)-5-(trimethylsilyl)-penta-2,4-dienamide (SI-24): R_f = 0.29 (40% acetone/CH_2Cl_2); IR (neat) ν_{max} 3277, 2951, 2876, 1665, 1624, 1613, 1545, 1530, 1451, 1341, 1248, 1225, 1175, 1128, 1117, 1042, 1007, 856, 839, 750, 721, 693; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.20 (d, *J* = 8.4, N*H*), 7.12 (dd, *J* = 15.0, 10.5, 1H), 6.88 (d, J = 10.1, 1H), 6.53 (dd, J = 18.3, 10.5, 1H), 6.28 (d, J = 18.3, 1H), 6.14 (dd, *J* = 10.1, 1.3, 1H), 5.90 (d, *J* = 15.0, 1H), 5.47 (d, *J* = 1.1, 1H), 4.93 (q, *J* = 7.0, 1H), 4.40 (br s, 1H), 3.76 (s, 3H), 3.64 (dt, J = 10.0, 6.7, 1H), 3.47−3.33 (m, 4H), 2.31 (qd, *J* = 12.9, 6.7, 2H), 1.94 (quintet, *J* = 6.6, 2H), 1.85 (dt, *J* = 11.2, 5.4, 2H), 0.09 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 187.1, 174.9, 169.7, 166.2, 146.0, 144.2, 143.7, 141.3, 127.7, 123.6, 101.3, 69.7, 56.2, 47.6, 46.8, 46.5, 42.7, 26.1, 24.2, −1.4; HRMS (ESI/TOF) calcd for $C_{22}H_{32}N_2O_5SiNa$ $[M + Na]^+$ 455.1978, found 455.1968.

(2*E*,4*E*)-*N*-((1*S*,2*S*,4′*S*,6*R*)-3-Methoxy-5,5′-dioxo-4′,5′-dihydro-3′*H*-7-oxaspiro[bicyclo[4.1.0]hept[3]ene-2,2′-furan]-4′-yl)-5-(trimethylsilyl)penta-2,4-dienamide (6). To a solution of **24** (41 mg, 0.091 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added acetic acid (0.5 mL) at rt. The solution was refluxed for 8 h and then concentrated in vacuo. The crude residue was purified by flash chromatography (50% → 70% EtOAc/Hex) to give **6** as an oil (23 mg, 67%): R_f = 0.44 (70% EtOAc/Hex); IR (neat) ν_{max} 3304, 2955, 2899, 2853, 1790, 1669, 1620, 1580, 1532, 1456, 1410, 1377 1350, 1310, 1275, 1248, 1229, 1200, 1182, 1101, 1084, 1049, 1040, 1007, 988, 953, 924, 864, 841, 739, 696, 656, 629; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.19 (dd, *J* = 15.0, 10.4 Hz, 1H), 6.59 (dd, *J* = 18.3, 10.5 Hz, overlapping N*H* and 1H), 6.35 (d, *J* = 18.2 Hz, 1H), 5.92 (d, *J* = 15.1 Hz, 1H), 5.27 (d, *J* = 1.9 Hz, 1H), 4.78 (td, *J* = 10.0, 6.8 Hz, 1H), 3.90 (d, *J* = 3.8 Hz, 1H), 3.77 (s, 3H), 3.55 (dd, *J* = 3.9, 2.0 Hz, 1H), 2.76 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.59 (dd, *J* = 13.3, 10.3 Hz, 1H), 0.11 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 191.7, 174.4, 169.9, 166.7, 145.7, 144.9, 141.0, 122.1, 98.5, 79.5, 57.3, 55.6, 52.9, 49.8, 38.0, −1.4; HRMS (ESI/TOF) calcd for $C_{18}H_{23}NO_6SiNa$ $[M + Na]^+$ 400.1192, found 400.1199. (*S,S*)-**6**: $[\alpha]^{20}$ +45.3 (*c* 0.8, $CHCl_3$). (*R,R*)-**6**: $[\alpha]^{20}$ −52.2 (*c* 0.74, $CHCl_3$).

