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A unified synthetic strategy toward oroidin-derived alkaloids premised on a biosynthetic proposal☆

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Abstract—Details of the evolution of a synthetic strategy toward the spirocyclic chlorocyclopentane core of oroidin-derived alkaloids, including the axinellamines and potentially adaptable to palau'amine, are described. A proposed refinement of the Kinnel–Scheuer biosynthetic proposal for palau'amine is posited. Studies undertaken to improve the regioselectivity and efficiency of a key Diels–Alder reaction utilizing a novel protecting group strategy, microwave chemistry, and other strategies are described. Further insights regarding the suitability of different protecting groups during the epoxidation/chlorination/ring contraction sequence are disclosed. Several interesting by-products from this reaction sequence are reported. These studies have led to a unified synthetic strategy to the axinellamines and palau'amine.

1. Introduction

Organisms produce a wide diversity of natural products, and while a common view is that they are produced as a defense mechanism against predators, the complexity of these structures, their ability to potently interact with mammalian proteins, and the metabolic mechanisms and processes that are known to produce them, raise a number of questions that may only be answered by a more holistic approach to natural products research. One such intriguing hypothesis named the 'screening hypothesis' seeks to overcome the inherent shortcomings of traditional evolutionary thought regarding the incredible diversity of metabolites produced by a given organism.[1]

While classical synthetic routes toward these complex and unusual architectures are possible, the convergent and efficient construction of these intriguing metabolites, building on knowledge garnered from consideration of possible biosynthetic origins, opens the possibility of discovering new chemistry and testing theories regarding their biosynthesis. In this regard, the oroidin family of marine alkaloids contains a large number of biogenetically related molecules that have inspired many to propose intriguing biosynthetic hypotheses.[2] The simple heterocyclic system, oroidin (**5a**), is thought to be a common precursor to this alkaloid family (Fig. 1). Among this family of alkaloids, axinellamine and palau'amine contain a common structural feature, namely a spirocyclic chlorocyclopentane ring. Several groups have described synthetic approaches to these hexacyclic oroidin-derived metabolites including those of Overman,[3] Carreira,[4] Lovely,[5] Austin,[6] and Harran.[7] Our synthetic approach to this class of bisguanidine alkaloids is premised on the biosynthetic hypothesis proposed by Kinnel and Scheuer.[8] Alternative biosynthetic proposals have been posited by Al Mourabit and Potier[9] and most recently by Baran.[10]

Kinnel and Scheuer proposed that palau'amine originates from a Diels–Alder reaction of dehydrophakellin (**7a**), which has not been isolated, and a truncated oroidin (AAPE, **5b**), which has been isolated. This is followed by a presumed chloroperoxidase-mediated chlorination initiating a 1,2-shift/ring contraction (Fig. 2), a process with some precedent.[11] In our synthetic studies of phakellstatin,[12] we found that aminals **6a** bearing a potential leaving group at C10 were unstable likely due to acyliminium formation while aminals **6b** bearing a leaving group at C6 were quite stable. The latter findings were in accord with concurrent work by Evans demonstrating the utility of pyrrolocarbinolamines as aldehyde surrogates.[13] These findings led to our successful enantioselective synthesis of phakellstatin and a proposed refinement of the biosynthetic proposal of Kinnel and Scheuer. The initial idea that dehydrophakellin (**7a**) could serve as a dienophile was unsettling as its reactivity would be expected to be low in this regard. However, if one considers the ring-opened form of dehydrophakellin (**7b**) consisting of an allylic acyliminium species, which may indeed be promoted in an enzyme active site, the expected high reactivity of the resulting acyliminium as

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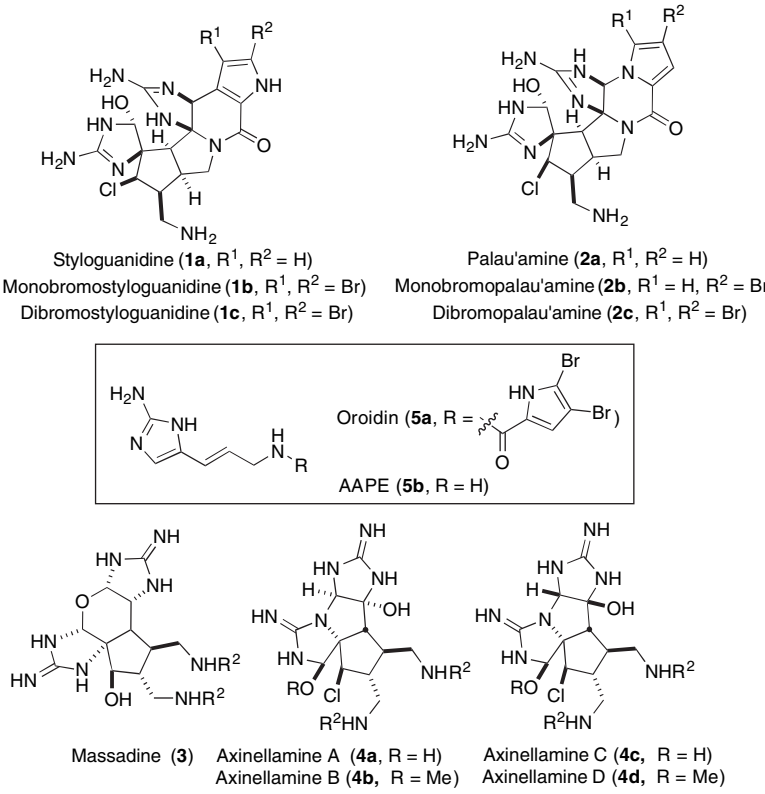


Figure 1. Oroidin-derived natural products.

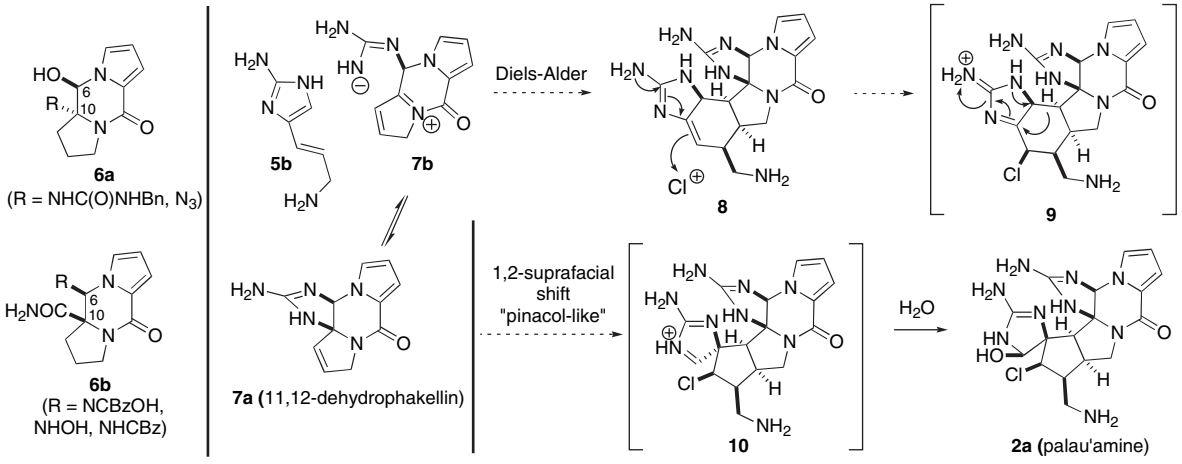


Figure 2. Stable/unstable aminals and carbinolamines **6** and Kinnel and Scheuer's proposed biosynthesis of palau'amine.

a dienophile is reminiscent of the allylic carbocations studied by Gassman and Singleton.[14] Thus, we propose a refinement to the Kinnel–Scheuer biosynthetic proposal that proceeds through the ring-opened acyliminium species **7b** leading to Diels–Alder adduct **8**. Chlorination initiates the 1,2-pinacol-like shift/ring contraction leading to cyclopentane bearing the iminium species **10**, which is trapped with water to deliver palau'amine.

1.1. Overall synthetic strategy premised on a proposed biosynthesis

Our initial interest in the oroidin alkaloids stemmed from the unique architecture presented by palau'amine in conjunction with its potent immunosuppressive activity. This parlayed into our group's interest in natural products displaying potent, cell-specific, physiological properties and the structurally distinct marine sponge isolate, pateamine A, is an example.[15] In the course of our studies toward palau'amine, a unified strategy toward both axinellamine and palau'amine evolved proceeding through a Diels–Alder reaction and then diverging to either axinellamine or palau'amine by virtue of either an inter- or intramolecular chlorination, respectively (Fig. 3).

This divergence addresses the proposed difference in relative stereochemistry between axinellamine and palau'amine at the chlorine bearing carbon C1 and that of C3. The

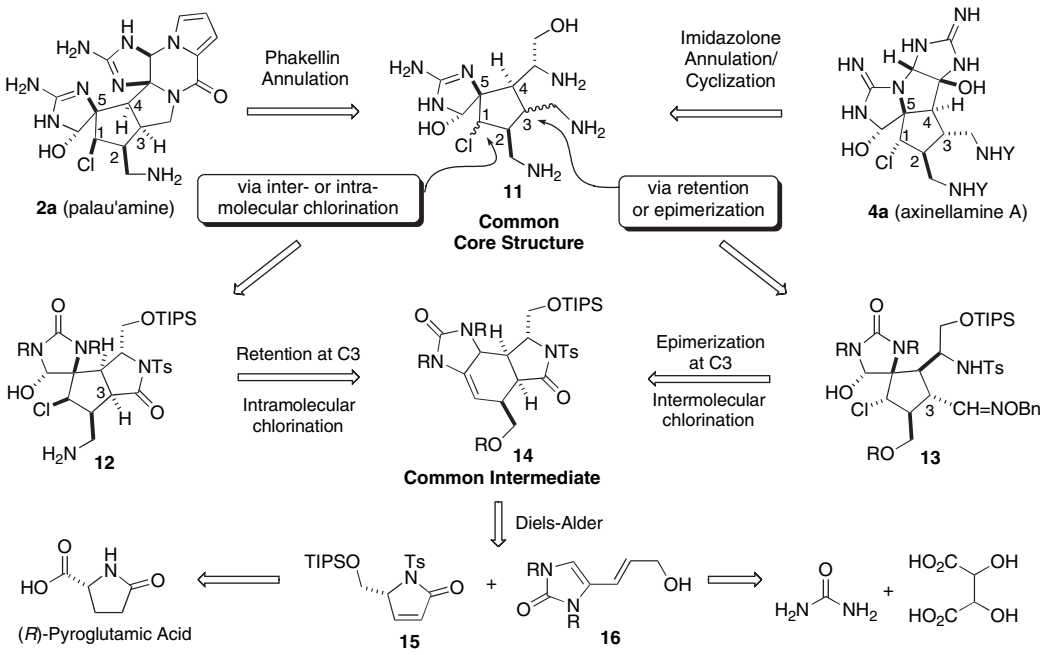


Figure 3. A unified synthetic strategy to the oroidin-derived alkaloids, axinellamine, and palau'amine.

anti-relationship between C1 and C2 found in axinellamine could be accessed by intermolecular chlorination as a result of the topography of the tricyclic common intermediate **14**. This chlorination of enamine **8** would be expected to initiate a pinacol-like, 1,2-shift of iminium **9** resulting in a ring contraction, as proposed by Kinnel and Scheuer.[16]

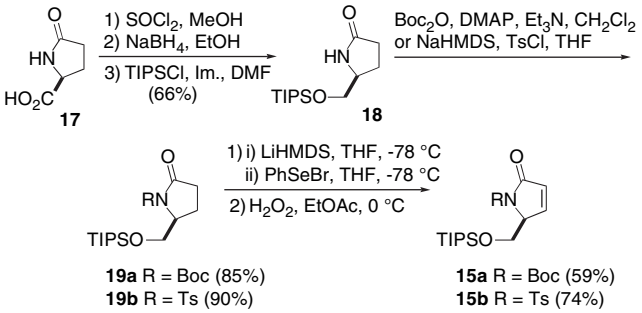
Common intermediate **14** would be obtained by a Diels–Alder reaction between the vinyl imidazolone **16** and a dienophile **15** derived from pyroglutamic acid. The absolute stereochemistry of axinellamine and palau'amine has not been confirmed, however, based on similarities in the CD spectra of palau'amine and dibromophakellin, the absolute configuration has been proposed to be as shown.[8] Based on biosynthetic considerations, one might predict that axinellamine will possess a related absolute configuration. Thus, to obtain the natural configuration of these targets would require the use of (*R*)-pyroglutamic acid and ultimately all stereocenters in these natural products would be derived from this single stereocenter. Due to cost considerations, the (*S*) enantiomer has been utilized in initial studies. The required diene is ultimately derived from urea and tartaric acid. A subsequent epimerization at C3 via an imine would be required to obtain the all *anti*-configuration about the cyclopentane as found in axinellamine (i.e., **13**). Subsequent imidazolone annulation, guanidinylation, and an oxidative cyclization are proposed to provide the final ring and deliver axinellamine.

Toward palau'amine, an intramolecular chlorination would be required to set the required stereochemistry between C1 and C2 (cf. **12**). In this case, the Diels–Alder process sets the required *syn*-stereochemistry at C3 and C4, thus epimerization is not required. Guanidinylation and annulation of the phakellin substructure onto core structure **11** would deliver palau'amine. Details of our synthetic studies in this area culminating in a unified strategy toward the oroidin alkaloids, axinellamine, and palau'amine are described herein.

2. Results and discussion

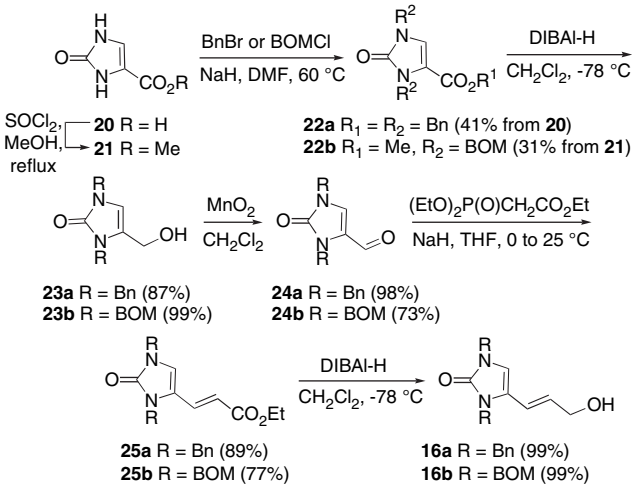
2.1. Studies of the Diels–Alder reaction toward common intermediate 14

2.1.1. Synthesis of the dienophiles and dienes. A series of dienophiles were prepared from L-(*S*)-pyroglutamic acid (**17**), following modified literature procedures,[17] to test their reactivity in the Diels–Alder reaction. Esterification was followed by reduction and protection of the resulting alcohol. Initially a *tert*-butylcarbamate (Boc, **19a**) was used to protect the lactam nitrogen, however, low reactivity as a dienophile subsequently led to the use of the *p*-toluenesulfonyl (Ts) protected lactam **19b**. A two-step sequence to introduce the unsaturation involving enolization with LDA, selenation, and finally oxidation with H_2O_2 provided enamides **15a**,**b** efficiently on ~1 g scale with no loss of optical purity as determined by Mosher ester analysis of the alcohol following TIPS deprotection. However, this reaction was only reproducible and scaleable when LiHMDS was used for enolization and ethyl acetate was used for the oxidation–elimination. In this way, the enamide **15b** could be obtained in high and reproducible yield on a large scale (~20 g) (Scheme 1).



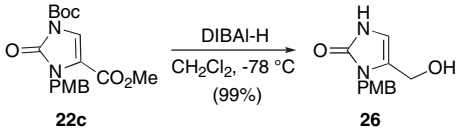
Scheme 1.

Formation of the diene commenced with imidazolone acid **20** prepared in one step from urea and tartaric acid.[18] Again, a number of different permutations of the diene were synthesized. Perbenzylation of the acid, followed by diisobutylaluminum hydride (DIBAl-H) reduction of the benzyl ester gave alcohol **23a** in good overall yield (Scheme 2 and Table 1). Oxidation with manganese dioxide followed by *E* selective olefination and reduction of the ester **25a** furnished the desired bis-benzylated diene **16a**. A benzyloxymethylene (BOM) protected diene **16b** was synthesized in a similar manner starting from the methyl ester **21**.



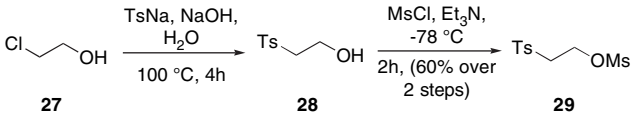
Scheme 2.

All other dienes synthesized (i.e., **16c–f**) incorporated orthogonal protecting groups requiring two-step protection but would allow for timed deprotection at later stages in the synthesis (Table 1). The synthesis of these dienes commenced from known methyl ester **21**.[18] Regioselective nitrogen protection is readily achieved due to steric (ester substituent) and electronic (increased acidity) properties of ester **21**.[19] Subsequent homologation was achieved in a manner similar to that described above for dienes **16a**,**b** (Table 1). While the Boc/*p*-methoxy (PMB) protected ester **22c** could be prepared, the acyl carbamate was not stable to DIBAl-H reduction conditions leading to alcohol **26** precluding its homologation (entry 1, Table 1). Dienes successfully synthesized in this manner include the Tse (*p*-tolylsulfonylethyl)/DMB-protected diene **16d**, Ts/PMB-protected diene **16e**, and the Ts/DMB (3,4-dimethoxybenzyl)-protected diene **16f** (Scheme 3).



Scheme 3.

The Tse group was installed using tosylethyl mesylate **29** (TseOMs) prepared in two steps from chloroethanol **27** on 100 g scale (Scheme 4). Importantly, the Tse/DMB-protected diene **16d** could be readily synthesized on 50–60 g scale with no need for chromatographic purification throughout the entire sequence.

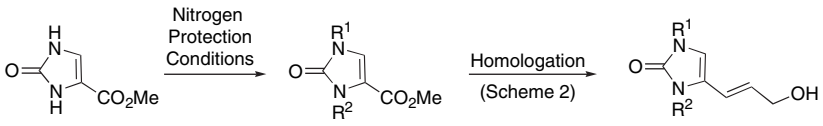


Scheme 4.

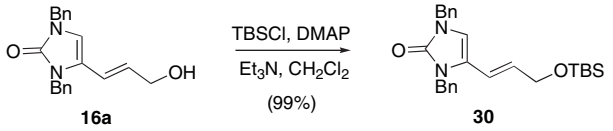
Dienes **16a–f** displayed varied acid sensitivity due to the presence of the allylic/benzylic alcohol and thus were typically prepared by DIBAl-H reduction and used directly in the Diels–Alder reaction without purification. Those dienes possessing an electron-withdrawing group (R^1) were notably more stable as expected. Protection of the hydroxyl moiety of diene **16a** as the *tert*-butyldimethylsilyl ether prior to the cycloaddition was briefly investigated in efforts to increase convergency (Scheme 5). While the silylation and subsequent purification proceeded smoothly, the instability of the silylated diene **30** appeared even more pronounced than that of the parent alcohol.

To further streamline the synthetic approach, incorporation of the pendant amine functionality, eventually required for

Table 1. Synthesis of dienes **16c–f** bearing orthogonal, nitrogen protecting groups

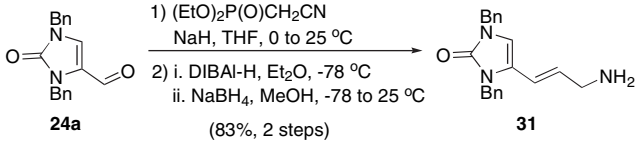


Entry	Nitrogen protection conditions (% yield, **22c–f**)	R^1	R^2	Esters **22**	Dienes **16c–f** (% yield)
1	i) Boc_2O, K_2CO_3, MeCN, 25 °C (54) ii) PMBBr, K_2CO_3, MeCN, 70 °C (53)	Boc	PMB	**22c**	**16c** (0)
2	i) TseOMs, $NaHCO_3$, DMSO, 70 °C (90) ii) DMBCl, K_2CO_3, DMF, 65 °C (100)	Tse	DMB	**22d**	**16d** (80)
3	i) TsCl, NaH, DMF, 25 °C (58) ii) PMBBr, K_2CO_3, MeCN, 70 °C (83)	Ts	PMB	**22e**	**16e** (64)
4	i) TsCl, NaH, DMF, 25 °C (58) ii) DMBCl, K_2CO_3, MeCN, 50 °C (64)	Ts	DMB	**22f**	**16f** (61)



Scheme 5.

the synthesis of palau'amine and axinellamine, into the diene was studied (Scheme 6). This approach involved a slight modification of the Horner–Wadsworth–Emmons olefination previously employed allowing installation of a vinyl cyanide, which was subsequently reduced to yield the amine diene **31** in excellent overall yield.



Scheme 6.

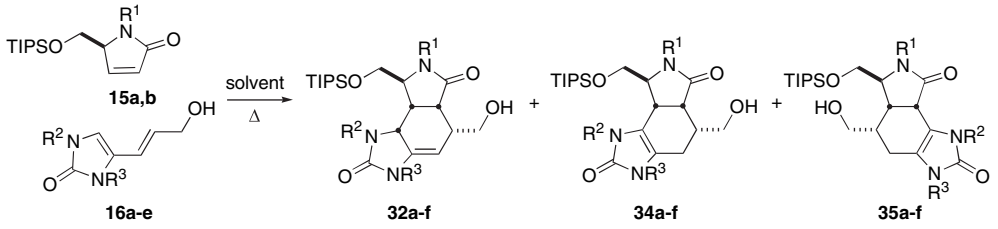
2.1.2. Facility and regioselectivity of the Diels–Alder reaction: effects of dienophile electronics. Building on precedence in the literature involving Diels–Alder reactions of related pyroglutamic acid derived dienophiles, the proposed cycloaddition was expected to proceed with high facial selectivity and *endo*-selectivity.[20] However, the regioselectivity was less certain given the fact that the diene is substituted with two nitrogens and each was expected to direct to opposite regioisomers (cf. diene **16**). A slight preference for the desired regiochemistry would be expected due to the presence of the alkyl substituent at the terminus. We recognized several possible strategies to overcome potential regiochemical issues including the use of Lewis acids, modifying the electronics of nitrogen protecting groups, and templated reactions.[21]

Our initial studies began with the Boc-protected lactam **15a** and bis-benzyl diene **16a** and while the cycloaddition did proceed, it required elevated temperatures providing cycloadduct **34a** in modest yields (28%, Table 2, entry 1). However, the expected initial Diels–Alder adduct **32a**, was not isolated, as the pseudoaromatic imidazolone was regenerated via double bond migration. Since the reactivity of the Boc-protected lactam **15a** was low, requiring high temperatures (~140 °C) for cycloaddition, the synthesis and use of a more reactive dienophile was warranted. The high reaction temperatures also contributed to the rather rapid degradation of diene **16a**. When the tosylated dienophile **15b** was used, the reaction proceeded at lower temperatures and provided higher yields (47%) of cycloadducts **34b**. Subsequent reactions performed in benzene and in the presence of 2,6-lutidine showed a marked improvement in yield (79%, Table 2, entry 3) suggestive of the acid instability of the dienes previously observed. Two regioisomers were produced in a ~4.3:1 ratio and the major isomer was determined to be the desired regioisomer based on extensive NMR studies including NOE data for the major regioisomer (Fig. 4a). The regioisomer **35b** proved to be crystalline and suitable for X-ray analysis providing further, albeit indirect, support for the structural assignment of the desired regioisomer (Fig. 4b).

Addition of Lewis acids to improve regioselectivity was investigated briefly as this led to rapid decomposition of diene **16a** even at low temperature. An exception was $MgBr_2 \cdot OEt_2$, which gave a slightly improved yield and regioisomeric ratio but importantly using only 1 equiv of diene (Table 2, entry 5 vs 6).

Other dienes were studied in efforts to facilitate protecting group removal late in the synthesis and also to improve convergency. The bis-BOM-protected diene **16b** provided a similar ratio of regioisomers in an unoptimized 36% yield (Table 2, entry 4). Cycloaddition of amino diene **31** and lactam **15b** was studied only briefly and provided low yields of the amino-substituted Diels–Alder adduct (not shown) due to extensive diene decomposition. Acylation or sulfonylation of this diene will reduce basicity and increase stability possibly rendering it more useful in Diels–Alder reactions. The

Table 2. Diels–Alder reactions providing the tricyclic common intermediates **34a–f**



Entry	Dienophile	R^1	Diene[a]	R^2	R^3	Reaction conditions	Products	% Yield[b]
1	**15a**	Boc	**16a** (1.1)	Bn	Bn	*o*-Xylene, 140 °C, 14 h	**34a**	28
2	**15b**	Ts	**16a** (2.5)	Bn	Bn	*o*-Xylene, 2,6-lut. (1.2 equiv), 90 °C, 28 h	**34b**	47
3	**15b**	Ts	**16a** (1.41)	Bn	Bn	PhH, 2,6-lut. (0.66 equiv), 95 °C, 4 d	**34b**, **35b**	64 (15)[c]
4	**15b**	Ts	**16b** (0.9)	BOM	BOM	PhH, 2,6-lut. (0.57 equiv), 95 °C, 24 h	**34c**, **35c**	30 (6)[c]
5	**15b**	Ts	**16d** (2.5)	Tse	DMB	PhH, 2,6-lut. (0.75 equiv), 95 °C, 3 d	**34d**, **35d**	54 (20)[c]
6	**15b**	Ts	**16d** (1.0)	Tse	DMB	PhH, $MgBr_2 \cdot OEt_2$ (0.5 equiv), 100 °C, 3 d	**34d**, **35d**	67 (12)[c]
7	**15b**	Ts	**16e** (1.0)	Ts	PMB	PhH, 2,6-lut. (0.55 equiv), 114 °C, 4 d	**34e**	59
8	**15b**	Ts	**16f** (1.45)	Ts	DMB	PhH, 2,6-lut. (0.46 equiv), 110 °C, 4 d	**34f**	74

[a] Equivalents of diene employed in parentheses.
[b] Refers to isolated yields.
[c] Yield for isolated regioisomers **35a–f** given in parentheses.

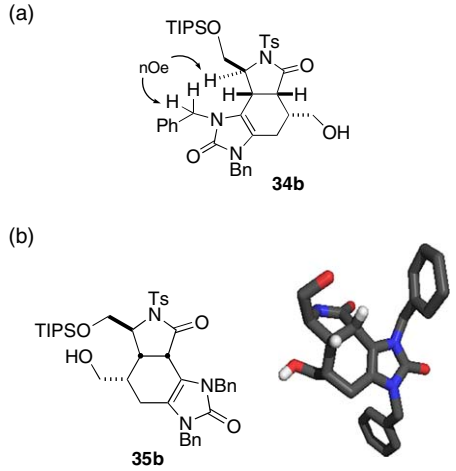
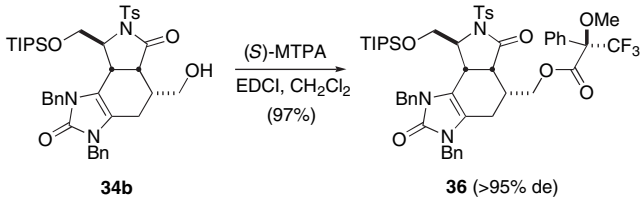


Figure 4. Regiochemical assignment of Diels–Alder adducts **34b** and **35b**. (a) Key NOE correlations observed confirming regiochemistry. (b) POV-chem rendering of the X-ray crystal structure of regioisomeric cycloadduct **35b** (protecting groups removed for clarity).

use of Tse/DMB diene **16d** was also studied for correlation to a product obtained from a tosylvinyl (Tsv) protected diene (**16g**, vide infra) and this gave diminished regioselectivity (~2.7:1, Table 2, entry 5). The Tse group was also advantageous from the standpoint of orthogonality with respect to the lactam Ts group.

Erosion of optical purity of the dienophile **15b** during the Diels–Alder reaction was possible due to the potential for pyrrole tautomer formation. Thus, the Mosher ester **36** of alcohol **34b** was prepared and integration of the diastereomeric methoxy protons by ^{1}H NMR spectroscopy indicated a diastereomeric excess of >95% for the cycloadduct (in comparison to that prepared from racemic dienophile **15b**). This confirmed ~2.5% epimerization of lactam **15b** under the Diels–Alder reaction conditions, which was >99% at the outset of the reaction as determined by chiral HPLC analysis (Scheme 7).



Scheme 7.

Notably, in all Diels–Alder reactions, the majority of unreacted dienophile **15b** could be cleanly recovered (~80–97% mass recovery) with minimal loss of optical purity (chiral HPLC analysis) after the cycloadditions, while the bis-alkylated dienes had decomposed.

2.1.3. Regioselectivity of the Diels–Alder reaction: effects of diene electronics. While Diels–Alder reactions employing bis-alkylated dienes **16a** and **16b** proceeded with high facial and *endo*-selectivity as anticipated, we sought alternative means to improve the modest regioselectivity (~4:1). One strategy involved varying the electronics of protecting groups on the nitrogen atoms of the diene imidazolone. We reasoned that use of an electron-withdrawing group on N^1 while maintaining an electron-donating group on N^2 would perturb the orbital coefficients of the diene leading to improved regioselectivity (Fig. 5).

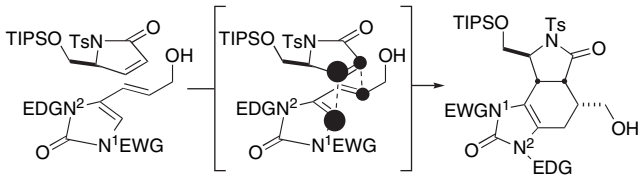


Figure 5. Electronics of vinyl imidazolones as dienes.

Indeed, initial studies employing the Ts/PMB diene **16e** provided for the first time, the initial Diels–Alder adduct **32e** that had not undergone olefin isomerization. Continued heating for a further two days resulted in conversion to the isomerized cycloadduct (**34e**) and importantly as a single regioisomer (59%, Table 2, entry 7). Further optimization was performed with Ts/DMB diene **16f** and ultimately led to a highly stereo- and regioselective Diels–Alder reaction providing adduct **34f** in good yield (74%, Table 2, entry 8).

2.1.4. Development of an electronically adjustable tosylvinyl (Tsv) nitrogen protecting group. In subsequent studies, we determined that while the Ts/DMB diene **16f** produced only one regioisomer in the Diels–Alder reaction, the resulting adduct and deprotected derivatives did not participate in the chlorination/rearrangement process (vide infra). Through our studies, we determined that an electron-withdrawing group (EWG) on N^1 was required for high regioselectivity in the Diels–Alder reaction while successful chlorination/rearrangement required an electron-donating group (EDG) on N^1 (Fig. 6). A typical way to address this issue would entail a protecting group switch, however, we were attracted to the possibility of utilizing a protecting group with readily adjusted electronics. This led us to consider the use of a *p*-tolylsulfonylvinyl (Tsv) group, which in a vinylogous manner provides the electron-withdrawing ability of the Ts group. However, reduction of the alkene provides the Tse group leading to an EDG suitable for the chlorination/rearrangement sequence.

A range of electrophiles were studied to install the Tsv group on imidazolone **21**. The use of commercially available *p*-toluenesulfonyl acetylene in the presence of a range of bases resulted in disubstituted product **37**. Similar methods were used by Arjona and Vilarrasa to protect thiols with the Tsv group (Scheme 8).[22]

Ultimately, only (*Z*)-1,2-di-*p*-toluenesulfonylethylene was found to be useful to install the Tsv group via an addition–elimination sequence using NaH as base.[23] Subsequent protection of the remaining nitrogen as the DMB amine provided ester **38**. Attempted reduction of ester **38** with DIBAl-H resulted in concomitant reduction of the Tsv group. Chemoselective reduction was finally achieved by activation of the acid functionality as either an acid chloride or a mixed anhydride and reduction with lithium borohydride. Following oxidation and olefination, this process was necessary

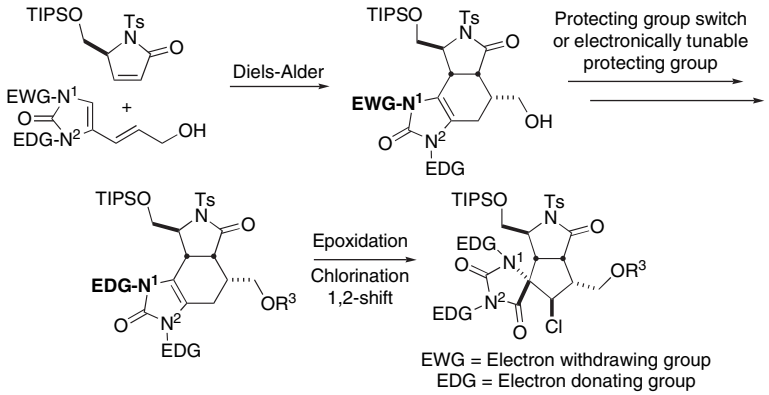
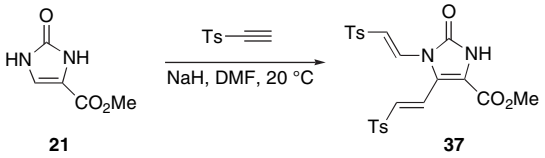
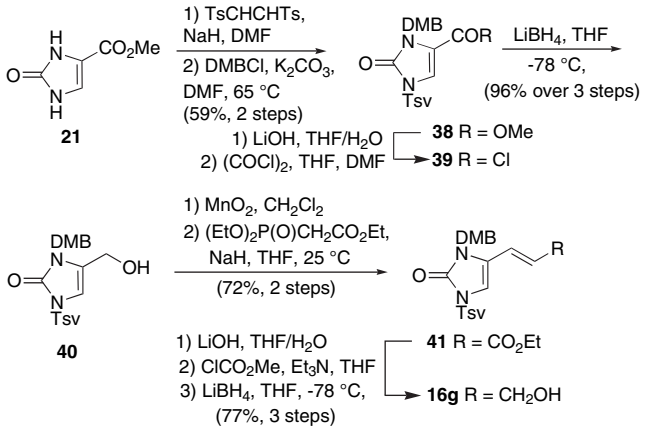


Figure 6. Electronic requirements for the Diels–Alder reaction and chlorination/rearrangement sequence and possible solutions.



Scheme 8.

once again to prevent Tsv reduction. However, formation of diene **16g** by this route was possible without recourse to silica gel chromatography throughout the entire sequence on large scale (Scheme 9).

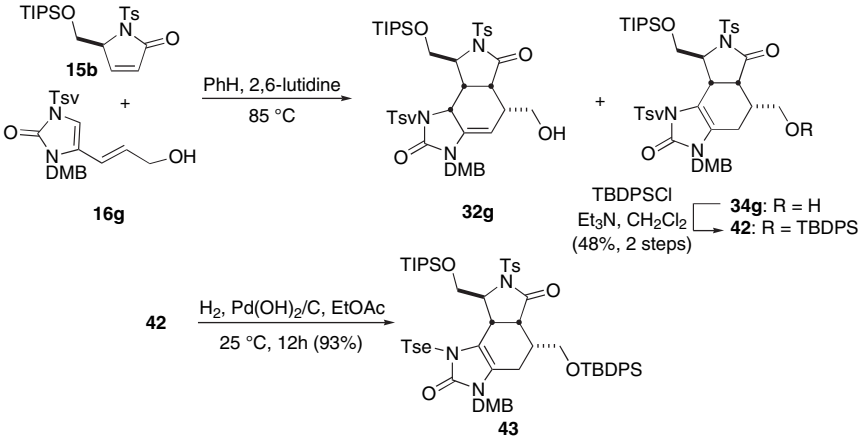


Scheme 9.

Use of the Tsv/DMB diene **16g** in the Diels–Alder reaction at 85 °C under the previously described conditions gave initial Diels–Alder adduct **32g** and regioisomer **34g** (Scheme 10). Upon increasing the reaction temperature to 95 °C, adduct **34g** was obtained as a single isomer as determined by ^{1}H NMR analysis of the crude reaction mixture (~20–30% conversion). A by-product isolated from the reaction mixture was derived from competing dimerization of the diene at the Tsv group (not shown). Attempts to improve the yield by the addition of multiple equivalents of diene at various reaction time points were unsuccessful. Following alcohol protection of adduct **34g**, the Tsv group of silyl ether **42** was hydrogenated to give the reduced product in 93% yield. This compound was correlated to the same cycloadduct (i.e., **34d**, Table 2) obtained by direct Diels–Alder reaction with the Tse/DMB diene **16d** and found to be identical thus confirming its structure.

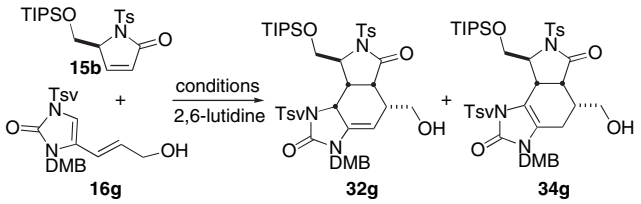
2.1.5. Microwave-assisted Diels–Alder reactions. The long reaction times for several of the Diels–Alder reactions described above, led us to consider the use of microwave irradiation to accelerate these cycloadditions. Microwave chemistry has developed into a very useful technique, and has proven particularly useful for accelerating sluggish cycloaddition reactions.[24]

Initial studies into the Diels–Alder reaction of Tsv-diene **16g** with dienophile **15b** under microwave conditions, employed 1 equiv of diene relative to dienophile and the crude reaction



Scheme 10.

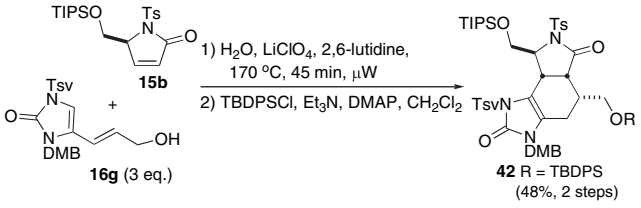
Table 3. Microwave-assisted Diels–Alder reactions



Entry	Reagents and conditions (with 0.6 equiv of 2,6-lutidine)	Ratio of **15b/32g/34g**
1	PhH/H_2O (1:4), 150 °C, 1 h	1:0.07:0.18
2	PhH/H_2O (1:1), $LiClO_4$, 170 °C, 5 h	1:0.07:0.44
3	H_2O, $LiClO_4$, 170 °C, 45 min	1:0:1.38
4	H_2O, $LiClO_4$, 170 °C, 45 min, 2 equiv of **16g**	1:0:2
5	H_2O, $LiClO_4$, 170 °C, 45 min, 3 equiv of **16g**	1:0:6

mixture was analyzed (^{1}H NMR) for the ratio of initial cycloadduct **32g**, isomerized cycloadduct **34g**, and dienophile **15b** (Table 3). In analogy to conventional thermal conditions, the regioisomer of **34g** was not observed under microwave conditions. When aqueous benzene was used, some degree of non-isomerized Diels–Alder adduct **32g** was observed (entry 1). Addition of $LiClO_4$ led to further conversion but only with extended reaction times (entry 2). Ultimately, using only water as the heating medium resulted in much shorter reaction times possibly due to hydrophobic effects,[25] and the initial cycloadduct **32g** was not observed (entry 3). As expected, increasing to 2.0 or 3.0 equiv of diene **16g** further improved the resulting ratio of product to dienophile **15b** (entries 4 and 5).

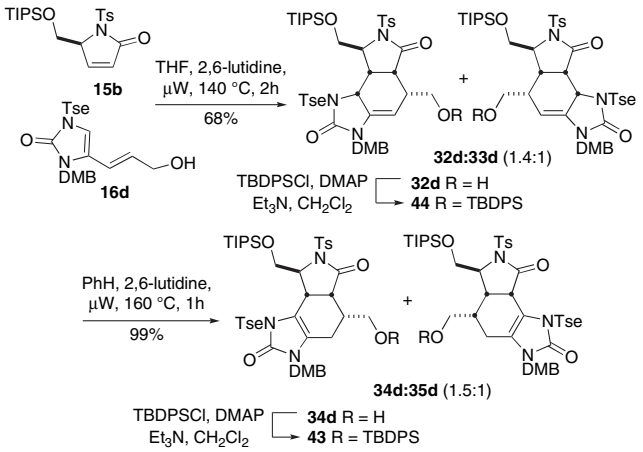
Under optimal microwave conditions, the Diels–Alder reaction of Tsv-diene **16g** gave a maximum overall yield of 48% yield after TBDPS protection (Scheme 11). Again the major side product was determined to be the competing dimerization of the Tsv-diene **16g**. The competing dimerization requiring excess diene to reach reaction completion has limited the use of this substrate in our synthetic efforts toward the axinellamines and palau'amine.



Scheme 11.

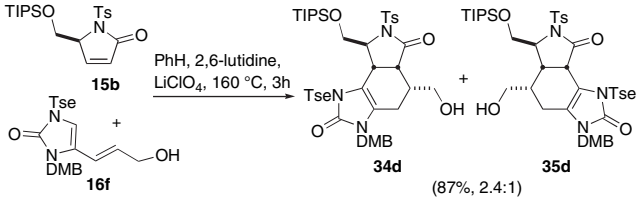
The cycloaddition of the Tse/DMB diene **16d** was also investigated under microwave conditions in THF at 140 °C for 2 h and this gave exclusively the initial Diels–Alder adduct **32d** and regioisomer **33d** (Scheme 12). Adduct **32d** is a useful substrate for direct chlorination and rearrangement as originally proposed in our overall synthetic strategy. These adducts could be converted to isomerized adducts **34d** and **35d** under microwave conditions in benzene in the presence of 2,6-lutidine.

Interestingly, conducting the Diels–Alder reaction of Tse/DMB diene **16d** in benzene under microwave conditions



Scheme 12.

with the weak Lewis acid, $LiClO_4$, resulted in the formation of isomerized adduct **34d** as the major product along with regioisomer **35d** (2.4:1 ratio) in 87% overall yield using only 1.1 equiv of diene (Scheme 13). This contrasts to conventional heating, which required 2–2.5 equiv of diene to achieve similar conversions. The addition of water to the reaction medium had no effect on conversion or regioselectivity.