(2*E*,4*E*)-*N*-((1*S*,2*S*,4′*S*,5*S*,6*S*)-5-Hydroxy-3-methoxy-5′-oxo-4′,5′-dihydro-3′*H*-7-oxaspiro[bicyclo[4.1.0]hept[3]ene-2,2′-furan]-4′-yl)-5-(trimethylsilyl)penta-2,4-dienamide (25). To a solution of **6** (9 mg, 0.02 mmol, 1.0 equiv) in THF (2 mL) at 0 °C was added a solution of $NaBH_4$ (3 mg, 0.08 mmol, 4.0 equiv) in H_2O (0.3 mL). The resulting solution was allowed to stir at 0 °C for an additional 1 h, at which time satd NH_4Cl (3 mL) and EtOAc (5 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (1 × 5 mL), filtered through a small pad of SiO_2, and concentrated in vacuo to provide a crude residue that was immediately used in the next step: R_f = 0.36 (20% THF/CH_2Cl_2); IR (neat) ν_{max} 3270, 2953, 2853, 1790, 1667, 1651, 1615, 1580, 1537, 1520, 1454, 1385, 1352, 1248, 1223, 1173, 1125, 1101, 1038, 1007, 988, 928, 864, 839, 745, 621; ^{1}H NMR (500 MHz; acetone-d_6) δ 7.86 (d, J = 7.4, 1H), 7.24 (br s, 1H), 7.13 (dd, J = 15.1, 10.5, 1H), 6.70 (dd, J = 18.3, 10.5, 1H), 6.33 (d, J = 18.3, 1H), 6.13 (d, J = 15.0, 1H), 4.77 (m, 1H), 4.59 (m, 2H), 4.21 (d, J = 7.9, 1H), 3.58−3.52 (m, 4H), 2.51 (dd, J = 10.1, 1.7, 2H), 0.10 (s, 9H); ^{13}C NMR (125 MHz; acetone-d_6) δ 174.6, 166.9, 153.5, 144.1, 143.5, 125.9, 98.2, 80.4, 66.2, 57.5, 56.2, 55.4, 50.9, 38.7, −0.8, *1 signal unresolved; HRMS (ESI/TOF) calcd for $C_{18}H_{25}NO_6SiNa$ $[M + Na]^+$ 402.1349, found 402.1352.

(2*E*,4*E*)-*N*-((1*S*,2*S*,4′*S*,6*S*)-3,5′-Dioxo-4′,5′-dihydro-3′*H*-7-oxaspiro[bicyclo[4.1.0]hept[4]ene-2,2′-furan]-4′-yl)-5-(trimethylsilyl)penta-2,4-dienamide (26). To a solution of the crude alcohol prepared above in CH_2Cl_2 (2 mL) and H_2O (0.5 mL) was added Cl_3CCO_2H (78 mg, 0.48 mmol, 24 equiv). The resulting biphasic solution was allowed to stir at rt for 6 h and then diluted with EtOAc (10 mL) and satd $NaHCO_3$ (10 mL). The layers were separated, and the organic layer was washed with satd $NaHCO_3$ (2 × 5 mL) and brine (1 × 10 mL). The solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (45% → 70% EtOAc/Hex) to give **26** as an oil (5 mg, 72% from **6**): R_f = 0.20 (60% EtOAc/Hex); IR (neat) ν_{max} 3194, 3403, 2949, 2918, 2849, 1790, 1771, 1686, 1667, 1651, 1622, 1580, 1574, 1537, 1514, 1383, 1348, 1335, 1312, 1267, 1248, 1236, 1217, 1181, 1121, 1105, 1082, 1049, 1007, 957, 864, 841, 772, 756, 747, 735, 712, 689, 650, 625; ^{1}H NMR (500 MHz; acetone-d_6) δ 7.89 (d, J = 6.9, 1H), 7.47 (dd, J = 10.0, 3.6, 1H), 7.13 (ddd, *J* = 10.6, 4.5, 0.6, 1H), 6.71 (dd, J = 18.0, 10.6, 1H), 6.34 (d, J = 18.3, 1H), 6.19 (dd, J = 9.9, 1.6, 1H), 6.13 (d, J = 15.1, 1H), 4.59−4.54 (m, 1H), 3.97 (d, J = 3.9, 1H), 3.84 (td, J = 4.0, 1.7, 1H), 2.67−2.55 (m, 1H), 0.11 (s, 9H); ^{13}C NMR (125 MHz; acetone-d_6) δ 194.1, 174.8, 167.1, 148.5, 144.5, 144.4, 142.8, 131.5, 125.8, 83.7, 56.5, 49.5, 48.9, 35.1, −0.8; HRMS (ESI/TOF) calcd for $C_{17}H_{21}NO_5SiNa$ $[M + Na]^+$ 370.1087, found 370.1074.