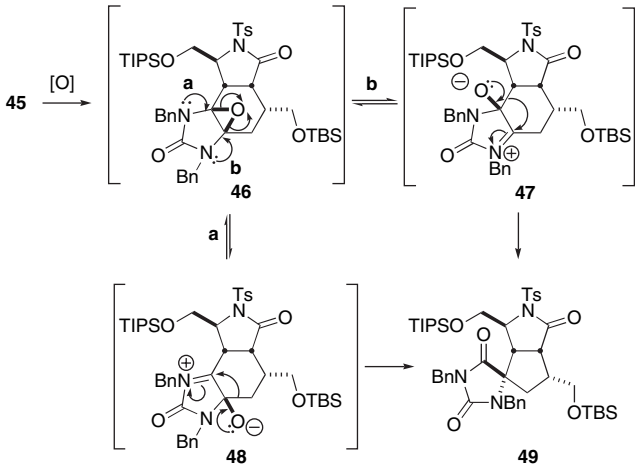


Scheme 13.

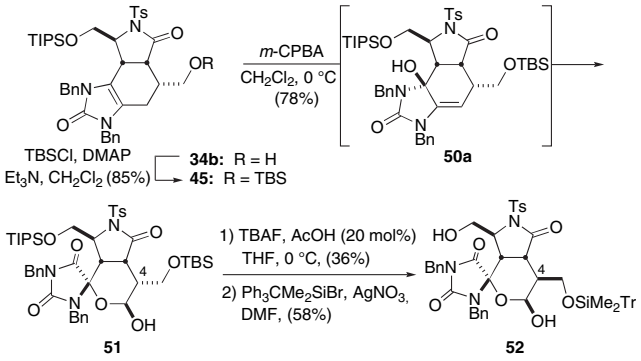
2.2. Attempted epoxidation/rearrangement of the Diels–Alder adduct leading to serviceable allylic alcohols for chlorination/rearrangement

Given that double bond isomerization of the initial Diels–Alder adduct was observed, we proceeded to study the viability of the proposed 1,2-shift/ring contraction sequence to furnish a deschlorospirocycle (i.e., **49**, Scheme 14). We reasoned that highly facial selective epoxidation on the convex face of the tricyclic imidazolone alkene would initiate the desired rearrangement. Following epoxidation of the electron-rich alkene of imidazolone **45** (cf. Scheme 15) or direct formation of a hydroxy iminium species **47** via enamine chemistry, carbinolurea **47** or **48** was expected to undergo subsequent 1,2-shift/ring contraction to yield deschlorospirocycle **49**. Importantly, it was inconsequential which C–C bond participated in the 1,2-shift since both pathways (**a** and **b**) would ultimately deliver spirohydantoin **49** provided high facial selectivity was achieved in the initial oxidation.

Toward deschlorospirocycle **49**, silyl protection of alcohol **34b** provided silyl ether **45**, which was then treated with excess *m*-chloroperbenzoic acid (*m*-CPBA) furnishing what



Scheme 14.



Scheme 15.

we initially believed to be allylic alcohol **50a** and not the rearranged spirohydantoin (Scheme 15). This structure was quickly excluded, since mass spectrometric analysis of the reaction product revealed incorporation of three oxygen atoms rather than one. Notably, the formation of the major reaction product was instantaneous at 0 °C, and lowering the reaction temperature appeared to have an effect on the reaction rate but not the reaction outcome suggestive of an

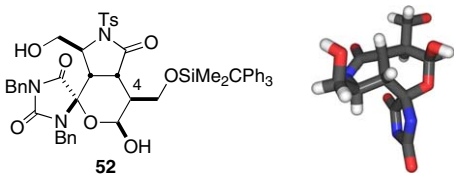
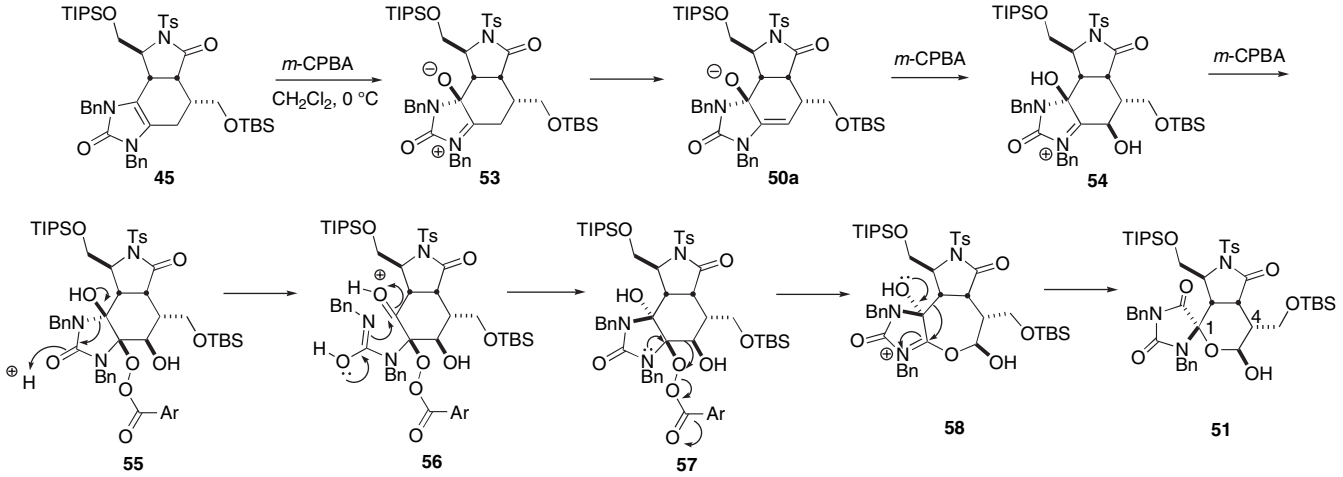


Figure 7. Structure of the derivatized over-oxidation product **52** and POV-chem rendering of the X-ray crystal structure (protecting groups are removed for clarity).

extremely facile transformation with *m*-CPBA. Indeed, use of 1.0 equiv of *m*-CPBA led to 33% yield of **51** and 66% recovered starting material.

The structure of this highly rearranged product could not be confirmed despite extensive spectral analysis although we recognized the presence of two acetal/aminal carbons and a hydantoin. Consequently, we attempted preparation of a crystalline derivative to confirm the proposed structure derived from plausible mechanistic scenarios. Toward this end, desilylation and mono-silylation with trityldimethylsilylbromide, a protecting group known to frequently produce crystalline derivatives,[26] provided colorless needles suitable for X-ray analysis. Thus, the structure of spirocycle **52** was confirmed as the lactol hydantoin (Fig. 7) and retrospectively the structure of the over-oxidation product was confirmed to be lactol **51** following careful analysis of changes occurring during the sequence leading to lactol **52** as described below (Fig. 7).

The hydroxymethylene bearing center (C4) had epimerized during the sequence and this was found to occur during the desilylation step presumably via the aldehyde. The stereochemistry at the spirocenter was unexpected for a suprafacial 1,2-shift, which was expected for this rearrangement. However, reasonable explanations for this inversion of stereochemistry could be conceived when considering possible mechanistic scenarios involved in the generation of this over-oxidation product (Scheme 16). One possible mechanism involves initial epoxidation of alkene **45** with *m*-CPBA or direct iminium ion formation by oxidation (cf. Scheme 14) followed by deprotonation to give alkene **50a**. A second epoxidation/ring opening sequence followed by



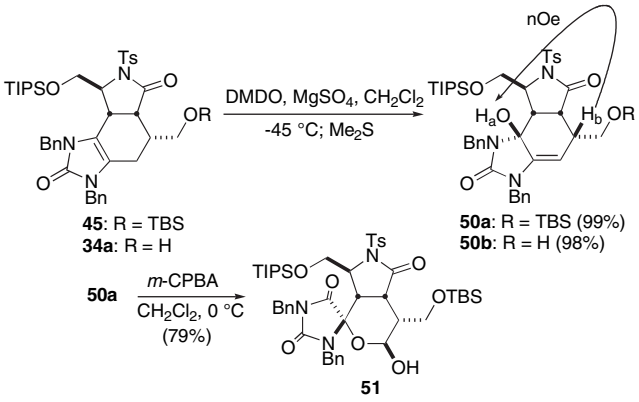
Scheme 16.

a Baeyer–Villiger type oxidation of the resulting iminium intermediate **54** yields oxepane **58**. Notably, while transformations of this type have not been reported for iminium species, analogous Baeyer–Villiger type oxidations of oxocarbenium intermediates have been described previously.[27] Considering this mechanistic proposal, the inverted stereochemistry at the quaternary center may be rationalized by invoking an acid-catalyzed epimerization of carbinolamine **55**. The epimerization may proceed via ketone **56** by reversible ring cleavage and readdition of the urea from the convex face. Subsequent 1,2-shift/ring contraction provides spirocyclic hydantoin **51** containing a tetrahydropyran. Another possible rationale for inversion at the quaternary center involves epimerization at the stage of the final hydantoin **51** via ring-opened intermediates (not shown).

While not useful toward the synthesis of the target core structure of oroidin-derived alkaloids, the over-oxidation product proved quite valuable. The formation of the spirohydantoin **51** lent credence to our proposed 1,2-shift/ring contraction. Furthermore, given the potential intermediacy of allylic alcohol **50a**, we recognized the utility of this substrate for the projected chlorination/rearrangement sequence. The placement of the alkene moiety in carbinol **50a** would facilitate the incorporation of a chlorine atom at C5 by electrophilic addition. Furthermore, C=O bond formation leading to a spirocyclic hydantoin as observed would provide an added driving force for the 1,2-shift/ring contraction. Therefore, we examined other oxidants with the expectation that milder conditions might allow isolation of alcohol **50a**. While initial oxidations with DMDO[28] gave complex reaction mixtures when performed at 22 °C, we ultimately generated allylic alcohol **50a** in a highly diastereoselective manner and in excellent yield by careful treatment of imidazolone **45** with DMDO at −45 °C, followed by quenching of excess DMDO with dimethylsulfide at low temperature. While alcohol **50a** could be purified by silica gel chromatography, substantial decomposition was observed. However, it could be stored neatly in the freezer for several days and it was of sufficient purity to be used directly in subsequent reactions. The structural and stereochemical proof of carbinolurea **50a** was provided by detailed spectral analysis including COSY and HMQC. Key data included the presence of a carbinolurea carbon in the ^{13}C NMR spectrum (δ 86.5, acetone-d_6). This chemical shift correlated well with that of known carbinolurea substructures found in related natural products.[29] In addition, a key NOE was observed between the hydroxyl proton H_a and the methine proton H_b (Scheme 17). Interestingly, the hydroxyl proton H_a appeared as a sharp singlet at δ 5.57 but was exchangeable with D_2O.

In support of the aforementioned mechanism for the generation of over-oxidation product **51**, treatment of alcohol **50a** with *m*-CPBA also led to the same oxepane **51** observed using *m*-CPBA alone (Scheme 17). Notably, DMDO oxidation of the unprotected Diels–Alder adduct **34a** with a pendant free hydroxyl furnished the analogous carbinolurea. Alternative oxidants that were briefly investigated included peracetic acid and hydrogen peroxide, which led to desilylation (−TBS) and recovery of starting material, respectively.

While the synthesis of allylic alcohol **50a** enabled further investigations toward the chlorination/ring contraction

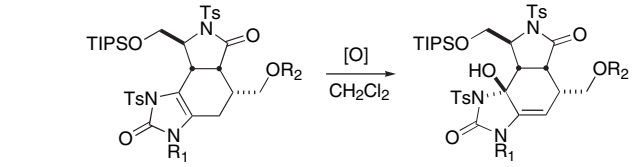


Scheme 17.

sequence (vide infra), synthesis of the corresponding carbinolureas derived from bis-tosyl Diels–Alder adducts **59** and **60** were also investigated since these had been obtained as single regioisomers in the cycloaddition. Not surprisingly, oxidation of the imidazolone alkene, now rendered less electron rich due to the tosyl substituent, did not proceed but only returned starting material (Table 4, entry 1). Increasing reaction temperature only furnished starting material contaminated to a varying degree with unidentified oxidation products (Table 4, entry 2). After unsuccessful oxidation attempts with H_2O_2 (Table 4, entry 3) and *m*-CPBA (Table 4, entry 4), the more reactive DMDO analog, methyl(trifluoromethyl)dioxirane[30] was utilized and gratifyingly yielded the desired allylic alcohol **50c** in nearly quantitative yield (Table 4, entry 5). The same reaction conditions could be employed to furnish the corresponding carbinolurea **50d** derived from the TBS-protected Diels–Alder adduct **60** (Table 4, entry 6).

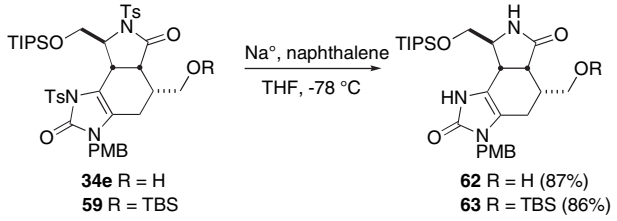
While these results were pleasing, the use of expensive and volatile methyl(trifluoromethyl)dioxirane on large scale would ultimately prevent the viability of this route. Therefore, we explored the possibility of removing the electron-withdrawing tosyl group prior to oxidation. Selective

Table 4. Oxidation of bis-sulfonylated Diels–Alder adducts



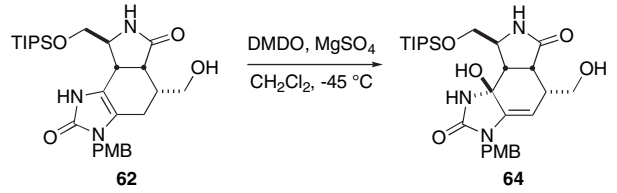
Entry	Imidazolone	Reaction conditions	Reaction outcome
1	**34e**	DMDO, $MgSO_4$, −45 °C	No reaction
2	**34e**	DMDO, $MgSO_4$, 22→41 °C	Mixture of products
3	**34e**	H_2O_2, 0 °C	No reaction
4	**59**	*m*-CPBA, 0 °C	Mixture of products
5	**59**	Methyl(trifluoromethyl)dioxirane, $MgSO_4$, −45 °C	**50c** (99%)
6	**60**	Methyl(trifluoromethyl)dioxirane, $MgSO_4$, −45 °C	**50d** (99%)

detosylation of Diels–Alder adduct **34e** and its silylated analog **59** proceeded smoothly with sodium naphthalenide at low temperature (Scheme 18).



Scheme 18.

Initial oxidation of these deprotected systems was conducted with imidazolone **62** devoid of the silyl protecting group. Treatment with DMDO did indeed produce a compound tentatively assigned as the desired allylic alcohol **64**, as confirmed by mass spectrometry, albeit not reproducibly (Scheme 19).



Scheme 19.

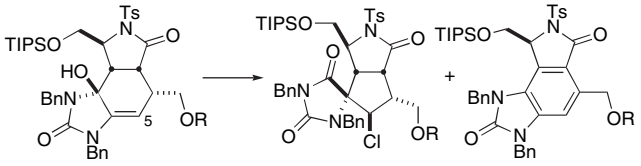
Ultimately, these attempted oxidation studies of *N*-unprotected Diels–Alder adducts (cf. **62**, **63**) in conjunction with findings made in subsequent chlorination studies (vide infra) led us to conclude that efficient formation of spirocyclic systems mandated nitrogen protection.

2.3. Development of a chlorination/1,2-shift/ring contraction sequence: synthesis of the spirocyclic core useful for axinellamine synthesis

Due to the ideal disposition of the double bond in allylic alcohol **50a** and encouraged by the spirohydantoin formation during the *m*-CPBA over-oxidation, we proceeded with investigation of the proposed halogenation/ring contraction sequence. It was expected that treatment of the distinctly cup-shaped carbinolurea **50a** with a source of electrophilic halogen would result in halide incorporation from the convex face of the tricyclic system. Initial attempts to effect the ring contraction by treatment of allylic alcohol **50a** with *N*-chlorosuccinimide (NCS) at −12 °C pleasingly gave a compound assigned as the desired spirohydantoin **65a** (49%) but contaminated with a painfully obtained aromatic system **66a** (loss of four stereocenters! Table 5, entry 1).[31] The formation of spirohydantoin likely involves initial chlorination, generating an iminium species, which subsequently undergoes a suprafacial 1,2-alkyl migration driven by C=O bond formation to yield the desired ring contracted spirocycle **65a**,**b** (cf. Fig. 2).

We postulated that acid-mediated eliminations of the carbinolurea **50a** may lead to cyclohexadiene intermediates, which could then be oxidized further by NCS to give

Table 5. Chlorination/1,2-shift/ring contractions of allylic alcohols **50a**,**b**



Entry	Substrate	Reaction conditions	**65a**,**b** (% yield)	**66a**,**b** (% yield)
1	**50a** (R=TBS)	NCS, −12 °C	49	16
2	**50a**	NCS, C_6H_{10} −78→−45 °C	75	Trace
3	**50b** (R=H)	NCS, C_6H_{10} −78→−45 °C	78	Trace

aromatic product **66a**. To minimize the generation of these side products, we employed cyclohexene as an acid buffer, a technique utilized by Hoye to absorb HOCl.[32] Pleasingly, the addition of cyclohexene, in conjunction with lowering the reaction temperature, furnished the desired spirocycle in good yield with only trace amounts of the aromatized by-product **66a**. Subsequent rearrangements of allylic alcohol **50a** were performed at −45 °C, affording consistent yields (75%) of spirocycle **65** (Table 5, entry 2). The sequence could also be performed on the unprotected allylic alcohol **50b** in similar yield (Table 5, entry 3).

Extensive NMR experiments were conducted to support the proposed relative stereochemistry of the halogenated spirohydantoins **65**. Most diagnostic were NOE experiments, which could be observed for chlorospirocycle **65** and its desilylated analog **67** (Fig. 8). Desilylation of the spirocycle **65** proved necessary since overlapping peaks precluded several key NOE's from being observed.

The *N*-benzyl protons on the series of compounds including the Diels–Alder adduct **34b**, allylic alcohol **50a**, and chlorocyclopentane **65** proved to be diagnostic markers for identifying the nature of the tricyclic system (Fig. 9). As often observed with benzyl protons in asymmetric environments, differences in chemical shift between the diastereotopic protons, *h*/*h*′ and *i*/*i*′, are reflective of the degree of steric congestion (i.e., conformational mobility) about these methylene groups. Thus, the benzylic protons are useful as probes for the nature of the tricyclic system in these and other systems in this series as the benzyl groups are readily distinguished (confirmed by NOE experiments) based on the

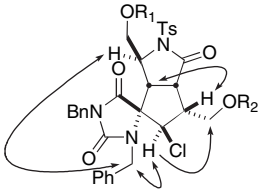


Figure 8. Key NOE enhancements observed for chlorinated spirocycles **65** and **67**.

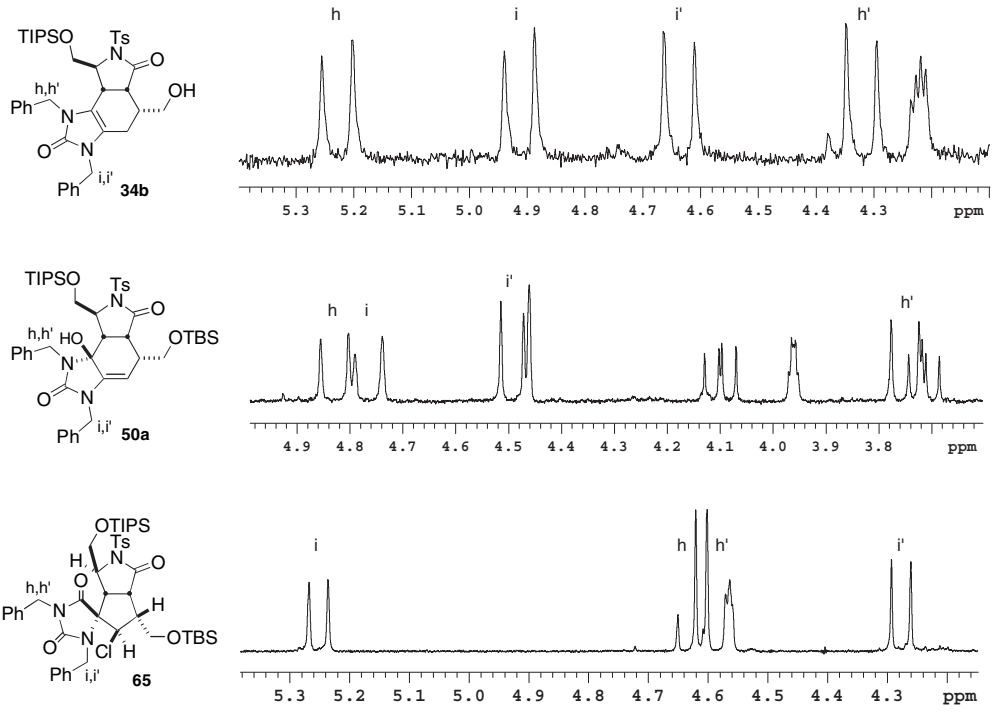
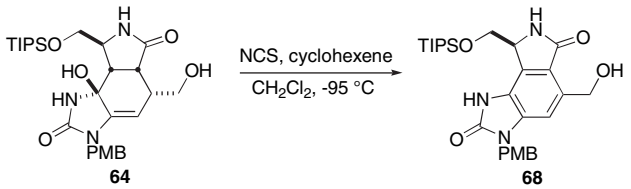


Figure 9. Benzyl protons of intermediates **34b**, **50a**, and **65** as diagnostic markers of steric congestion and structure.

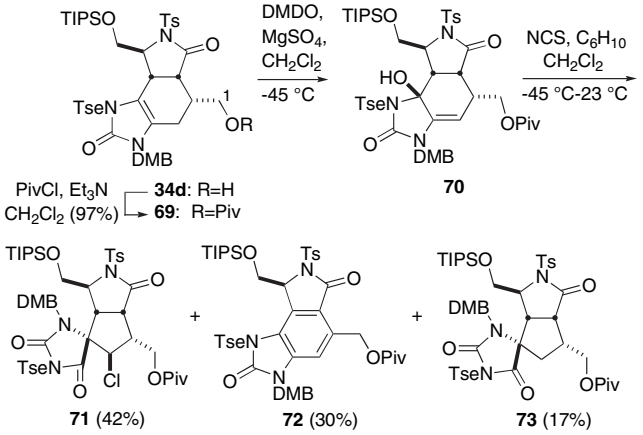
$\Delta\delta$ for these protons. For example, on conversion of the allylic alcohol **50a** to the spirocycle **65**, one observes a complete reversal in the $\Delta\delta$ for protons *h* and *i*. Namely, protons *h* of alcohol **50a**, which are present in the bay region of the tricycle have a large $\Delta\delta$ relative to protons *i* since these have greater conformational mobility. A complete reversal in this effect is observed following rearrangement/ring contraction since protons *i* are situated in the concave face of the spirocyclic system.

In analogy to the oxidation sequence, we were again interested in applying the rearrangement to the bis-sulfonylated Diels–Alder adducts (i.e., **61**, **50c**,**d**) as they were obtained as single regioisomers. NCS, 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one, sodium hypochlorite, chloramine-T, and chlorine gas were all studied in attempts to effect the rearrangement of allylic alcohol **50d**. All these reaction conditions furnished either starting allylic alcohol **50d** or produced only traces of the desired rearranged compound, frequently only identifiable after mass spectrometric analysis of the crude product. Attempted rearrangement of the detosylated analog **64** led to the aromatized product even at low (−95 °C) temperature (Scheme 20).



Scheme 20.

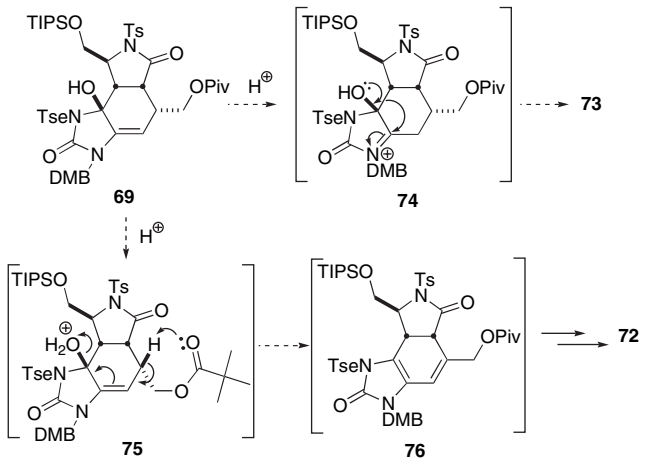
These results reinforced the need for electron-donating groups on N^1/N^2 of the Diels–Alder adduct for the oxidation/chlorination/rearrangement sequence (cf. Fig. 6). This added further impetus to development of the Tsv/Tse protecting group strategy described above. In further studies, it was also found that the choice of protecting group for the alcohol at C1 was also critical to this reaction (Scheme 21). Previous studies toward the chlorocyclopentane ring had been conducted using a TBS-protected alcohol, however, further endeavors toward axinellamine required an acidic stable protecting group. This led to the use of the pivaloate group, however, conducting the rearrangement under conditions previously utilized for the Tse/DMB-protected imidazolone resulted in non-reproducible yields of the spirocycle **71**.



Scheme 21.

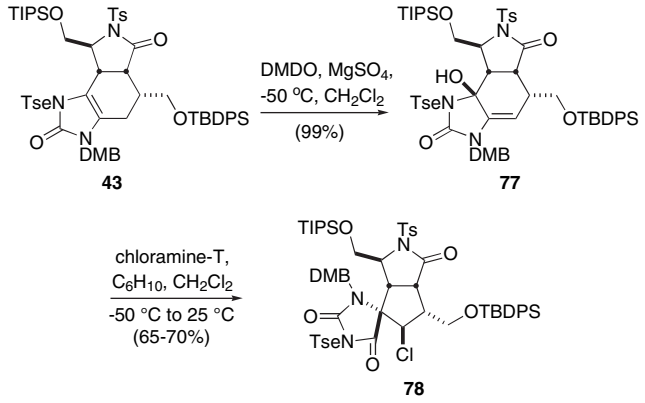
The desired chlorocyclopentane **71** (42%) remained as the major component and two by-products were identified as the aromatized compound **72** (30%) and the deschlorospirocycle **73** (17%). The presence of adventitious acid may lead

to protonation of enamine **69** rather than chlorination leading to deschlorocyclopentane **73** via iminium **74**. Alternatively, the acid presumably leads to the loss of the alcohol and formation of an iminium intermediate, for example, **75**. The increased amount of aromatized product **72** produced in this case compared to other protecting groups studied leads us to speculate that the pivaloate group may assist in diene formation by intramolecular deprotonation via intermediate **75** (Scheme 22). Subsequent α-chlorination and elimination or air oxidation of diene **76** may lead to the aromatized adduct **72**.



Scheme 22.

These findings led us to explore the more acid stable *tert*-butydiphenylsilyl (TBDPS) protecting group at C1 and as previously observed with the TBS ether, the chlorination/rearrangement sequence proceeded without incident (Scheme 23). However, while NCS gave isolable quantities of the aromatized product, chloramine-T nearly eliminated the formation of this by-product and gave highly reproducible yields of chlorocyclopentane **81** on gram scale (65–70%, Scheme 23).



Scheme 23.

3. Conclusion

We have developed a unified synthetic strategy to the oroidin alkaloids that will allow access to several members of this family of marine natural products. While Diels–Alder reactions of vinyl imidazolones provide adducts that have undergone facile olefin isomerization, subsequent oxidation provides a surprisingly stable allylic alcohol that serves as an excellent substrate for the key halogenation/ring contraction sequence. This involves a sequential chlorination/1,2-shift/ring contraction sequence allowing rapid access to a tricyclic spirocyclopentane (i.e., **78**), which serves as a point of departure for current synthetic studies toward the axinellamines. The requirement of imidazolone nitrogen protecting groups with differing electronics led to the development of several strategies for controlling regioselectivity in the Diels–Alder process and promoting the chlorination/rearrangement sequence. One strategy involved the development of a Tsv/Tse protecting group strategy, which allows for facile electronic tuning of this protecting group without recourse to a protecting group switch. The described synthetic studies have paved the way for our ongoing synthetic approaches to several members of the oroidin family of bioactive marine natural products that will ultimately enable further study of their precise biological modes of action.

4. Experimental

4.1. General

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried (120 °C) glassware unless noted otherwise. Tetrahydrofuran (THF, EM Science) and diethyl ether (Et_2O, EM Science) were distilled immediately prior to use from sodium metal/benzophenone ketyl. Methylene chloride (CH_2Cl_2, EM Science) and benzene (PhH, EM Science) were distilled from calcium hydride prior to use. Methanol (MeOH, EM Science) was distilled from magnesium methoxide. *N*-Chlorosuccinimide (NCS) was recrystallized from glacial acetic acid prior to use. Solutions of dimethyldioxirane[28] (DMDO) in acetone and methyl (trifluoromethyl)dioxirane[30] in 1,1,1-trifluoroacetone were prepared according to literature procedures. All other commercially available reagents were used as received unless specified otherwise.

Infrared spectra were recorded with a Nicolet Impact 410 FTIR spectrometer. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian Unity-500, Inova-500, Unity-300 or VXR-300 spectrometer. Mass spectra were obtained on a VG analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer (for FAB), an MDS Sciex (Concord, Ontario, Canada) API Qstar Pulsar (for ESI) or a ThermoFinnigan (San Jose, CA) LCQ Deca Mass Spectrometer (for APCI) at the Mass Spectrometry Application and Collaboration Facility (Texas A&M University). Flash column chromatography was performed using 60 Å Silica Gel (EM Science, 230–400 mesh) as a stationary phase. Enantiomeric excess (ee) was determined by HPLC analysis (RAININ SD-200 with DYANMAX UV-C DETECTOR) using a Chiralpak® AD column. Microwave reactions were carried out in a CEM® Explorer™/Discover™ microwave system.

4.1.1. General procedure for N-alkylation of imidazol-2-one as described for 1,3-bis-(benzyl)-4-(benzyloxy-carbonyl)imidazol-2-one (22a). To a slurry of NaH (3.79 g,

158 mmol) in anhydrous DMF (90 mL) was added imidazolone carboxylic acid **20** (4.01 g, 31.2 mmol) at 0 °C. The ice bath was removed and the reaction was allowed to warm to 22 °C. After stirring for 30 min, benzyl bromide (19.0 mL, 160 mmol) was added and the reaction was stirred for an additional 10 h at 22 °C. Water was added and the mixture was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1→1:9) gave benzyl ester **22a** (5.1 g, 41%) as a light yellow solid: R_f=0.30 (hexanes/EtOAc, 7:3); IR (thin film) 1724, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 15H), 7.01 (s, 1H), 5.25 (s, 2H), 5.15 (s, 2H), 4.86 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 153.5, 137.8, 135.7, 135.4, 129.0, 128.4, 128.36, 128.3, 128.2, 128.0, 127.9, 127.8, 127.3, 120.5, 113.6, 66.1, 47.6, 45.6; HRMS (FAB) Calcd for $C_{25}H_{23}N_2O_3$ [M+H]: 399.1781. Found: 399.1726.

4.1.2. 1,3-Bis(benzyloxymethyl)-4-(methoxycarbonyl)-imidazol-2-one (22b). R_f=0.40 (hexanes/EtOAc, 7:3); IR (thin film) 1731, 1593 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.49 (s, 1H), 7.38–7.21 (m, 10H), 5.49 (s, 2H), 5.19 (s, 2H), 4.60 (s, 2H), 4.59 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 160.1, 154.5, 139.2, 138.5, 129.0, 128.9, 128.5, 128.4, 128.2, 128.17, 122.3, 114.4, 73.5, 71.8, 71.4, 71.3, 51.8; HRMS (FAB) Calcd for $C_{21}H_{23}N_2O_5$ [M+H]: 383.1607. Found: 383.1597.

4.1.3. 1-*tert*-Butoxycarbonyl-4-(methoxycarbonyl)imidazol-2-one (Boc-21). To a slurry of imidazolone methyl ester **21** (943 mg, 6.64 mmol) in 50 mL CH_3CN was added K_2CO_3 (873 mg, 6.32 mmol) and Boc_2O (1.42 g, 6.50 mmol). Upon completion of the reaction as monitored by TLC the reaction mixture was concentrated in vacuo and purified by flash chromatography on SiO_2 eluting with CH_2Cl_2/MeOH (10:0→9.5:0.5) to yield the Boc-protected imidazolone methyl ester **Boc-21** (872 mg, 54%) as an off-white solid. In a separate reaction the crude product was found to be sufficiently pure for alkylation: R_f=0.43 (MeOH/CH_2Cl_2, 1:9); IR (thin film) 1796, 1753, 1738 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.90 (br s, 1H), 7.35 (s, 1H), 3.81 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 160.0, 150.2, 147.9, 116.4, 115.9, 84.9, 52.3, 27.9; HRMS (ESI) Calcd for $C_{10}H_{15}N_2O_5$ [M+H]: 243.0981. Found: 243.0889.

4.1.4. Methanesulfonic acid 2-(toluene-4-sulfonyl)-ethyl ester (29). To a stirred solution of the sodium salt of toluene sulfinic acid (100 g, 561 mmol) and sodium hydroxide (45 g, 1.12 mol) in water (1000 mL) was added chloroethanol (75.0 mL, 1.12 mol) at 100 °C and stirring continued for 5 h. The reaction was cooled to room temperature and extracted with ethyl acetate (3×500 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Solvents were removed in vacuo and the crude alcohol isolated as an orange oil. Triethylamine (69.6 mL, 499 mmol) was added to a stirred solution of the crude alcohol in dichloromethane (1000 mL) at 0 °C, followed by the addition of MsCl (38.6 mL, 499 mmol) and stirring continued for 30 min. The organic layer was washed with water and dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the crude mesylate. Recrystallization from ethyl acetate/hexane gave mesylate **29** (81.0 g, 52%) as a colorless solid: mp 89–91 °C; R_f=0.38 (hexanes/EtOAc, 6:4); IR (thin film) 1593 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J=8.1 Hz, 2H), 7.40 (d, J=8.1 Hz, 2H), 4.55 (t, J=6.0 Hz, 2H), 3.53 (t, J=6.0 Hz, 2H), 2.98 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 136.3, 130.4, 128.4, 62.2, 55.5, 38.0, 22.0; LRMS (APCI) Calcd for $C_{10}H_{15}S_2O_5$ [M+H]: 279. Found: 279.

4.1.5. Synthesis of 2-oxo-1-[2-(toluene-4-sulfonyl)-ethyl]-2,3-dihydro-1*H*-imidazole-4-carboxylic acid methyl ester (Tse-21). A solution of imidazolone (45.0 g, 317 mmol) in 900 mL DMSO at 25 °C was treated with sodium hydrogen carbonate (53.2 g, 634 mmol). After 10 min at 70 °C, TseOMs (88.1 g, 317 mmol) was added to the resulting solution. The reaction was further stirred for 12 h, and poured onto ice (300 g). The resulting solution was filtered to give a brown solid. The crude solid was purified by dissolution of impurities in ethyl acetate and the solid residue was filtered to afford **Tse-21** (>95% purity, 78.0 g, 76%) as a tan solid. R_f=0.34 (EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.76 (AB, J=8.5 Hz, 2H), 7.35 (AB, J=8.5 Hz, 2H), 7.03 (d, J=2.0 Hz, 1H), 4.16 (t, J=6.5 Hz, 2H), 3.84 (s, 3H), 3.55 (t, J=6.5 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 152.2, 145.3, 136.0, 130.1, 127.8, 120.1, 113.1, 54.1, 51.9, 38.5, 21.6; MS (ESI) 331 [M+Li], 325 [M+H]. HRMS (ESI) Calcd for $C_{14}H_{16}N_2O_5SLi$ [M+Li]: 331.0940. Found: 331.0942.

4.1.6. Synthesis of 2-oxo-1,5-bis-[2-(toluene-4-sulfonyl)-vinyl]-2,3-dihydro-1*H*-imidazole-4-carboxylic acid methyl ester (37). A solution of imidazolone **21** (25.0 mg, 0.18 mmol) in 3 mL DMF at 0 °C was treated with potassium carbonate (1.20 mg, 0.0087 mmol). A solution of 1-ethynesulfonyl-4-methylbenzene (32 mg, 0.18 mmol) in 2 mL DMF was added to the stirred solution dropwise over the period of an hour. The mixture was allowed to warm to room temperature over 12 h. Solvents were removed in vacuo and the crude solid was purified by flash chromatography (SiO_2, EtOAc/hexane, 4:6) to afford **37** (29.0 mg, 66%) as a colorless solid: mp 160–165 °C (dec); R_f=0.60 (EtOAc/hexane, 2:3); IR (thin film) 3587, 1721, 1703, 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82–7.78 (m, 5H), 7.35 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 7.23 (s, 1H), 6.86 (d, J=8.5 Hz, 1H), 6.83 (d, J=13.5.5 Hz, 1H), 6.40 (d, J=8.5 Hz, 1H), 3.85 (s, 3H), 2.44 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 149.1, 145.3, 144.9, 137.8, 137.0, 132.3, 130.2, 130.0, 128.6, 128.3, 123.2, 127.8, 18.4, 117.3, 116.6, 52.7, 21.82, 21.77; MS (ESI) 509 [M+Li]. HRMS (ESI) Calcd for $C_{23}H_{22}N_2O_7S_2Li$ [M+Li]: 509.1028. Found: 509.1016.

4.1.7. 1-Toluenesulfonyl-4-(methoxycarbonyl)imidazol-2-one (Ts-21). To a stirred solution of NaH (219 mg, 9.14 mmol) in 50 mL anhydrous DMF at 0 °C was added imidazolone methyl ester **21** (1.29 g, 9.06 mmol) followed by TsCl (1.74 g, 9.12 mmol). The reaction mixture was heated at 65 °C for 19 h, diluted with pH 7 buffer and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4. Solvents were removed in vacuo and the crude solid

was purified by flash chromatography on SiO_2, eluting with CH_2Cl_2/MeOH (10:0→9:1) to furnish tosylated methyl ester **Ts-21** (1.55 g, 58%) as an off-white solid: mp 191–192 °C (EtOAc/hexanes); R_f=0.40 (hexanes/EtOAc, 6:4); IR (thin film) 1724 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 10.06 (br s, 1H), 8.01 (d, J=8.5 Hz, 2H), 7.50 (d, J=8.5 Hz, 2H), 7.46 (s, 1H), 3.86 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.6, 149.7, 147.2, 134.9, 130.8, 117.0, 116.1, 52.4, 21.6; HRMS (ESI) Calcd for $C_{12}H_{13}N_2O_5S$ [M+H]: 297.0539. Found: 297.0560.

4.1.8. General procedure for the N-alkylation of the acylated or sulfonylated imidazol-2-one as described for 1-*tert*-butoxycarbonyl-3-(4-methoxybenzyl)-4-(methoxycarbonyl)imidazol-2-one (22c). To crude Boc imidazolone methyl ester **Boc-21** (3.41 g, 14.1 mmol) in 100 mL acetonitrile was added K_2CO_3 (6.15 g, 44.5 mmol) and PMBBr (4.00 mL, 28.7 mmol). The reaction mixture was heated to reflux for 16 h, diluted with pH 7 buffer, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (10:0→7:3) gave PMB-protected imidazolone **22c** (2.69 g, 53%) as a light yellow solid: R_f=0.52 (hexanes/EtOAc, 6:4); IR (thin film) 1796, 1753, 1724 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.36 (s, 1H), 7.31 (d, J=8.5 Hz, 2H), 6.77 (d, J=8.5 Hz, 2H), 5.08 (s, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.3, 158.9, 150.9, 146.7, 129.5, 129.3, 116.5, 115.1, 113.6, 85.3, 55.0, 51.8, 44.6, 27.3; HRMS (ESI) Calcd for $C_{18}H_{23}N_2O_6$ [M+H]: 363.1556. Found: 363.1454.

4.1.9. 3-(3,4-Dimethoxybenzyl)-2-oxo-1-[2-(toluene-4-sulfonyl)-ethyl]-2,3-dihydro-1*H*-imidazole-4-carboxylic acid methyl ester (22d). R_f=0.50 (EtOAc); IR (neat) 1721, 1692 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.59 (d, J=8.0 Hz, 2H), 7.23 (m, 2H), 6.66 (d, J=8.0 Hz, 2H), 6.56 (m, 2H), 5.19 (s, 2H), 3.63 (t, J=7.0, 5.5 Hz, 2H), 3.52 (s, 3H), 3.334 (s, 3H), 3.332 (s, 3H), 3.11 (t, J=7.0, 5.5 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.8, 153.0, 150.1, 149.7, 144.4, 137.3, 131.3, 129.8, 128.0, 121.2, 121.1, 113.3, 113.1, 112.3, 55.6, 55.5, 53.7, 50.8, 45.3, 38.7, 21.1; HRMS (ESI) Calcd for $C_{23}H_{27}N_2O_7S$ [M+H]: 475.1539. Found: 475.1529.

4.1.10. 1-Toluenesulfonyl-3-(4-methoxybenzyl)-4-(methoxycarbonyl)imidazol-2-one (22e). R_f=0.32 (hexanes/EtOAc, 7:3); IR (thin film) 1726 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.01 (d, J=8.5 Hz, 2H), 7.55 (s, 1H), 7.52 (d, J=8.5 Hz, 2H), 7.12 (d, J=9.0 Hz, 2H), 6.79 (d, J=9.0 Hz, 2H), 4.98 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 160.1, 159.9, 150.4, 147.5, 134.6, 130.9, 130.1, 129.9, 129.4, 117.1, 114.6, 55.4, 52.4, 45.5, 21.6; HRMS (ESI) Calcd for $C_{20}H_{21}N_2O_6S$ [M+H]: 417.1120. Found: 417.1078.

4.1.11. 1-Toluenesulfonyl-3-(3,4-dimethoxybenzyl)-4-(methoxycarbonyl)imidazol-2-one (22f). R_f=0.36 (hexanes/EtOAc, 6:4); IR (thin film) 1731, 1724 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.03 (d, J=8.5 Hz, 2H), 7.56 (s, 1H), 7.51 (d, J=8.5 Hz, 2H), 6.78 (m, 1H), 6.77 (s, 1H), 6.71 (m, 1H), 4.98 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.8, 150.3, 150.1, 149.8, 147.5, 134.6, 130.8, 130.7, 130.6, 129.4, 120.9, 117.0, 112.4, 112.3, 55.9, 55.8, 52.4, 45.7, 21.6; HRMS (ESI) Calcd for $C_{21}H_{23}N_2O_7S$ [M+H]: 447.1226. Found: 447.1205.