(2*E*,4*E*)-5-Iodo-*N*-((1*S*,2*S*,4′*S*,6*R*)-3-methoxy-5,5′-dioxo-4′,5′-dihydro-3′*H*-7-oxaspiro[bicyclo[4.1.0]hept[3]ene-2,2′-furan]-4′-yl)penta-2,4-dienamide (27). To a solution of **6** (20. mg, 0.053 mmol, 1.0 equiv) in HFIP (5 mL) at 0 °C was added NIS (30. mg, 0.13 mmol, 2.5 equiv) in one portion. The resulting solution was stirred for 10 min, at which time the reaction mixture was diluted with EtOAc (20 mL) and satd $Na_2S_2O_3$ (20 mL) and stirred for 15 min. The layers were separated, and the organic solution was washed with H_2O (3 × 5 mL) and brine (1 × 10 mL). The solution was then dried over Na_2SO_4, filtered through a small pad of SiO_2 eluting with EtOAc, and concentrated in vacuo. The residue was purified by flash chromatography (60% → 95% EtOAc/Hex) to give **27** as an oil (17.6 mg, 77%): R_f = 0.31 (70% EtOAc/Hex); IR (neat) ν_{max} 3233, 3061, 2945, 1778, 1709, 1667, 1616, 1532, 1427, 1375, 1350, 1292, 1231, 1179, 1042, 990, 922, 851, 818, 637; ^{1}H NMR (500 MHz; acetone-d_6) δ 8.13 (d, J = 6.9, N*H*), 7.28 (dd, J = 14.3, 11.1, 1H), 7.15 (m, 2H), 6.19 (d, J = 14.8, 1H), 5.30 (d, J = 1.9, 1H), 4.74 (dt, J = 10.0, 7.5, 1H), 4.00 (d, J = 4.0, 1H), 3.83 (s, 3H), 3.50 (dd, J = 3.9, 2.0, 1H), 2.76 (dd, J = 10.0, 3.3, 1H); ^{13}C NMR (125 MHz; acetone-d_6) δ 192.2, 179.0, 174.3, 171.4, 144.3, 140.9, 124.7, 98.6, 89.5, 79.5, 57.6, 56.6, 53.6, 50.2, 37.4; HRMS (ESI/TOF) calcd for $C_{15}H_{14}NO_6INa$ $[M + Na]^+$ 453.9764, found 453.9756.

(2*S*)-3-((2*S*)-2-Hydroxy-3-oxo-7-oxabicyclo[4.1.0]hept-4-en-2-yl)-2-((2*E*,4*E*)-5-iodopenta-2,4-dienamido)propyl Acetate (5). To a solution of **27** (13 mg, 0.03 mmol, 1.0 equiv) in THF (3 mL) at 0 °C was added $NaBH_4$ (6 mg, 0.2 mmol, 7 equiv) in H_2O (0.6 mL). The solution was allowed to stir at 0 °C for an additional 2 h, and then the ice bath was removed and the solution was allowed to stir at rt for 6 h. The solution was diluted with $(CH_3)_2CO$ (10 mL), stirred for 1 h, and then concentrated in vacuo. The crude residue was redissolved in 1:1 Ac_2O/pyridine (3 mL) and stirred for 6 h at rt and then concentrated in vacuo. The resulting crude residue was redissolved in CH_2Cl_2 (3 mL), and to this was added H_2O (0.3 mL) and then Cl_3CCO_2H (49 mg, 0.30 mmol, 10 equiv) at rt. The mixture was vigorously stirred for 4 h, at which time the mixture was diluted with EtOAc (15 mL) and satd $NaHCO_3$ (15 mL) and stirred for 10 min. The layers were separated, and the organic extract was washed with additional satd $NaHCO_3$ (2 × 5 mL), H_2O (3 × 5 mL), and brine (1 × 10 mL). The solution was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude residue was redissolved in CH_2Cl_2 (5 mL), and to this was added DBU (13 μL, 0.084 mmol, 3 equiv) at rt. The solution was stirred for 10 min and then diluted with EtOAc (25 mL) and satd NH_4Cl (20 mL). The layers were separated, and the organic extract was washed with additional satd NH_4Cl (2 × 10 mL), H_2O (3 × 10 mL) and brine (1 × 10 mL). The solution was then dried over Na_2SO_4, filtered through a small pad of SiO_2 eluting with EtOAc, and concentrated