4.1.12. General procedure for DIBAl-H reduction of imidazolone ester as described for 1,3-bis(benzyl)-4-(hydroxymethylene)imidazol-2-one (23a). To a cooled (−78 °C) solution of benzyl ester **22a** (8.61 g, 21.6 mmol) in 165 mL CH_2Cl_2 was added a 0.99 M solution of DIBAl-H in CH_2Cl_2 (54.6 mL, 53.8 mmol). The reaction was stirred for 3 h at −78 °C and additional DIBAl-H was added (11.0 mL, 1.0 M, 11.2 mmol). After 4 h MeOH (40 mL) was added at −78 °C followed by a solution of Rochelle's salt and the heterogeneous mixture was allowed to warm to 22 °C overnight. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1→1:9) afforded alcohol **23a** (5.55 g, 87%) as an off-white solid: R_f=0.28 (hexanes/EtOAc, 3:7); IR (thin film) 3360, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 10H), 6.01 (s, 1H), 4.95 (s, 2H), 4.73 (s, 2H), 4.15 (s, 2H), 2.92 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 137.6, 136.7, 128.8, 128.7, 128.0, 127.9, 127.5, 127.2, 122.3, 109.0, 55.3, 47.1, 44.9; HRMS (ESI) Calcd for $C_{18}H_{19}N_2O_2$ [M+H]: 295.1497. Found: 295.1584.

4.1.13. 1,3-Bis(benzyloxymethyl)-4-(hydroxymethylene)imidazol-2-one (23b). R_f=0.09 (hexanes/EtOAc, 6:4); IR (thin film) 3491, 1702 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.37–7.25 (m, 9H), 7.13–7.07 (m, 1H), 6.54 (s, 1H), 5.30 (s, 2H), 5.09 (s, 2H), 4.59 (s, 2H), 4.56 (s, 2H), 4.51 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 154.8, 138.8, 138.7, 130.1, 128.94, 128.93, 128.43, 128.41, 128.25, 128.23, 126.5, 124.1, 109.8, 72.9, 71.2, 70.9, 70.8, 55.0; HRMS (FAB) Calcd for $C_{20}H_{23}N_2O_4$ [M+H]: 355.1650. Found: 355.1658.

4.1.14. 3-(3,4-Dimethoxybenzyl)-4-hydroxymethyl-1-[2-(toluene-4-sulfonyl)-ethyl]-1,3-dihydro-imidazol-2-one (23d). R_f=0.15 (EtOAc); IR (film) 3367, 1670 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.75 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 6.85 (s, 1H), 6.78 (m, 2H), 6.22 (s, 1H), 4.80 (s, 2H), 4.22 (s, 2H), 4.01 (t, J=6.5 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.50 (t, J=7.0, 6.5 Hz, 2H), 2.42 (s, 3H), 2.32 (br s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.2, 149.1, 148.5, 145.1, 136.0, 130.0, 129.8, 127.8, 122.5, 119.6, 111.1, 110.8, 109.6, 55.9, 55.8, 55.1, 54.3, 44.6, 38.0, 21.6; HRMS (ESI) Calcd for $C_{22}H_{27}N_2O_6S$ [M+H]: 453.1672. Found: 453.1647.

4.1.15. 3-(4-Methoxybenzyl)-1-toluenesulfonyl-4-(hydroxymethylene)imidazol-2-one (23e). R_f=0.07 (hexanes/EtOAc, 7:3); IR (thin film) 3411, 1709 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.95 (d, J=8.5 Hz, 2H), 7.46 (d, J=8.5 Hz, 2H), 7.10 (d, J=8.5 Hz, 2H), 6.81 (d, J=8.5 Hz, 2H), 6.77 (s, 1H), 4.74 (s, 2H), 4.29 (s, 2H), 3.75 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 160.1, 151.3, 146.6, 135.6, 130.6, 129.9, 129.4, 128.8, 114.7, 105.9, 55.4, 55.2, 44.7, 21.5; HRMS (ESI) Calcd for $C_{19}H_{20}N_2O_5SLi$ [M+Li]: 395.1253. Found: 395.1234.

4.1.16. 3-(3,4-Dimethoxybenzyl)-1-toluenesulfonyl-4-(hydroxymethylene)imidazol-2-one (23f). Mp 135–136 °C (EtOAc/hexanes); R_f=0.09 (hexanes/EtOAc, 6:4); IR (thin film) 3418, 1716 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.96 (d, J=8.5 Hz, 2H), 7.48 (d, J=8.5 Hz, 2H), 6.81 (d, J=7.5 Hz, 1H), 6.77 (app t, J=1.5 Hz, 1H), 6.68 (dd, J=7.5, 1.5 Hz, 1H), 4.74 (s, 2H), 4.29 (d, J=5.5 Hz, 2H), 3.75 (s, 3H), 3.62 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 150.7, 149.8, 149.2, 146.0, 135.1, 130.9, 129.9, 128.3, 126.9, 119.7, 112.0, 111.3, 105.2, 55.4, 55.2, 54.6, 44.4, 20.9; HRMS (ESI) Calcd for $C_{20}H_{23}N_2O_6S$ [M+H]: 419.1277. Found: 419.1189.

4.1.17. General procedure for oxidation of 4-(hydroxymethylene)imidazol-2-one as described for 1,3-bis(benzyl)4-(carboxaldehyde)imidazol-2-one (24a). To activated MnO_2 (13.1 g, 151 mmol) was added alcohol **23a** (5.55 g, 18.9 mmol) in 40 mL CH_2Cl_2, rinsing twice with 20 mL CH_2Cl_2 to complete the transfer. After stirring for 10 h at ambient temperature the reaction mixture was filtered through Celite and concentrated in vacuo to yield aldehyde **24a** (5.38g, 98%) as a yellow viscous oil. No further purification was required: R_f=0.67 (hexanes/EtOAc, 3:7); IR (thin film) 1702, 1658 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.43–7.23 (m, 10H), 6.89 (s, 1H), 5.23 (s, 2H), 4.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 153.3, 137.4, 135.1, 129.1, 128.5, 128.4, 128.2, 127.6, 127.2, 47.8, 45.9; HRMS (FAB) Calcd for $C_{18}H_{17}N_2O_2$ [M+H]: 293.1290. Found: 293.1279.

4.1.18. 1,3-Bis(benzyloxymethyl)-4-(carboxaldehyde)-imidazol-2-one (24b). R_f=0.25 (hexanes/EtOAc, 6:4); IR (thin film) 1731, 1673 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 9.36 (s, 1H), 7.72 (s, 1H), 7.36–7.28 (m, 10H), 5.49 (s, 2H), 5.23 (s, 2H), 4.62 (br s, 4H); ^{13}C NMR (125 MHz, acetone-d_6) δ 178.3, 156.3, 139.1, 138.3, 129.7, 129.0, 128.9, 128.5, 128.4, 128.16, 128.13, 124.0, 73.6, 72.1, 71.5, 71.3; HRMS (FAB) Calcd for $C_{20}H_{21}N_2O_4$ [M+H]: 353.1501. Found: 353.1507.

4.1.19. 3-(3,4-Dimethoxybenzyl)-2-oxo-1-(2-tosylethyl)-2,3-dihydro-1*H*-imidazole-4-carbaldehyde (24d). Mp 150–152 °C; R_f=0.39 (EtOAc); IR (KBr) 2837, 1708, 1660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.21 (s, 1H), 7.72 (d, J=8.5 Hz, 2H), 7.29 (d, J=8.5 Hz, 2H), 7.14 (s, 1H), 7.02 (d, J=2.0 Hz, 1H), 6.97 (dd, J=8.0, 2.0 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 5.04 (s, 2H), 4.19 (t, J=6.5, 5.5 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.56 (t, J=6.5, 5.5 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 152.6, 148.8, 148.6, 145.4, 136.0, 130.1, 129.8, 128.3, 127.6, 122.8, 121.0, 111.9, 110.9, 55.8, 53.7, 45.6, 38.9, 21.6; HRMS (ESI) Calcd for $C_{22}H_{24}N_2O_6SLi$ [M+Li]: 451.1515. Found: 451.1496.

4.1.20. 3-(4-Methoxybenzyl)-1-toluenesulfonyl-4-(carboxaldehyde)imidazol-2-one (24e). R_f=0.31 (hexanes/EtOAc, 7:3); IR (thin film) 2836, 1731, 1673 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 9.45 (s, 1H), 8.02 (d, J=8.5 Hz, 2H), 7.99 (s, 1H), 7.52 (d, J=8.5 Hz, 2H), 7.17 (d, J=8.5 Hz, 2H), 6.80 (d, J=8.5 Hz, 2H), 4.97 (s, 2H), 3.74 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 179.9, 159.6, 149.6, 147.1, 133.8, 130.3, 129.5, 128.9, 124.1, 113.9, 54.8, 45.2, 21.0; HRMS (ESI) Calcd for $C_{19}H_{18}N_2O_5SLi$ [M+Li]: 393.1096. Found: 393.1081.

4.1.21. 3-(3,4-Dimethoxybenzyl)-1-toluenesulfonyl-4-(carboxaldehyde)imidazol-2-one (24f). R_f=0.23 (hexanes/EtOAc, 6:4); IR (thin film) 2836, 1731, 1673 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.42 (s, 1H), 8.01 (d, J=8.4 Hz, 2H), 7.98 (s, 1H), 7.51 (d, J=8.4 Hz, 2H), 6.82–6.74 (m, 3H), 4.96 (s, 2H), 3.73 (s, 3H), 3.62 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.0, 150.21, 150.17, 150.0, 147.7, 134.4, 130.9, 130.5, 129.5, 125.5, 124.7, 121.1, 112.6, 112.5, 56.0, 55.8, 46.0, 21.6; HRMS (ESI) Calcd for $C_{20}H_{21}N_2O_6S$ [M+H]: 417.1120. Found: 417.1089.

4.1.22. General procedure for Horner–Wadsworth–Emmons reaction as described for 1,3-bis(benzyl)-4-(ethylpropenoate)imidazol-2-one (25a). To a cooled (0 °C) suspension of NaH (11.8 mg, 0.49 mmol) in 2.5 mL THF was slowly added triethylphosphonoacetate (98.0 μL, 0.49 mmol). After stirring the reaction at 0 °C for 5 min the ice bath was removed and the mixture was stirred at 22 °C for 1 h. Aldehyde **24a** (131 mg, 0.45 mmol) was added at ambient temperature in 2 mL THF. After 2 h pH 4 buffer was added and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organics were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a mixture of product and starting material. The crude reaction mixture was resubjected to the reaction conditions and furnished upon purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1→4:6) ester **25a** (44.7 mg, 89%) as a light yellow solid: R_f=0.34 (hexanes/EtOAc, 6:4); IR (thin film) 1687, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.20 (m, 10H), 7.14 (d, J=15.9 Hz, 1H), 6.57 (s, 1H), 5.90 (d, J=15.9 Hz, 1H), 5.02 (s, 2H), 4.86 (s, 2H), 4.12 (q, J=7.2 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 153.5, 136.5, 135.9, 129.8, 128.8, 128.7, 128.0, 127.9, 127.5, 126.6, 120.1, 114.4, 114.2, 60.2, 47.3, 45.1, 14.1; HRMS (FAB) Calcd for $C_{22}H_{23}N_2O_2$ [M+H]: 363.1709. Found: 363.1691. Generally, the HWE olefination proceeded smoothly and all the aldehyde was consumed, such that the crude reaction mixture did not have to be resubjected.

4.1.23. 1,3-Bis(benzyloxymethyl)-4-(ethylpropenoate)-imidazol-2-one (25b). R_f=0.40 (hexanes/EtOAc, 6:4); IR (thin film) 1702, 1636 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.39–7.25 (m, 12H), 6.39 (d, J=16.0 Hz, 1H), 5.31 (s, 2H), 5.17 (s, 2H), 4.62 (s, 2H), 4.59 (s, 2H), 4.18 (q, J=7.0 Hz, 2H), 1.26 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 167.2, 154.8, 138.6, 138.56, 131.0, 129.0, 128.6, 128.5, 128.3, 121.4, 118.0, 115.8, 73.3, 71.7, 71.3, 70.9, 66.6, 14.6; HRMS (FAB) Calcd for $C_{24}H_{27}N_2O_5$ [M+H]: 423.1920. Found: 423.1922.

4.1.24. 3-{3-(3,4-Dimethoxybenzyl)-2-oxo-1-[2-(toluene-4-sulfonyl)-ethyl]-2,3-dihydro-1*H*-imidazol-4-yl}-acrylic acid ethyl ester (25d). A solution of triethylphosphonoacetate (10.3 mL, 52.0 mmol) in 100 mL THF was cooled to 0 °C and treated with 80% NaH (1.43 g, 49.5 mmol), allowed to warm to 25 °C and further stirred for 40 min. To the resulting solution was added dropwise a solution of

aldehyde **49** (22.0 g, 49.5 mmol) in 300 mL THF and then stirring was continued for 2 h. The reaction was quenched with 100 mL of pH 4 buffer solution. THF was removed in vacuo and the aqueous phase was extracted with EtOAc (3×300 mL). The organic layers were combined and dried ($MgSO_4$). Solvents were removed in vacuo and the crude ester **50** was isolated as a yellow oil. The ester was generally used without purification.

4.1.25. 3-(4-Methoxybenzyl)-1-toluenesulfonyl-4-(ethylpropenoate)imidazol-2-one (25e). R_f=0.25 (hexanes/EtOAc, 7:3); IR (thin film) 1724, 1716 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.99 (d, J=8.5 Hz, 2H), 7.56 (s, 1H), 7.51 (d, J=8.5 Hz, 2H), 7.22 (d, J=16.5 Hz, 1H), 7.04 (d, J=8.5 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 6.36 (d, J=16.5 Hz, 1H), 4.87 (s, 2H), 4.14 (q, J=7.0 Hz, 2H), 3.75 (s, 3H), 2.48 (s, 3H), 1.23 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.3, 160.2, 150.9, 147.1, 135.1, 130.8, 129.9, 129.3, 129.1, 128.9, 123.7, 119.9, 115.0, 110.7, 61.0, 55.5, 44.8, 21.6, 14.5; HRMS (ESI) Calcd for $C_{23}H_{24}N_2O_6S$ [M+H]: 457.1433. Found: 457.1415.

4.1.26. 3-(3,4-Dimethoxybenzyl)-1-toluenesulfonyl-4-(ethylpropenoate)imidazol-2-one (25f). R_f=0.25 (hexanes/EtOAc, 6:4); IR (thin film) 1724, 1716 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.01 (d, J=8.5 Hz, 2H), 7.57 (app t, J=0.5 Hz, 1H), 7.51 (d, J=8.5 Hz, 2H), 7.25 (dd, J=16.0, 0.5 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H), 6.73 (d, J=2.0 Hz, 1H), 6.62 (dd, J=8.0, 2.0 Hz, 1H), 6.37 (dd, J=16.0, 0.5 Hz, 1H), 4.87 (s, 2H), 4.14 (q, J=7.0 Hz, 2H), 3.75 (s, 3H), 3.63 (s, 3H), 2.48 (s, 3H), 1.22 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.3, 150.8, 150.5, 149.9, 147.1, 135.1, 130.8, 129.9, 129.8, 129.2, 123.7, 119.9, 119.8, 112.8, 111.5, 110.6, 61.0, 56.0, 55.8, 45.1, 21.6, 14.8; HRMS (ESI) Calcd for $C_{24}H_{27}N_2O_7S$ [M+H]: 487.1539. Found: 487.1568.

4.1.27. General procedure for preparation of diene as described for 1,3-bis(benzyl)-4-(3-hydroxypropenyl)-imidazol-2-one (16a). To a cooled (−78 °C) solution of α,β-unsaturated ester **25a** (1.10 g, 3.05 mmol) was added a 1.0 M solution of DIBAl-H in CH_2Cl_2 (9.15 mL, 9.15 mmol). After 2 h, MeOH (15 mL) was added followed by Rochelle's salt solution. Upon stirring for 8 h the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give diene **16a** (977 mg, 99%) as a yellow foam. No further purification was required: R_f=0.17 (hexanes/EtOAc, 3:7); IR (thin film) 3404, 1673 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.39–7.25 (m, 10H), 6.64 (s, 1H), 6.24 (d, J=15.5 Hz, 1H), 6.04 (dt, J=5.5, 15.5 Hz, 1H), 4.96 (s, 2H), 4.85 (s, 2H), 4.07 (app t, J=5.5 Hz, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 154.3, 139.3, 139.0, 130.3, 129.4, 129.3, 128.5, 128.3, 128.0, 127.6, 122.7, 116.5, 108.3, 62.8, 47.3, 45.1; HRMS (ESI) Calcd for $C_{20}H_{21}N_2O_2$ [M+H]: 321.1603. Found: 321.1595.

4.1.28. 1,3-Bis(benzyloxymethyl)-4-(3-hydroxypropenyl) imidazol-2-one (16b). R_f=0.31 (hexanes/EtOAc, 3:7); IR (thin film) 3404, 1687 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) 7.20–7.09 (m, 10H), 6.51 (s, 1H), 6.23 (d, J=16.0 Hz, 1H), 6.14 (dt, J=5.0, 16.0 Hz, 1H), 5.03 (s, 2H), 4.93 (s, 2H), 4.42 (s, 2H), 4.39 (s, 2H), 4.05 (br s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 154.7, 138.8, 138.7, 136.9, 131.3, 130.2, 128.94, 128.93, 128.4, 128.3, 126.5, 123.2, 116.2, 109.1, 73.2, 71.3, 70.9, 70.8, 62.9; HRMS (FAB) Calcd for $C_{22}H_{25}N_2O_4$ [M+H]: 381.1814. Found: 381.1800.

4.1.29. 3-(3,4-Dimethoxybenzyl)-4-(3-hydroxypropenyl)-1-[2-(toluene-4-sulfonyl)-ethyl]-1,3-dihydro-imidazol-2-one (16d). Mp 81–83 °C (EtOAc/hexanes); R_f=0.16 (EtOAc); IR (film) 3432, 1713 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.70 (d, J=8.0 Hz, 2H), 6.90 (d, J=2.0 Hz, 1H), 6.82 (dd, J=8.0, 2.0 Hz, 1H), 6.73 (d, J=8.0 Hz, 2H), 6.54 (d, J=8.0 Hz, 1H), 6.09 (d, J=16.0 Hz, 1H), 5.90 (s, 1H), 5.78 (dt, J=16.0, 5.5 Hz, 1H), 4.73 (s, 2H), 3.86 (br s, 2H), 3.86 (t, J=6.5, 6.0 Hz, 2H), 3.50 (s, 3H), 3.33 (s, 3H), 3.21 (t, J=6.5, 6.0 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.4, 150.4, 149.6, 137.5, 130.6, 129.8, 129.4, 128.3, 127.9, 122.1, 119.7, 116.6, 112.4, 111.9, 108.1, 62.9, 55.7, 55.5, 54.4, 44.8, 38.2, 21.1; HRMS (ESI) Calcd for $C_{24}H_{28}N_2O_6SNa$ [M+Na]: 473.1746. Found: 473.1704.

4.1.30. 3-(4-Methoxybenzyl)-1-toluenesulfonyl-4-(3-hydroxypropenyl)imidazol-2-one (16e). R_f=0.36 (hexanes/EtOAc, 3:7); IR (thin film) 3491, 1709 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.96 (d, J=8.5 Hz, 2H), 7.48 (d, J=8.5 Hz, 2H), 7.02 (d, J=8.5 Hz, 2H), 6.95 (s, 1H), 6.80 (d, J=8.5 Hz, 2H), 6.33 (dt, J=4.0, 16.5 Hz, 1H), 6.24 (m, 1H), 4.71 (s, 2H), 4.14 (m, 2H), 3.75 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 160.0, 151.0, 146.6, 135.5, 135.3, 130.6, 129.7, 129.0, 128.9, 126.3, 114.7, 114.6, 104.0, 62.3, 55.4, 44.5; HRMS (ESI) Calcd for $C_{21}H_{23}N_2O_5S$ [M+H]: 415.1328. Found: 415.1297.

4.1.31. 3-(3,4-Dimethoxybenzyl)-1-toluenesulfonyl-4-(3-hydroxypropenyl)imidazol-2-one (16f). R_f=0.24 (hexanes/EtOAc, 3:7); IR (thin film) 3433, 1716 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.77 (d, J=8.5 Hz, 2H), 7.48 (d, J=8.5 Hz, 2H), 6.95 (s, 1H) 6.79 (d, J=8.0 Hz, 1H), 6.72 (d, J=2.0 Hz, 1H), 6.62 (dd, J=8.0, 2.0 Hz, 1H), 6.33 (dt, J=16.0, 4.0 Hz, 1H), 6.27 (m, 1H), 4.71 (s, 2H), 4.18 (br s, 2H), 3.75 (s, 3H), 3.62 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 151.0, 150.4, 149.8, 146.6, 135.6, 135.3, 130.6, 130.3, 128.9, 126.3, 120.0, 114.7, 112.7, 111.7, 103.9, 62.4, 56.0, 55.8, 44.8, 21.5; HRMS (ESI) Calcd for $C_{22}H_{25}N_2O_6S$ [M+H]: 445.1433. Found: 445.1452.

4.1.32. Diels–Alder adduct 34a. A heterogeneous mixture of diene **16a** (33.9 mg, 0.11 mmol) and dienophile **15a** (36.3 mg, 0.10 mmol) in 500 μL *o*-xylene was heated to 140 °C for 24 h. The reaction mixture was concentrated in vacuo and purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (7:3→3:7) furnished Diels–Alder adduct **34a** (19.1 mg, 28%) as a light yellow solid: R_f=0.54 (hexanes/EtOAc, 3:7); $[\alpha]_D^{25}$ −55.3° (*c* 1.64, CH_2Cl_2); IR (thin film) 3418, 1724, 1680, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.22 (m, 8H), 7.12 (m, 2H), 5.16 (d, J=16.2 Hz, 1H), 4.93 (d, J=15.9 Hz, 1H), 4.69 (d, J=15.9 Hz, 1H), 4.65 (d, J=16.2 Hz, 1H), 3.96–3.85 (m, 4H), 3.69 (dd, J=6.3, 14.4 Hz, 1H), 3.43 (dd, J=3.6, 7.5 Hz, 1H), 3.14 (d, J=7.5 Hz, 1H), 2.50 (ddd,

J=2.7, 12.0, 15.9 Hz, 1H), 2.22 (m, 1H), 2.03–1.95 (m, 1H), 1.40 (s, 9H), 0.98–0.95 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 154.7, 149.4, 137.3, 137.1, 128.9, 128.8, 127.7, 127.6, 127.3, 126.6, 120.5, 114.7, 88.7, 64.5, 63.7, 62.0, 46.1, 45.4, 44.9, 36.8, 33.9, 27.9, 19.2, 17.9, 11.8; HRMS (ESI) Calcd for $C_{39}H_{56}N_3O_6Si$ [M+H]: 690.3938. Found: 690.3939.

4.1.33. Diels–Alder adduct 34b. To a solution of dienophile **15b** (2.77 g, 6.55 mmol) in 50 mL PhH was added diene **16a** (2.81 g, 6.52 mmol) and 2,6-lutidine (450 μL, 3.95 mmol). The reaction mixture was heated to 95 °C in a sealed tube for three days. Upon cooling additional diene **16a** (891 mg, 2.79 mmol) was added. After stirring at 95 °C for an additional 24 h, the reaction was concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (8:2→1:9) gave 3.09 g (64%) Diels–Alder adduct **34b** as a yellow foam along with 714.1 mg (15%) of regioisomer **35b**. **34b**: R_f=0.69 (hexanes/EtOAc, 3:7); $[\alpha]_D^{25}$ −53.0° (*c* 2.53, CH_2Cl_2); IR (thin film) 3475, 1738, 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J=8.1 Hz, 2H), 7.34–7.10 (m, 12H), 5.23 (d, J=16.2 Hz, 1H), 4.91 (d, J=16.2 Hz, 1H), 4.62 (d, J=16.2 Hz, 1H), 4.32 (d, J=16.2 Hz, 1H), 4.21 (dd, J=2.7, 5.1 Hz, 1H), 4.04 (dd, J=5.1, 10.5 Hz, 1H), 3.92 (dd, J=2.7, 10.5 Hz, 1H), 3.74 (app t, J=3.9 Hz, 2H), 3.41 (dd, J=3.0, 6.9 Hz, 1H), 3.18 (app br d, J=6.9 Hz, 1H), 2.40 (s, 3H), 2.00–1.90 (m, 2H), 1.88–1.80 (m, 1H), 1.05–0.95 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 154.6, 145.1, 137.03, 137.0, 135.0, 129.4, 128.9, 128.8, 128.5, 128.4, 127.9, 127.6, 127.1, 127.0, 120.8, 114.0, 65.2, 64.3, 64.1, 45.6, 45.0, 44.7, 36.4, 35.5, 21.7, 18.9, 17.9, 11.8; HRMS (FAB) Calcd for $C_{41}H_{53}N_3O_6SSiNa$ [M+Na]: 766.3322. Found: 766.3314. **35b**: R_f=0.42 (hexanes/EtOAc, 3:7); $[\alpha]_D^{25}$ −24.1° (*c* 1.85, CH_2Cl_2); mp 76.0–78.0 °C; IR (thin film) 3385, 1737, 1690 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.91 (d, J=8.0 Hz, 2H), 7.36–7.26 (m, 10H), 7.10 (d, J=8.0 Hz, 2H), 5.09 (d, J=16.5 Hz, 1H), 5.01 (d, J=16.5 Hz, 1H), 4.91 (d, J=16.0 Hz, 1H), 4.71 (d, J=16.0 Hz, 1H), 4.36 (br s, 1H), 4.25 (dd, J=3.5, 11.0 Hz, 1H), 4.02 (m, 1H), 3.85 (m, 1H), 3.62 (d, J=7.5 Hz, 1H), 3.52–3.49 (m, 1H), 3.22 (m, 1H), 3.00–2.97 (m, 1H), 2.69 (dd, J=4.0, 16.5, 1H), 2.42 (s, 3H), 2.34 (ddd, J=2.5, 4.0, 16.5 Hz, 1H), 2.27–2.22 (m, 1H), 0.94–0.93 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 172.4, 154.7, 146.1, 139.4, 139.1, 136.5, 130.2, 129.3, 129.2, 128.9, 128.0, 127.9, 127.7, 127.1, 118.8, 111.2, 66.1, 63.1, 60.6, 45.2, 44.9, 40.2, 39.2, 37.5, 21.5, 20.8, 18.2, 12.5; HRMS (FAB) Calcd for $C_{41}H_{54}N_3O_6SSi$ [M+H]: 744.3503. Found: 744.3508.

4.1.34. Diels–Alder adduct 34c. To dienophile **15b** (275 mg, 0.65 mmol) and diene **16b** (230 mg, 0.61 mmol) was added 5 mL PhH and 2,6-lutidine (40.0 μL, 0.34 mmol). The reaction mixture was heated to 95 °C in a sealed vial for 17 h, concentrated in vacuo, and purified by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1→1:1) to furnish 148 mg (30%) Diels–Alder adduct **34c** along with the 31.1 mg presumed regioisomer: R_f=0.62 (hexanes/EtOAc, 3:7); IR (thin film) 3476, 1738 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.64 (d, J=8.5 Hz, 2H), 7.48 (d, J=8.5 Hz, 2H), 7.37–7.24 (m, 10 H), 5.15 (d, J=11.0 Hz, 1H), 5.11 (d, J=11.0 Hz, 1H), 5.09 (d, J=11.0 Hz, 1H), 5.05 (d, J=11.0 Hz, 1H), 4.80 (d, J=12.5 Hz, 1H), 4.74 (app t, J=4.0 Hz, 1H), 4.71 (d, J=12.5 Hz, 1H), 4.50 (d, J=12.0 Hz, 1H), 4.43 (d, J=12.0 Hz, 1H), 4.17 (d, J=4.0 Hz, 2H), 3.90–3.80 (m, 2H), 3.65 (dd, J=3.0, 7.0 Hz, 1H), 3.60 (m, 1H), 2.41 (ddd, J=1.0, 4.5, 15.5 Hz, 1H), 1.99–1.91 (m, 1H), 1.71 (ddd, J=3.0, 11.5, 15.5 Hz, 1H), 1.14–1.12 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.6, 155.2, 145.6, 138.8, 138.7, 136.4, 130.0, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 121.1, 115.9, 71.7, 71.4, 70.9, 70.8, 65.8, 64.2, 63.3, 42.4, 38.1, 35.6, 21.5, 19.6, 18.4, 12.6; HRMS (MALDI) Calcd for $C_{43}H_{58}N_3O_8SSi$ [M+H]: 804.3708. Found: 804.3698.

4.1.35. Diels–Alder adduct 34e. To dienophile **15b** (663 mg, 1.57 mmol) and diene **16e** (650 mg, 1.57 mmol) was added 7 mL PhH and 2,6-lutidine (100 μL, 0.86 mmol). The reaction mixture was heated to 114 °C in a sealed vial for 19 h, concentrated in vacuo and purified by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1→1:1) to furnish 494 mg (59%) Diels–Alder adduct **34e** as a single regioisomer: R_f=0.25 (hexanes/EtOAc, 6:4); IR (thin film) 3476, 1731 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.94 (d, J=8.0 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H), 7.51 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.5 Hz, 2H), 6.67 (s, 4H), 4.66 (d, J=16.0 Hz, 1H), 4.41 (t, J=2.0 Hz, 1H), 4.36 (dd, J=2.5, 6.0 Hz, 2H), 4.05 (d, J=16.0 Hz, 1H), 3.87 (m, 1H), 3.81–3.75 (m, 2H), 3.73 (s, 3H), 3.71 (m, 1H), 2.51 (s, 3H), 2.46 (s, 3H), 2.01 (br s, 1H), 2.00–1.96 (m, 1H), 1.72 (m, 1H), 1.14–1.11 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 175.0, 159.9, 152.6, 146.7, 146.0, 138.6, 135.1, 130.6, 130.5, 129.1, 129.0, 128.6, 127.9, 127.8, 114.7, 114.6, 67.2, 66.0, 63.2, 55.4, 44.1, 43.8, 39.0, 37.0, 21.7, 21.6, 20.5, 18.4, 12.6; HRMS (ESI) Calcd for $C_{42}H_{56}N_3O_9S_2Si$ [M+H]: 838.3227. Found: 838.3303.

4.1.36. Diels–Alder adduct 34f. R_f=0.44 (hexanes/EtOAc, 3:7); $[\alpha]_D^{25}$ −71.9° (*c* 1.66, CH_2Cl_2); IR (thin film) 3440, 1724 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.96 (d, J=8.5 Hz, 2H), 7.63 (d, J=8.5 Hz, 2H), 7.49 (d, J=7.5 Hz, 2H), 7.32 (d, J=7.5 Hz, 2H), 6.66 (d, J=8.0 Hz, 1H), 6.57 (d, J=2.0 Hz, 1H), 6.23 (dd, J=8.0, 2.0 Hz, 1H), 4.68 (d, J=16.0 Hz, 1H), 4.42 (s, 1H), 4.37 (m, 2H), 4.03 (d, J=16.0 Hz, 1H), 3.87 (m, 1H), 3.82–3.75 (m, 2H), 3.76–3.71 (m, 2H), 3.74 (s, 3H), 3.58 (s, 3H), 2.49 (s, 3H), 2.47 (s, 3H), 2.10 (m, 1H), 2.01–1.95 (m, 1H), 1.74 (m, 1H), 1.14–1.23 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 175.0, 152.3, 150.4, 149.8, 146.8, 146.0, 136.6, 135.8, 130.6, 130.5, 129.7, 129.2, 127.9, 127.5, 119.6, 114.8, 112.4, 111.5, 67.3, 66.1, 63.2, 56.0, 55.9, 44.2, 44.1, 39.0, 37.1, 21.7, 21.6, 20.5, 18.41, 18.40, 12.7; HRMS (ESI) Calcd for $C_{43}H_{57}N_3O_{10}S_2SiNa$ [M+Na]: 890.3152. Found: 890.3201.

4.1.37. 3-(3,4-Dimethoxybenzyl)-2-oxo-1-[2-(toluene-4-sulfonyl)-vinyl]-2,3-dihydro-1*H*-imidazole-4-carboxylic acid methyl ester (38). To a stirred solution of **21** (3.80 g, 26.7 mmol) in 200 mL of DMF at 25 °C was added 80% sodium hydride (722 mg, 24.1 mmol), the resulting mixture was stirred for 15 min. To the slurry was added dropwise a solution of *cis*-1,2-di-*p*-toluenesulfonylethylene (6.30 g, 18.7 mmol) in 100 mL of DMF. Stirring was continued for 13 h, the reaction was cooled to 0 °C and then ethyl acetate (200 mL) and water (200 mL) were added to quench the

reaction. The organic layer was washed with water (6×100 mL) and dried ($MgSO_4$). Solvents were removed in vacuo and the crude solid was purified by dissolution of impurities in ethyl acetate and filtering the residue to afford the Tsv-protected imidazolone ester **Tsv-21** (>95% purity, 3.41 g, 56%) as a light yellow solid (mp 239–241 °C (EtOAc/hexanes)). To a solution of **Tsv-21** (13.4 g, 41.4 mmol) in 300 mL of DMF at 25 °C was added potassium carbonate (6.30 g, 45.6 mmol) followed by DMBCl (8.10 g, 43.5 mmol). The reaction was heated to 60 °C and stirring continued for 16 h. On cooling to 25 °C the reaction was diluted with 200 mL of ethyl acetate and washed with water (6×100 mL). The organic layer was dried ($MgSO_4$). Solvents were removed in vacuo to afford the ester **38** (19.6 g, 99%), which was of sufficient purity to be taken onto the next step without purification. A small sample of crude **38** was taken and purified by flash chromatography for analysis on SiO_2, eluting with EtOAc/hexanes (2:5) affording ester **38** as a colorless foam: R_f=0.31 (EtOAc/hexanes, 2:5); IR (neat) 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J=14.0 Hz, 1H), 7.77 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 7.12 (s, 1H), 6.97 (d, J=2.0 Hz, 1H), 6.91 (dd, J=8.5, 2.0 Hz, 1H), 6.85 (d, J=14.0 Hz, 1H), 6.76 (d, J=8.5 Hz, 1H), 5.13 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 151.3, 148.8, 148.6, 144.5, 137.8, 132.9, 130.0, 129.3, 127.5, 120.8, 117.0, 116.6, 115.8, 111.7, 110.9, 55.9, 55.8, 52.1, 45.4, 21.6; HRMS (ESI) Calcd for $C_{23}H_{25}N_2O_7S$ [M+H]: 473.1382. Found: 473.1410.

4.1.38. 3-(3,4-Dimethoxybenzyl)-4-hydroxymethyl-1-[2-(toluene-4-sulfonyl)-vinyl]-1,3-dihydro-imidazol-2-one (40). To a stirred solution of crude ester **38** (19.6 g, 41.4 mmol) in 400 mL of THF/H_2O (v/v; 3:1) at 25 °C was added LiOH (1.14 g, 47.5 mmol) and stirred continuously for 2 h and then the THF was removed in vacuo. EtOAc (400 mL) was added and the mixture was extracted (the organic phase was discarded). HCl (1 M, 500 mL) was added to the aqueous phase and extracted with EtOAc (3×500 mL). Organic layers were combined and dried ($MgSO_4$). Solvents were removed in vacuo to yield the crude acid as a yellow foam (18.2 g, 96%). The crude acid (18.1 g, 39.5 mmol) was dissolved in 400 mL of THF and 0.5 mL of DMF at 25 °C, oxalyl chloride (3.70 mL, 43.4 mmol) was added dropwise to the solution, and the mixture was stirred for 1 h. The reaction mixture was cooled to −78 °C and $LiBH_4$ in THF (2 M, 59.2 mL, 118 mmol) was added dropwise. The reaction mixture was stirred for 2 h, 100 mL of H_2O was added to quench the reaction, and then THF was removed in vacuo. HCl (1 M, 500 mL) was added to the aqueous phase and extracted with EtOAc (3×500 mL). Organic layers were combined and dried ($MgSO_4$). Solvents were removed in vacuo and the crude alcohol **40** (17.1 g, 97%) isolated as a yellow solid, which was of sufficient purity to be taken onto the next step without purification. A small amount was taken and purified by flash chromatography for analysis on SiO_2 eluting with EtOAc/hexanes (2:5) to afford alcohol **40** as a yellow solid: mp 138–140 °C (EtOAc/hexanes); R_f=0.14 (EtOAc/hexanes, 4:1); IR (film) 3466, 1711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=14.0 Hz, 1H), 7.75 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 6.85 (d, J=2.0, 1H), 6.81 (dd, J=8.0, 2.0 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 6.46 (d, J=14.0 Hz, 1H), 6.31 (s, 1H), 4.87 (s, 2H), 4.29 (s, 2H), 3.827 (s, 3H), 3.825 (s, 3H), 2.50 (br s, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 149.5, 149.0, 144.6, 138.5, 133.9, 130.2, 129.0, 127.5, 127.4, 120.1, 113.2, 111.4, 111.1, 105.4, 56.2, 56.1, 55.3, 45.2, 21.8; HRMS (ESI) Calcd for $C_{22}H_{25}N_2O_6S$ [M+H]: 445.1407. Found: 445.1407.

4.1.39. 3-{3-(3,4-Dimethoxybenzyl)-2-oxo-1-[2-(toluene-4-sulfonyl)-vinyl]-2,3-dihydro-1*H*-imidazol-4-yl}-acrylic acid ethyl ester (41). To a slurry of activated manganese dioxide (heated with a heat gun under vacuum) (32.4 g, 373 mmol) in 60 mL of dichloromethane at 25 °C was added a solution of **40** (13.8 g, 31.0 mmol) in 400 mL of dichloromethane. The resulting solution was stirred for 12 h and filtered through a pad of Celite®. Solvents were removed in vacuo and the crude aldehyde (9.90 g, 72%) was isolated as a yellow solid (mp 150–152 °C). A solution of triethylphosphonoacetate (4.78 mL, 24.1 mmol) in 100 mL of THF was cooled to 0 °C and treated with 80% NaH (658 mg, 21.9 mmol), after warming to 25 °C and stirring for an additional 40 min. The resulting solution was added dropwise to a solution of the crude aldehyde (9.70 g, 21.9 mmol) in 300 mL of THF and stirring was continued for 30 min. The reaction was quenched with 50 mL of pH 4 buffer solution. THF was removed in vacuo and the aqueous phase was extracted with EtOAc (3×300 mL). The organic layers were combined and dried ($MgSO_4$). Solvents were removed in vacuo and the crude ester **41** isolated as a yellow oil (13.2 g). A small amount of the crude ester was taken and purified by flash chromatography for analysis on SiO_2, eluting with EtOAc/hexanes (2:3) to afford ester **41** as a colorless foam: R_f=0.41 (EtOAc/hexanes, 2:3); IR (film) 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J=14.0 Hz, 1H), 7.79 (d, J=8.5 Hz, 2H), 7.33 (d, J=8.5 Hz, 2H), 7.22 (d, J=16.0 Hz, 1H), 6.80–6.76 (m, 4H), 6.67 (d, J=14.0 Hz, 1H), 6.14 (d, J=16.0 Hz, 1H), 4.89 (s, 2H), 4.20 (q, J=7.0 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.43 (s, 3H), 1.28 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 151.8, 149.6, 149.1, 144.7, 138.7, 133.2, 130.2, 128.8, 128.3, 127.7, 124.3, 119.74, 119.69, 115.3, 111.5, 110.6, 108.5, 61.2, 56.2, 56.1, 45.5, 21.9, 14.4; HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_7S$ [M+H]: 513.1695. Found: 513.1692.

4.1.40. 3-(3,4-Dimethoxybenzyl)-4-(3-hydroxypropenyl)-1-[2-(toluene-4-sulfonyl)-vinyl]-1,3-dihydro-imidazol-2-one (16g). To a stirred solution of crude **41** (13.2 g, 25.8 mmol) in 400 mL of THF/H_2O (v/v; 3:1) at 25 °C was added LiOH (788 mg, 32.9 mmol) and stirring was continued for 12 h and then THF was removed in vacuo. EtOAc (150 mL) was added and the mixture extracted, the organic phase was discarded. HCl (1 M, 150 mL) was added to the aqueous phase and extracted with EtOAc (3×300 mL). Organic layers were combined and dried ($MgSO_4$). Solvents were removed in vacuo and the crude acid was isolated (8.10 g, 76%) as a yellow solid (mp 99–102 °C (EtOAc/hexanes)). Due to the instability of the diene, a portion of the acid (1.00 g, 2.06 mmol) was dissolved in 100 mL of THF at 0 °C. To the solution was added triethylamine (288 μL, 2.06 mmol), followed by methyl chloroformate (174 μL, 2.06 mmol), and the mixture was stirred for 15 min or until

TLC indicated complete formation of the mixed anhydride. The reaction mixture was cooled to −78 °C and $LiBH_4$ in THF (2 M, 2.06 mL, 4.13 mmol) was added dropwise. The reaction mixture was stirred for 15 min, after which 50 mL of H_2O was added to quench the reaction and the solvents were removed in vacuo. HCl (1 M, 100 mL) was added to the aqueous phase and extracted with CH_2Cl_2 (3×200 mL). The organic layers were combined and dried ($MgSO_4$) and solvents were removed in vacuo and the crude alcohol **16g** (972 mg, 99%) was isolated as a yellow foam: R_f=0.16 (EtOAc); IR (film) 3391, 1721 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.11 (d, J=14.0 Hz, 1H), 7.82 (d, J=8.0 Hz, 2H), 6.80 (d, J=2.0 Hz, 1H), 6.77–6.73 (m, 4H), 6.48 (d, J=8.0 Hz, 1H), 6.02 (m, 1H), 5.74 (dt, J=16.0, 2.0 Hz, 1H), 5.45 (s, 1H), 4.55 (s, 2H), 3.77 (dd, J=4.5, 2.0 Hz, 2H), 3.40 (s, 3H), 3.30 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 151.7, 150.3, 149.8, 143.3, 140.1, 133.6, 132.7, 129.8, 129.75, 129.71, 125.9, 119.8, 114.9, 113.9, 112.1, 111.8, 102.9, 62.3, 55.5, 55.4, 44.7, 21.0; HRMS (ESI) Calcd for $C_{24}H_{27}N_2O_6S$ [M+H]: 471.1590. Found: 471.1609.