in vacuo. The residue was purified by flash chromatography (70% → 100% EtOAc/Hex) to give **5** as an oil (6 mg, 45% from **27**): R_f = 0.24 (80% EtOAc/Hex); IR (neat) ν_{max} 3329, 3053, 2955, 2924, 2853, 1736, 1697, 1653, 1616, 1539, 1456, 1433, 1368, 1339, 1235, 1169, 1044, 990, 862, 835, 694; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.12 (m, 2 overlapping signals, 2H), 6.89 (d, J = 13.7 Hz, 1H), 6.23 (dd, J = 9.9, 1.6 Hz, 1H), 6.04 (br d, J = 6.7 Hz, N*H*), 5.81 (d, J = 13.9 Hz, 1H), 4.28 (q, J = 6.6 Hz, 1H), 4.15 (m, 1H), 4.05 (m, 2 overlapping signals, O*H* and 1H), 3.72 (d, J = 3.9 Hz, 1H), 3.59 (m, 1H), 2.08 (s, 3H), 1.97 (m, 2H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 197.8, 171.4, 165.4, 145.1, 143.1, 140.7, 130.3, 123.4, 89.2, 76.8, 66.0, 56.0, 48.2, 45.9, 37.5, 21.1; HRMS (ESI/TOF) calcd for $C_{16}H_{18}NO_6INa$ $[M + Na]^+$ 470.0077, found 470.0063.

(2*E*,4*E*,6*E*)-*N*-((1*S*,2*S*,4′*S*,6*R*)-3-Methoxy-5,5′-dioxo-4′,5′-dihydro-3′*H*-7-oxaspiro[bicyclo[4.1.0]hept[3]ene-2,2′-furan]-4′-yl)hexadeca-2,4,6-trienamide (32). To a solution of (*E*)-1-iodoundec-1-ene (11 mg, 0.039 mmol, 1.2 equiv) in THF (2 mL) at −78 °C was added *t*-BuLi (1.7 M in pentane, 46 μL, 0.078 mmol, 2.4 equiv) dropwise. A solution of $ZnBr_2$ (37 mg, 0.16 mmol, 5.0 equiv) in THF (2 mL) was cannulated over to the solution described above, and the resulting clear solution was allowed to warm to rt. After being stirred for 15 min at rt, the vinylzinc solution was cannulated over to a solution of **27** (14 mg, 0.032 mmol, 1.0 equiv) in THF (2 mL), at which time $Pd(PPh_3)_4$ (2 mg, 0.002 mmol, 0.06 equiv) was added and the mixture stirred for 10 min. The mixture was diluted with EtOAc (15 mL) and satd NH_4Cl (10 mL) and stirred for 10 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a short pad of SiO_2 eluting with EtOAc, and concentrated in vacuo. The residue was purified by flash chromatography (50% → 70% EtOAc/Hex) to give **32** as an oil (11 mg, 75%): R_f = 0.42 (70% EtOAc/Hex); IR (neat) ν_{max} 3337, 3021, 2953, 2924, 2853, 1790, 1672, 1615, 1526, 1454, 1412, 1375, 1312, 1275, 1229, 1192, 1111, 1084, 1051, 1005, 988, 953, 924, 843, 741, 723, 653, 629; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.27 (app dd overlapping with $CHCl_3$, 1H), 6.54 (dd, J = 14.9, 10.7 Hz, 1H), 6.33 (d, J = 6.3 Hz, N*H*), 6.17 (m, 2H), 5.95 (m, 1H), 5.85 (d, J = 14.9 Hz, 1H), 5.27 (s, 1H), 4.71 (m, 1H), 3.89 (d, J = 3.8 Hz, 1H), 3.77 (s, 3H), 3.55 (s, 1H), 2.76 (dd, J = 13.1, 9.6 Hz, 1H), 2.59 (dd, J = 13.4, 10.2 Hz, 1H), 2.14 (q, J = 7.1 Hz, 2H), 1.41 (m, 2H), 1.28 (br m, 12H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 191.7, 174.9, 170.0, 166.9, 143.4, 141.8, 141.2, 129.9, 127.6, 120.7, 98.5, 79.5, 57.3, 55.6, 52.9, 49.7, 37.7, 33.3, 32.1, 29.75, 29.69, 29.51, 29.47, 29.2, 22.9, 14.3; HRMS (ESI/TOF) calcd for $C_{26}H_{35}NO_6Na$ $[M + Na]^+$ 480.2362, found 480.2346.