4.1.41. TBDPS-protected Diels–Alder adduct 42. To a solution of crude diene **16g** (10.0 mg, 0.02 mmol) in 1 mL of benzene at 25 °C in a sealed tube was added dienophile **15b** (9.0 mg, 0.02 mmol), followed by 2,6-lutidine (1.85 μL, 0.02 mmol). The resulting solution was stirred for 24 h at 95 °C. Another portion (10.0 mg, 0.02 mmol) of diene **16g** was added every 24 h until 4.0 equiv had been added. Solvents were removed in vacuo and the crude oil was purified by passing through a plug of SiO_2, eluting with EtOAc to afford recovered dienophile **15b** (5.0 mg), and a single Diels–Alder regioisomer as a colorless oil (~80% purity). A solution of the Diels–Alder adduct in 3 mL of dichloromethane at 25 °C was treated with TBDPSCl (3.20 μL, 0.01 mmol), followed by triethylamine (1.7 μL, 0.01 mmol) and DMAP (catalytic). After 24 h at 25 °C, solvents were removed in vacuo and the crude oil was purified by flash chromatography on SiO_2, eluting with EtOAc/hexanes (7:3) to afford silyl ether **42** (11.5 mg, 48%) as a clear oil: R_f=0.73 (EtOAc/hexanes, 2:3); IR (film) 1723 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.93 (d, J=8.5 Hz, 2H), 7.79 (s, 2H), 7.76–7.73 (m, 4H), 7.65 (d, J=8.5 Hz, 2H), 7.27–7.24 (m, 6H), 6.88 (d, J=2.0 Hz, 1H), 6.85 (d, J=8.5 Hz, 2H), 6.71 (dd, J=8.0, 2.0 Hz, 1H), 6.61 (d, J=8.5 Hz, 2H), 6.55 (d, J=8.0 Hz, 1H), 4.68 (d, J=15.0 Hz, 1H), 4.27 (dd, J=10.5, 3.5 Hz, 1H), 4.23 (dd, J=7.0, 3.5 Hz, 1H), 4.19 (app d, J=8.0 Hz, 2H), 3.97 (dd, J=10.5, 7.0 Hz, 1H), 3.68 (d, J=15.0 Hz, 1H), 3.43 (s, 3H), 3.36 (s, 3H), 3.29 (dd, J=6.0, 3.5 Hz, 1H), 3.20 (m, 1H), 2.13 (m, 1H), 1.95 (s, 3H), 1.88 (m, 1H), 1.84 (s, 3H), 1.71 (m, 1H), 1.17–1.13 (m, 30H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.4, 151.9, 150.5, 150.1, 145.0, 143.6, 140.0, 135.8, 135.4, 133.7, 133.6, 132.4, 130.1, 130.0, 129.5, 129.2, 128.1, 127.5, 127.4, 123.9, 120.3, 116.6, 112.14, 112.09, 112.07, 64.8, 64.5, 62.4, 55.6, 55.5, 44.5, 41.4, 36.7, 34.3, 27.0, 21.3, 21.0, 19.8, 19.3, 18.3, 18.2, 12.0; HRMS (ESI) Calcd for $C_{61}H_{78}N_3O_{10}S_2Si_2$ [M+H]: 1132.4667. Found: 1132.4666.

4.1.42. TBDPS-protected Diels–Alder adduct (43). To a stirred solution of Tsv-protected adduct **42** (56.0 mg, 0.05 mmol) in 3 mL of EtOAc at 25 °C was added $Pd(OH)_2/C$ (spatula tip). The reaction was placed under an atmosphere of hydrogen and the reaction stirred for 24 h. The reaction mixture was filtered through a pad of Celite® and solvents were removed in vacuo to afford a yellow oil. Purification by flash chromatography on SiO_2, eluting with EtOAc/hexanes (3:2) afforded Tse-protected Diels–Alder adduct **43** (52.0 mg, 93%) as a colorless oil. R_f=0.40 (EtOAc/hexanes, 2:5); IR (film) 1738 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.79 (d, J=8.0 Hz, 2H), 7.73–7.70 (m, 4H), 7.63 (d, J=8.0 Hz, 2H), 7.25–7.20 (m, 6H), 6.97 (d, J=1.5 Hz, 1H), 6.78 (dd, J=8.0, 1.5 Hz, 1H), 6.72 (d, J=8.0 Hz, 2H), 6.66 (d, J=8.0 Hz, 2H), 6.61 (d, J=8.0 Hz, 1H), 4.79 (d, J=15.5 Hz, 1H), 4.39 (m, 2H), 4.24 (app t, J=7.5 Hz, 1H), 4.20–4.16 (m, 2H), 4.14–4.07 (m, 2H), 3.99 (d, J=15.5 Hz, 1H), 3.97–3.91 (m, 2H), 3.82 (br d, J=6.0 Hz, 1H), 3.56 (s, 3H), 3.39 (s, 3H), 3.25 (dd, J=6.0, 2.5 Hz, 1H), 2.95 (m, 1H), 2.23 (m, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.84 (s, 3H), 1.22–1.07 (m, 30H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.1, 153.9, 150.7, 149.7, 144.6, 144.1, 137.9, 136.2, 135.9, 133.94, 133.92, 130.4, 130.1, 130.0, 129.7, 129.5, 127.9, 120.4, 119.6, 114.7, 112.3, 111.7, 65.2, 65.1, 64.6, 55.8, 55.6, 53.3, 53.0, 44.4, 41.9, 37.8, 36.5, 35.0, 27.1, 21.3, 21.1, 20.1, 19.4, 18.30, 18.28, 12.2; HRMS (ESI) Calcd for $C_{61}H_{80}N_3O_{10}S_2Si_2$ [M+H]: 1134.4824. Found: 1134.4818.

4.1.43. Typical procedure for microwave-assisted Diels–Alder reactions. To a specially designed reaction tube equipped with a magnetic stirrer was added dienophile **15b** (122 mg, 0.29 mmol), Tse-diene **16d** (204 mg, 0.43 mmol), and lithium perchlorate (3.0 mg, 0.03 mmol) sequentially, followed by benzene (2.0 mL) and 2,6-lutidine (20 μL, 0.17 mmol). The reaction vessel was sealed and heated under microwave conditions. The temperature was set to 160 °C and the reaction time was 3 h. After 3 h, the reaction mixture was cooled down and concentrated in vacuo. Flash chromatography (75% EtOAc/hexanes to 90% EtOAc/hexanes) afforded isomerized Diels–Alder adduct **34d** along with its regioisomer (224 mg, 87%) as light yellow foam. The regioisomeric ratio was 2.4:1 in favor of **34d** based on ^1H NMR integration. Compound **34d** can be separated from its regioisomer by automated MPLC purification.

4.1.44. Initial Diels–Alder adduct 32d and TBDPS-protected adduct 44. To a microwave reaction tube equipped with a magnetic stirrer was added dienophile **15b** (12 mg, 0.028 mmol) and Tse-diene **16d** (16 mg, 0.034 mmol), followed by anhydrous THF (0.3 mL) and 2,6-lutidine (2 μL, 0.017 mmol). The reaction mixture was heated to 140 °C under microwave for 2 h. Then the reaction mixture was cooled down and concentrated. Silica gel flash chromatography (50% EtOAc/hexanes to 75% EtOAc/hexanes) gave initial Diels–Alder adduct **32d** and its regioisomer **33d** (17 mg, 68%) as off-white foam. The regioisomeric ratio was 1.4:1 in favor of **32d** based on NMR integration. Compound **32d** cannot be separated from its regioisomer at this stage. They have same R_f values (0.34, 60% EtOAc/hexanes). The mixture was subjected to TBDPS protection. To a solution of **32d** and its regioisomer (33.0 mg, 0.037 mmol) in CH_2Cl_2 (0.50 mL) was added Et_3N (20 μL, 0.142 mmol) at room temperature, followed by TBDPSCl (11 μL, 0.041 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at ambient temperature for 24 h. The

solvent was removed in vacuo and purified by flash chromatography on SiO_2 (20% → 40% EtOAc/hexanes) afforded the silyl-protected adduct **44** as a colorless film (25.0 mg, 60%). R_f=0.74 (60% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 8.02 (d, J=8.5 Hz, 2H), 7.82 (m, 2H), 7.75 (m, 4H), 7.16–7.29 (m, 6H), 6.98 (d, J=2.0 Hz, 1H), 6.81 (dd, J=8.0, 2.0 Hz, 1H), 6.78 (d, J=8.5 Hz, 2H), 6.75 (d, J=8.5 Hz, 2H), 6.59 (d, J=8.0 Hz, 1H), 4.93 (d, J=15.0 Hz, 1H), 4.49 (dd, J=8.5, 10.0 Hz, 1H), 4.39 (t, J=3.5 Hz, 1H), 4.36 (m, 1H), 4.05–4.16 (m, 5H), 3.58 (s, 3H), 3.52 (m, 1H), 3.48 (d, J=15.0 Hz, 1H), 3.38 (m, 1H), 3.32 (s, 3H), 3.22 (dd, J=3.5, 9.0 Hz, 1H), 2.97–3.04 (m, 2H), 2.31 (m, 1H), 1.86 (s, 3H), 1.85 (s, 3H), 1.17 (s, 9H), 1.12–1.16 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.9, 158.4, 150.6, 149.7, 144.5, 144.2, 137.17, 137.11, 137.0, 136.0, 135.87, 135.83, 134.1, 134.0, 129.9, 129.88, 129.87, 129.6, 129.14, 128.61, 128.23, 119.7, 112.4, 111.5, 93.22, 66.42, 63.78, 59.23, 55.7, 55.5, 54.0, 52.39, 44.70, 42.36, 39.52, 36.57, 36.32, 27.06, 21.04, 19.4, 18.23, 18.21, 18.2, 12.2; IR (thin film) 2940, 2858, 1726, 1680, 1255, 1117 cm^{-1}; HRMS (ESI) calculated for $C_{61}H_{79}N_3O_{10}S_2Si_2Li$ [M+Li]: 1140.4905. Found: 1140.4898.

4.1.45. Mosher ester 36. To a solution of (*S*)-MTPA (58.2 mg, 0.25 mmol) and EDCI (68.3 mg, 0.36 mmol) in 500 μL CH_2Cl_2 was added Diels–Alder adduct **34b** (8.80 mg, 0.01 mmol) in 500 μL CH_2Cl_2. The reaction mixture was stirred for 18 h, washed with H_2O, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 7:3) gave 11.0 mg (97%) ester **36** as an off-white solid: R_f=0.37 (hexanes/EtOAc, 6:4); $[\alpha]_D^{25}$ −27.7° (*c* 1.26, CH_2Cl_2); IR (thin film) 1745, 1702, 1658 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.58 (d, J=8.7 Hz, 2H), 7.45–7.24 (m, 15H), 7.11 (m, 2H), 5.09 (d, J=15.9 Hz, 1H), 4.87 (d, J=15.9 Hz, 1H), 4.81 (d, J=15.9 Hz, 1H), 4.73 (d, J=10.5 Hz, 1H), 4.54 (dd, J=5.4, 10.5 Hz, 1H), 4.34 (d, J=15.9 Hz, 1H), 4.25 (dd, J=3.3, 6.0 Hz, 1H), 4.13–4.09 (m, 1H), 3.49 (m, 1H), 3.45 (m, 1H), 3.35 (s, 3H), 2.50 (s, 3H), 2.41 (m, 1H), 2.26–2.14 (m, 1H), 1.78 (m, 1H), 1.07–1.05 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.9, 166.7, 155.2, 146.2, 139.0, 138.8, 136.2, 133.0, 130.6, 130.4, 129.5, 129.4, 129.3, 128.4, 128.2, 128.1, 128.0, 127.7, 120.2, 114.9, 68.0, 65.8, 64.7, 55.8, 45.6, 44.7, 43.0, 35.7, 34.4, 21.7, 20.6, 18.32, 18.31, 12.6; HRMS (ESI) Calcd for $C_{51}H_{61}F_3N_3O_8SSi$ [M+H]: 960.3901. Found: 960.3988.

4.1.46. General procedure for the silylation of Diels–Alder adducts as described for *tert*-butyldimethylsilyl ether 45. To a solution of Diels–Alder adduct **34b** (24.8 mg, 0.03 mmol) in 400 μL CH_2Cl_2 was added DMAP (catalytic), Et_3N (35.0 μL, 0.25 mmol), and TBSCl (26.3 mg, 0.18 mmol). The reaction was stirred at ambient temperature for 8 h, diluted with CH_2Cl_2, and washed with H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 7:3) gave 27.5 mg (96%) silylated Diels–Alder adduct **45** as an off-white foam: R_f=0.73 (hexanes/EtOAc, 3:7); $[\alpha]_D^{25}$ +8.7° (*c* 1.0, CH_2Cl_2); IR (thin film) 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, 8.4 Hz, 2H), 7.34–7.20 (m, 10H), 7.10 (m, 2H), 5.15 (d, J=15.9 Hz, 1H), 4.93 (d, J=15.6 Hz, 1H), 4.71 (d, J=15.9 Hz, 1H), 4.25 (d, J=15.6 Hz, 1H), 4.21 (dd, J=3.6, 6.0 Hz, 1H), 4.02–3.95 (m, 2H), 3.87 (dd, J=6.9, 9.6 Hz, 1H), 3.75 (dd, J=7.2, 9.6 Hz, 1H), 3.31–3.24 (m, 2H), 2.44 (s, 3H), 2.06 (dd, J=3.9, 15.0 Hz, 1H), 1.89–1.78 (m, 1H), 1.67 (m, 1H), 1.04–1.02 (m, 21H), 0.80 (s, 9H), 0.00 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 154.5, 144.8, 137.2, 137.0, 135.3, 129.3, 128.8, 128.7, 127.9, 127.6, 127.5, 127.3, 127.0, 120.6, 114.5, 64.7, 63.6, 63.4, 45.4, 44.6, 41.3, 37.6, 34.8, 25.8, 21.7, 19.6, 17.9, 11.8, −5.5; HRMS (FAB) Calcd for $C_{47}H_{68}N_3O_6SSi_2$ [M+H]: 858.4367. Found: 858.4355.

4.1.47. *tert*-Butyldimethylsilyl ether 59. R_f=0.68 (hexanes/EtOAc, 6:4); $[\alpha]_D^{25}$ +25.3° (*c* 0.95, CH_2Cl_2); IR (thin film) 1726 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.96 (d, J=8.5 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H), 7.51 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 6.66 (s, 4H), 4.69 (d, J=15.5 Hz, 1H), 4.38 (m, 3H), 4.03 (d, J=15.5 Hz, 1H), 3.89 (d, J=7.5 Hz, 1H), 3.73 (s, 3H), 3.60 (dd, J=3.0, 7.5 Hz, 1H), 2.51 (s, 3H), 2.46 (s, 3H), 2.03–2.02 (m, 1H), 1.99–1.95 (m, 1H), 1.67 (ddd, J=3.0, 11.0, 16.0 Hz, 1H), 1.44–1.12 (m, 21H), 0.82 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.1, 159.3, 151.9, 146.1, 145.4, 136.0, 134.5, 130.0, 129.9, 128.54, 128.51, 128.0, 127.2, 126.8, 114.2, 114.1, 66.6, 65.4, 63.7, 54.8, 43.3, 42.9, 38.2, 36.6, 25.6, 21.1, 17.8, 12.1, −5.8, −5.9; HRMS (ESI) Calcd for $C_{48}H_{70}N_3O_9S_2Si_2$ [M+H]: 952.4092. Found: 952.4079.

4.1.48. Lactol 51. To a cooled (0 °C) solution of silylated Diels–Alder adduct **45** (16.7 mg, 0.02 mmol) in 250 μL CH_2Cl_2 was added *m*-CPBA (4.50 mg, 0.03 mmol). Additional *m*-CPBA (5.0 mg, 4.8 mg) was added after 1.5 and 3.5 h, respectively. Following the addition of *m*-CPBA the reaction was stirred for 1.5 h and diluted with saturated $NaHCO_3$ (2.0 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 6:4) furnished 13.7 mg (78%) lactol **51** as a light yellow solid: R_f=0.30 (hexanes/EtOAc, 8:2); $[\alpha]_D^{25}$ −52.0° (*c* 0.34, CH_2Cl_2); IR (thin film) 3476, 1789, 1724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J=8.0 Hz, 2H), 7.40–7.25 (m, 12H), 5.69 (dd, J=2.5, 8.5 Hz, 1H), 4.92 (d, J=17.0 Hz, 1H), 4.69 (d, J=15.0 Hz, 1H), 4.54 (d, J=15.0 Hz, 1H), 4.43 (d, J=2.5 Hz, 1H), 4.35 (dd, J=9.5, 11.0 Hz, 1H), 4.28 (d, J=17.0 Hz, 1H), 3.98 (app d, J=11.0 Hz, 1H), 3.97 (dd, J=6.0, 11.0 Hz, 1H), 3.62 (br s, 1H), 3.55 (dd, J=7.0, 8.5 Hz, 1H), 2.68 (dd, J=1.5, 11.0 Hz, 1H), 2.51 (d, J=8.5 Hz, 1H), 2.41 (s, 3H), 1.98–1.91 (m, 1H), 0.87–0.84 (m, 30H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 167.8, 156.9, 144.8, 137.8, 135.8, 135.1, 129.3, 129.0, 128.8, 128.7, 128.6, 128.1, 127.9, 127.2, 94.2, 87.7, 65.3, 61.3, 59.6, 42.55, 42.47, 42.1, 41.1, 38.7, 25.8, 21.6, 17.8, 11.6, −5.5, −5.6; HRMS (FAB) Calcd for $C_{47}H_{68}N_3O_9SSi_2$ [M+H]: 906.4215. Found: 906.4207.

4.1.49. Trityldimethylsilyl ether 52. To a cooled (0 °C) solution of lactol **51** (303 mg, 0.34 mmol) in 3.0 mL THF was

added a solution of TBAF containing 20 mol % AcOH in THF (3.5 mL). After 1 h pH 7 buffer was added and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (7:3→0:1) gave 75.4 mg (36%) desilylated triol as a white solid: R_f=0.28 (hexanes/EtOAc, 3:7); $[\alpha]_D^{25}$ −23.1° (*c* 3.67, CH_2Cl_2); IR (thin film) 3437, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.1 Hz, 2H), 7.45–7.26 (m, 12H), 5.39 (d, *J*=1.8 Hz, 1H), 4.91 (d, *J*=15.6 Hz, 1H), 4.65 (d, *J*=14.7 Hz, 1H), 5.54 (d, *J*=14.7 Hz, 1H), 4.20 (d, *J*=15.6 Hz, 1H), 3.80 (d, *J*=5.1 Hz, 2H), 3.64 (dd, *J*=2.1, 12.0 Hz, 1H), 3.50 (br s, 1H), 3.22–3.12 (m, 2H), 2.70–2.62 (m, 3H), 2.41 (s, 3H), 1.82 (dd, *J*=1.2, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 170.0, 156.7, 145.4, 138.4, 135.3, 134.6, 129.4, 129.1, 128.9, 128.8, 128.7, 128.2, 128.1, 94.1, 87.5, 63.3, 62.2, 60.9, 42.5, 42.3, 39.8, 37.1, 36.0, 21.7; HRMS (ESI) Calcd for $C_{32}H_{34}N_3O_9S$ [M+H]: 636.2016. Found: 636.2078.

To a solution of the desilylated triol obtained above (10.5 mg, 0.02 mmol) in 220 μL anhydrous DMF was added Ph_3CSiMe_2Br (34.0 mg, 0.09 mmol) and $AgNO_3$ (17.5 mg, 0.10 mmol). The reaction was stirred in the dark for 20 h and filtered through cotton. The filtrate was diluted with Et_2O and washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (8:2→6:4) gave monosilylated lactol **52** (9.0 mg, 58%) as an off-white film, which was recrystallized from hexanes/Et_2O/EtOAc: R_f=0.65 (hexanes/EtOAc, 6:4); $[\alpha]_D^{25}$ −40.0° (*c* 1.43, CH_2Cl_2); mp 98.0–100.0 °C; IR (thin film) 3426, 1726, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.5 Hz, 2H), 7.41–7.16 (m, 25H), 6.99 (m, 2H), 4.94 (d, *J*=2.0 Hz, 1H), 4.86 (d, *J*=15.5 Hz, 1H), 4.63 (d, *J*=14.5 Hz, 1H), 4.54 (d, *J*=14.5 Hz, 1H), 4.12 (d, *J*=15.5 Hz, 1H), 3.86 (dd, *J*=3.5, 10.0 Hz, 1H), 3.75 (dd, *J*=6.5, 10.0 Hz, 1H), 3.63 (dd, *J*=2.0, 12.0 Hz, 1H), 3.45 (br s, 1H), 2.95 (d, *J*=10.0 Hz, 1H), 2.86 (t, *J*=10.0 Hz, 1H), 2.60–2.54 (m, 1H), 2.41 (s, 3H), 1.82 (d, *J*=12.0 Hz, 1H), 0.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 169.8, 156.8, 145.4, 145.2, 138.6, 135.4, 134.9, 130.1, 129.3, 129.0, 128.89, 128.86, 128.8, 128.21, 128.19, 128.15, 128.11, 128.0, 125.7, 94.5, 87.6, 63.8, 62.3, 60.3, 54.8, 42.5, 42.2, 39.4, 36.0, 35.6, 29.7, 21.7, 0.3, −0.7; LRMS (ESI) Calcd for $C_{53}H_{54}N_3O_9SSi$ [M+H]: 935. Found [M+H−Tr]: 692.