(2*S*)-2-((2*E*,4*E*,6*E*)-Hexadeca-2,4,6-trienamido)-3-((2*S*)-2-hydroxy-3-oxo-7-oxabicyclo[4.1.0]hept-4-en-2-yl)propyl Acetate (4). To a solution of **32** (8 mg, 0.02 mmol, 1.0 equiv) in THF (3 mL) at 0 °C was added $NaBH_4$ (3 mg, 0.08 mmol, 4 equiv) in H_2O (0.6 mL). The solution was allowed to stir at 0 °C for 2 h, and then the ice bath was removed and the solution was allowed to stir at rt for an additional 6 h. The solution was diluted with $(CH_3)_2CO$ (10 mL), stirred for 1 h, and then concentrated in vacuo. The crude residue was redissolved in 1:1 Ac_2O/pyridine (3 mL), stirred for 6 h at rt, and then concentrated in vacuo. The resulting crude residue was redissolved in CH_2Cl_2 (3 mL), and to this was added H_2O (0.3 mL) and then Cl_3CCO_2H (49 mg, 0.30 mmol, 15 equiv) at rt. The mixture was vigorously stirred for 4 h, at which time the mixture was diluted with EtOAc (15 mL) and satd $NaHCO_3$ (15 mL) and stirred for 10 min. The layers were separated, and the organic extract was washed with sat. $NaHCO_3$ (2 × 5 mL), H_2O (3 × 5 mL) and brine (1 × 10 mL). The solution was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude residue was redissolved in CH_2Cl_2 (5 mL), and to this was added DBU (13 μL, 0.087 mmol, 4 equiv) at rt. The solution was stirred for 10 min and then diluted with EtOAc (25 mL) and satd NH_4Cl (20 mL). The layers were separated, and the organic extract was washed with satd NH_4Cl (2 × 10 mL), H_2O (3 × 10 mL), and brine (1 × 10 mL). The solution was then dried over Na_2SO_4, filtered through a small pad of SiO_2 eluting with EtOAc, and concentrated in vacuo. The residue was purified by flash chromatography (60% → 80% EtOAc/Hex) to give **4** as an oil (6 mg, 50% from **27**): R_f = 0.55 (15% THF/CH_2Cl_2); IR (neat) ν_{max} 3293, 2957, 2924, 2870, 2855, 1734, 1701, 1653, 1647, 1611, 1541, 1534, 1458, 1431, 1389, 1364, 1314, 1233, 1157, 1121, 1042, 1005, 885, 860, 835, 810, 768, 621; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.23 (dd, J = 14.7, 11.2 Hz, 1H), 7.15 (dd, J = 9.9, 4.0 Hz, 1H), 6.51 (dd, J = 14.7, 10.7 Hz, 1H), 6.24 (dd, J = 9.9, 1.6 Hz, 1H), 6.15 (m, 2H), 5.93 (m, 1H), 5.74 (d, J = 14.9 Hz, 1H), 4.27 (m, 2H), 4.14 (m, 1H), 4.05 (s, O*H*), 3.73 (d, J = 3.9 Hz, 1H), 3.59 (td, J = 3.9, 1.7 Hz, 1H), 2.14 (q, J = 7.0 Hz, 2H), 2.08 (s, 3H), 1.99 (d, J = 6.3 Hz, 2H), 1.40 (m, 2H), 1.27 (br m, 12H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 197.8, 171.3, 166.3, 145.0, 142.3, 141.0, 140.6, 130.3, 130.0, 127.7, 121.9, 76.8, 66.1, 56.0, 48.2, 45.7, 37.8, 33.2, 32.1, 29.92, 29.69, 29.53, 29.43, 29.2, 22.9, 21.1, 14.3; HRMS (ESI/TOF) calcd for $C_{27}H_{39}NO_6Na$ $[M + Na]^+$ 496.2675, found 496.2679.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra; HPLC traces for compounds **22**, **8**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. There were several typographical errors in the version published on 1/21/2011. These were fixed in the version published on 2/4/2011.