4.1.50. Allylic alcohol 50a. To a cooled (−45 °C) solution of silylated Diels–Alder adduct **45** (87.3 mg, 0.10 mmol) in 1.1 mL CH_2Cl_2 was added a 0.09 M solution of DMDO (1.15 mL, 0.103 mmol). After 4 h the reaction was quenched with Me_2S, filtered through cotton, and concentrated in vacuo to give 88.9 mg (99%) allylic alcohol **50a** as an off-white foam: R_f=0.75 (hexanes/EtOAc, 6:4); $[\alpha]_D^{25}$ −115.4° (*c* 1.41, CH_2Cl_2); IR (thin film) 3273, 1731, 1680 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.80 (d, *J*=8.5 Hz, 2H), 7.54 (d, *J*=7.5 Hz, 2H), 7.48 (d, *J*=8.0 Hz, 2H), 7.42 (app t, *J*=7.5 Hz, 2H), 7.36–7.22 (m, 6H), 5.57 (s, 1H), 4.83 (d, *J*=15.5 Hz, 1H), 4.76 (d, *J*=15.5 Hz, 1H), 4.50 (d, *J*=16.0 Hz, 1H), 4.47 (d, *J*=3.3 Hz, 1H), 4.10 (dd, *J*=8.0, 9.5 Hz, 1H), 3.97 (app s, 1H), 3.76 (d, *J*=16.0 Hz, 1H), 3.72 (dd, *J*=8.0, 9.5 Hz, 1H), 3.53 (dd, *J*=2.5, 11.0 Hz, 1H), 3.20 (dd, *J*=4.5, 9.0 Hz, 1H), 3.09–3.03 (m, 1H), 2.89 (d, *J*=9.0 Hz, 1H), 2.56 (d, *J*=11.0 Hz, 1H), 2.50 (s, 3H), 0.99–0.97 (m, 21H), 0.90 (s, 9H), −0.05 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 173.9, 158.8, 145.8, 141.1, 139.7, 137.7, 130.6, 129.8, 129.4, 128.8, 128.2, 127.6, 98.2, 86.4, 66.0, 63.8, 62.5, 62.1, 46.5, 45.2, 44.6, 43.8, 38.4, 26.3, 21.7, 18.5, 13.6, −5.0; HRMS (FAB) Calcd for $C_{47}H_{67}N_3O_7SSi_2Na$ [M+Na]: 896.4136. Found: 896.4139.

4.1.51. Allylic alcohol 50b. R_f=0.55 (hexanes/EtOAc, 6:4); $[\alpha]_D^{25}$ −38.7° (*c* 2.08, CH_2Cl_2); IR (thin film) 3396, 1721, 1680 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.78 (d, *J*=8.5 Hz, 2H), 7.53 (d, *J*=7.5 Hz, 2H), 7.47 (d, *J*=8.5 Hz, 2H), 7.41 (app t, *J*=7.5 Hz, 2H), 7.35–7.24 (m, 6H), 5.54 (s, 1H), 4.79 (d, *J*=16.0 Hz, 1H), 4.74 (d, *J*=15.5 Hz, 1H), 4.59 (d, *J*=3.5 Hz, 1H), 4.51 (d, *J*=15.5 Hz, 1H), 4.00–3.98 (dd, *J*=1.5, 2.5 Hz, 1H), 3.85 (d, *J*=16.0 Hz, 1H), 3.82–3.78 (m, 1H), 3.76–3.71 (m, 1H), 3.58 (app t, *J*=6.0 Hz, 1H), 3.55 (dd, *J*=2.5, 10.5 Hz, 1H), 3.21 (dd, *J*=4.5, 9.0 Hz, 1H), 3.06–3.02 (ddd, *J*=3.5, 7.5, 11.0 Hz, 1H), 2.93 (d, *J*=9.0 Hz, 1H), 2.63 (dd, *J*=1.5, 10.5 Hz, 1H), 2.49 (s, 3H), 1.01–0.97 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.4, 158.8, 145.8, 141.1, 139.7, 137.8, 137.5, 130.5, 129.7, 129.5, 129.3, 128.8, 128.3, 128.0, 127.9, 98.6, 86.3, 65.9, 63.3, 62.3, 46.2, 45.8, 45.1, 43.9, 38.1, 21.6, 18.4, 18.3, 12.5; HRMS (ESI) Calcd for $C_{41}H_{53}N_3O_7SSiLi$ [M+Li]: 766.3534. Found: 766.3632.

4.1.52. Allylic alcohol 50c. To a cooled (−40 °C) slurry of silylated Diels–Alder adduct **59** (83.3 mg, 0.09 mmol) and $MgSO_4$ was added 0.7 M methyl(trifluoromethyl)dioxirane (450 μL, 0.32 mmol) via Teflon cannula. Me_2S was added after 5 h and the mixture was filtered through cotton and concentrated in vacuo to give 84.6 mg (99%) allylic alcohol **50c** as a light orange residue: R_f=0.25 (hexanes/EtOAc, 8:2); $[\alpha]_D^{25}$ −12.4° (*c* 1.80, CH_2Cl_2); IR (thin film) 3432, 1731, 1650 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.06 (d, *J*=8.5 Hz, 2H), 7.83 (d, *J*=8.5 Hz, 2H), 7.45 (d, *J*=8.5 Hz, 2H), 7.42 (d, *J*=8.5 Hz, 2H), 7.03 (d, *J*=8.5 Hz, 2H), 6.77 (d, *J*=8.5 Hz, 2H), 4.68 (d, *J*=8.5 Hz, 1H), 4.56 (br s, 1H), 4.53 (d, *J*=16.0 Hz, 1H), 4.33 (br s, 2H), 4.12 (dd, *J*=8.0, 9.5 Hz, 1H), 3.77 (d, *J*=16.0 Hz, 1H), 3.72 (s, 3H), 3.65 (dd, *J*=1.5, 9.0 Hz, 1H), 3.36 (dd, *J*=4.5, 9.0 Hz, 1H), 3.00–2.95 (m, 1H), 2.48 (s, 3H), 2.45 (s, 3H), 1.10–1.08 (m, 21H), 0.84 (s, 9H), 0.01 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.6, 160.0, 152.1, 145.8, 145.7, 138.2, 137.4, 137.2, 130.6, 130.02, 129.96, 129.4, 128.6, 128.0, 114.7, 101.3, 89.1, 66.6, 63.5, 63.4, 55.4, 48.0, 44.6, 44.4, 37.9, 26.2, 21.57, 21.51, 18.4, 18.3, 12.7, −5.2, −5.3; LRMS (ESI) Calcd for $C_{48}H_{70}N_3O_{10}S_2Si_2$ [M+H]: 968. Found: 968.

4.1.53. Allylic alcohol 50d. R_f=0.26 (hexanes/EtOAc, 7:3); $[\alpha]_D^{25}$ +3.8° (*c* 2.12, CH_2Cl_2); IR (thin film) 3426, 1724, 1690 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.10 (d, *J*=8.0 Hz, 2H), 7.80 (d, *J*=8.0 Hz, 2H), 7.66 (dd, *J*=8.0, 1.5 Hz, 2H), 7.65 (dd, *J*=8.0, 1.5 Hz, 2H), 7.46–7.38 (m, 10H), 6.71 (d, *J*=8.5 Hz, 1H), 6.65 (dd, *J*=8.5, 2.0 Hz, 1H), 6.52 (d, *J*=2.0 Hz, 1H), 5.61 (s, 1H), 4.71 (d, *J*=4.0 Hz, 1H), 4.58 (app d, *J*=1.5, 1H), 4.54 (d, *J*=16.0 Hz, 1H), 4.35 (d, *J*=1.5 Hz, 2H), 4.23 (dd, *J*=9.5, 8.0 Hz, 1H), 3.80 (dd, *J*=9.5, 8.0 Hz, 1H), 3.70 (s, 3H),

3.67 (dd, J=9.0, 1.5 Hz, 1H), 3.61 (d, J=16.0 Hz, 1H), 3.47 (s, 3H), 3.45 (dd, J=9.0, 4.0 Hz, 1H), 3.12–3.08 (m, 1H), 2.46 (s, 3H), 2.45 (s, 3H), 1.16–1.02 (m, 21H), 0.91 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.6, 152.2, 145.9, 145.7, 138.1, 137.5, 137.3, 136.2, 134.3, 130.6, 130.5, 130.1, 130.0, 128.6, 128.5, 120.7, 112.3, 111.7, 101.2, 89.1, 66.9, 64.5, 63.5, 56.0, 55.5, 48.3, 44.8, 44.3, 37.9, 27.2, 21.6, 21.5, 19.7, 18.42, 18.39, 17.8, 12.7; HRMS (ESI) Calcd for $C_{59}H_{75}N_3O_{11}S_2SiNa$ [M+Na]: 1144.4279. Found: 1144. 4290.

4.1.54. Lactam 63. To a cooled (−78 °C) solution of silylated Diels–Alder adduct **59** (50.3 mg, 0.53 mmol) in 1 mL THF was added a 0.27 M solution of sodium naphthalenide in THF (1.0 mL, 0.27 mmol). After stirring the resulting yellow solution for 3.5 h pH 7 buffer was added and the mixture was diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (8:2→0:10) gave 29.1 mg (86%) detosylated cycloadduct **63** as an off-white residue: R_f=0.14 (hexanes/EtOAc, 3:7); $[\alpha]_D^{25}$ +14.4° (c 1.55, CH_2Cl_2); IR (thin film) 1685 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 10.00 (br s, 1H), 7.23 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.5 Hz, 2H), 6.76 (br s, 1H), 4.74 (d, J=15.5 Hz, 1H), 4.66 (d, J=15.5 Hz, 1H), 4.08 (d, J=6.5 Hz, 2H), 3.88 (d, J=5.0 Hz, 2H), 3.76 (s, 3H), 3.63 (m, 1H), 3.34 (d, J=7.0 Hz, 1H), 3.16 (dd, J=2.5, 7.0 Hz, 1H), 2.46 (d, J=11.5 Hz, 1H), 2.08–2.01 (m, 2H), 1.08–1.07 (m, 21H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (acetone-d_6) δ 176.9, 159.9, 155.6, 131.4, 129.5, 119.8, 115.7, 114.7, 66.7, 65.2, 59.2, 55.4, 43.8, 40.7, 38.8, 37.0, 26.3, 21.1, 18.3, 12.6, −5.2; LRMS (ESI) Calcd for $C_{34}H_{58}N_3O_5Si_2$ [M+H]: 644. Found: 644.

4.1.55. Chlorospirohydantoin 65a. To a cooled (−45 °C) solution of allylic alcohol **50a** (19.0 mg, 0.02 mmol) in 200 μL CH_2Cl_2 was added cyclohexene (11.0 μL, 0.11 mmol). A cooled (−45 °C) solution of *N*-chlorosuccinimide (9.60 mg, 0.07 mmol) in 100 μL CH_2Cl_2 was added and the resulting reaction mixture was stirred at ambient temperature overnight. Water was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1→8:2) and gave 14.7 mg (75%) spirohydantoin **65a** as a white foam: R_f=0.47 (hexanes/EtOAc, 8:2); $[\alpha]_D^{25}$ −8.4° (c 0.75, CH_2Cl_2), IR (thin film) 1782, 1745, 1716 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.08 (d, J=8.5 Hz, 2H), 7.49 (d, J=8.5 Hz, 2H), 7.43 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.5 Hz, 2H), 7.34–7.30 (m, 6H), 5.32 (d, J=16.0 Hz, 1H), 4.70 (d, J=15.0 Hz, 1H), 4.65 (d, J=15.0 Hz, 1H), 4.63 (m, 1H), 4.37 (d, J=16.0 Hz, 1H), 4.10 (d, J=12.5 Hz, 1H), 4.09 (dd, J=3.5, 10.5 Hz, 1H), 4.05 (dd, J=8.5, 10.0 Hz, 1H), 3.92 (dd, J=1.5, 10.5 Hz, 1H), 3.79 (dd, J=4.0, 10.0 Hz, 1H), 3.48 (t, J=8.5 Hz, 1H), 3.29 (d, J=8.5 Hz, 1H), 3.15–3.07 (m, 1H), 2.44 (s, 3H), 0.98–0.83 (m, 30H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 173.8, 171.9, 157.8, 146.8, 138.4, 137.3, 136.9, 130.8, 129.5, 129.44, 129.39, 129.2, 128.8, 128.7, 128.6, 76.8, 65.7, 61.3, 60.6, 59.7, 48.7, 47.7, 46.9, 46.3, 43.4, 41.0, 26.4, 18.4, 18.3, 12.7, −5.2; HRMS (FAB) Calcd for $C_{47}H_{66}ClN_3O_7SSi_2Na$ [M+Na]: 930.3746. Found: 930.3785. An aromatic side product **66a** was also isolated in this reaction: R_f=0.35 (hexanes/EtOAc, 8:2); $[\alpha]_D^{25}$ −24.5° (c 0.44, CH_2Cl_2); IR (thin film) 1711; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.82 (d, J=7.8 Hz, 2H), 7.43–7.31 (m, 12H), 5.63 (d, J=16.2 Hz, 1H), 5.36 (d, J=15.9 Hz, 1H), 5.30 (dd, J=1.5, 3.0 Hz, 1H), 5.25 (d, J=15.9 Hz, 1H), 5.16 (d, J=16.2, 1H), 5.07 (br s, 2H), 4.30 (dd, J=3.0, 10.8 Hz, 1H), 4.03 (dd, J=1.5, 10.8 Hz, 1H), 2.39 (s, 3H), 0.90 (s, 9H), 0.68–0.64 (m, 21H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.8, 156.2, 145.6, 138.1, 138.0, 137.7, 137.2, 135.0, 130.3, 129.9, 129.6, 128.7, 128.6, 128.5, 128.0, 127.4, 126.3, 122.9, 121.0, 107.0, 65.4, 62.4, 61.4, 46.8, 45.6, 26.3, 18.8, 17.9, 17.8, 12.3, −5.3; HRMS (ESI) Calcd for $C_{47}H_{64}N_3O_6SSi_2$ [M+H]: 854.4054. Found: 854.3971.

4.1.56. Chlorospirohydantoin 65b. R_f=0.39 (hexanes/EtOAc, 7:3); $[\alpha]_D^{25}$ −16.8° (c 2.13, CH_2Cl_2), IR (thin film) 3454, 1716 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.05 (d, J=8.5 Hz, 2H), 7.49 (d, J=8.5 Hz, 2H), 7.43 (d, J=7.0 Hz, 2H), 7.38 (d, J=7.5 Hz, 2H), 7.34–7.26 (m, 6H), 5.23 (d, J=16.0 Hz, 1H), 4.71 (d, J=15.0 Hz, 1H), 4.66 (d, J=15.0 Hz, 1H), 4.63 (br s, 1H), 4.39 (d, J=16.0 Hz, 1H), 4.25 (d, J=12.5 Hz, 1H), 4.02 (dd, J=3.5, 11.0 Hz, 1H), 3.84 (dd, J=2.0, 11.0 Hz, 1H), 3.78–3.72 (m, 2H), 3.52 (app t, J=9.0 Hz, 1H), 3.36 (d, J=9.0 Hz, 1H), 3.30 (m, 1H), 3.08 (m, 1H), 2.46 (s, 3H), 0.98–0.90 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.0, 173.6, 157.8, 146.8, 138.2, 137.1, 136.4, 130.7, 129.4, 129.3, 129.2, 129.0, 128.7, 128.6, 128.4, 76.6, 65.2, 61.6, 60.0, 58.6, 48.2, 47.5, 46.8, 46.2, 43.2, 21.5, 18.2, 18.1, 12.5; HRMS (ESI) Calcd for $C_{41}H_{53}ClN_3O_7SSi$ [M+H]: 794.3062. Found: 794.2923.

4.1.57. Chlorocyclopentane 71 and deschlorocyclopentane 73. A solution of **69** (320 mg, 0.33 mmol) and magnesium sulfate (30 mg) in 10 mL dichloromethane was cooled to −60 °C and treated with dimethyldioxirane (0.09 M in acetone, 3.99 mL, 0.36 mmol) over 2 h. Stirring continued for a further 2 h, after which the reaction was quenched with 100 μL of methyl sulfide. Solvents were removed in vacuo to afford crude allylic alcohol **40** (320 mg, 99%) as a colorless foam. A solution of crude allylic alcohol (150 mg, 0.15 μmol) in 10 mL dichloromethane was cooled to −50 °C and treated with cyclohexene (76.0 μL, 0.75 mmol) and sodium hydrogen carbonate (25.3 mg, 0.30 mmol) followed by NCS (50.0 mg, 0.38 mmol). The reaction mixture was allowed to warm to 25 °C, and further stirred for a total of 26 h. The reaction was quenched with 2 mL of pH 7 buffer. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried ($MgSO_4$). Solvents were removed in vacuo and the crude oil was purified by flash chromatography (SiO_2, EtOAc/hexane, 4:6) to afford a mixture of the chlorospirocyclic pentane **71** and the aromatic compound **72** (52.0 mg, 50%). These were further purified to obtain analytically pure samples. Chlorocyclopentane **71**: R_f=0.47 (EtOAc/hexane, 2:3); ^{1}H NMR (500 MHz, C_6D_6) δ 8.19 (d, J=8.5 Hz, 2H), 7.87 (d, J=8.5 Hz, 2H), 7.47 (d, J=2.0, 1H), 7.39 (dd, J=8.5, 2.0 Hz, 1H), 6.86 (d, J=8.5 Hz, 2H),

6.74 (d, J=8.5, 2H), 6.53 (d, J=8.5 Hz, 1H), 5.83 (d, J=15.5, 1H), 4.88 (s, 1H), 4.79 (dd, J=11.0, 9.5 Hz, 1H), 4.71 (d, J=15.5 Hz, 1H), 4.58 (d, J=12.0 Hz, 1H), 4.55 (dd, J=11.0, 4.0 Hz, 1H), 4.20 (dd, J=11.0, 2.5 Hz, 1H), 4.08 (dd, J=11.0, 1.3 Hz, 1H), 3.75 (m, 3H), 3.66 (s, 3H), 3.55 (ddd, J=15.0, 9.0, 3.0 Hz, 1H), 3.38 (ddd, J=16.0, 7.0, 3.0 Hz, 1H), 3.33 (s, 3H), 3.22 (ddd, J=15.0, 9.0, 3.0 Hz, 1H), 2.91 (ddd, J=16.0, 7.0, 2.5 Hz, 1H), 1.87 (s, 3H), 1.82 (s, 3H), 1.19 (s, 9H), 0.96–0.88 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.1, 173.2, 171.4, 156.8, 150.5, 150.1, 145.1, 144.8, 136.3, 135.8, 129.9, 129.7, 129.1, 127.6, 127.4, 127.2, 121.5, 113.2, 112.3, 76.6, 65.5, 61.3, 60.3, 55.8, 55.4, 50.5, 48.3, 47.5, 46.1, 45.4, 38.8, 33.4, 27.3, 21.2, 21.1, 18.2, 12.2; HRMS (ESI) Calcd for $C_{50}H_{68}N_3O_{12}S_2SiClLi$ [M+Li]: 1036.3862. Found: 1036.3912. Further elution gave the deschloro spirocyclic pentane **73**: R_f=0.38 (EtOAc/hexane, 2:3); IR (thin film) 1713 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 8.22 (d, J=8.5 Hz, 2H), 7.88 (d, J=8.5 Hz, 2H), 7.27 (d, J=2.0 Hz, 1H), 7.15 (dd, J=8.5, 2.0 Hz, 1H), 6.86 (d, J=8.5 Hz, 2H), 6.76 (d, J=8.5, 2H), 6.53 (d, J=8.5 Hz, 1H), 5.83 (d, J=16.0, 1H), 4.87 (s, 1H), 4.69 (d, J=16.0 Hz, 1H), 4.66 (dd, J=11.0, 8.5 Hz, 1H), 4.28 (dd, J=11.0, 6.5 Hz, 1H), 4.18 (dd, J=11.0, 2.5 Hz, 1H), 4.09 (dd, J=11.0, 2.5 Hz, 1H), 3.62 (m, 3H), 3.60–3.50 (m, 3H), 3.43–3.37 (m, 5H), 3.36 (s, 3H), 3.27 (ddd, J=15.0, 8.5, 3.0 Hz, 1H), 3.04 (ddd, J=15.0, 7.0, 3.0 Hz, 1H), 2.12 (app t, J=13.5 Hz, 1H), 1.87 (m, 2H), 1.86 (s, 3H), 1.82 (s, 3H), 1.13 (s, 9H), 0.97–0.90 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.2, 177.0, 172.5, 156.4, 150.5, 149.8, 144.9, 144.8, 136.4, 135.9, 130.7, 129.9, 129.6, 129.2, 128.3, 128.1, 127.9, 120.4, 112.5, 112.4, 71.9, 65.5, 63.3, 61.6, 55.8, 55.5, 50.9, 50.3, 49.6, 45.8, 40.4, 38.7, 35.7, 33.1, 27.2, 21.14, 21.08, 18.2, 18.1 12.2; MS (ESI) 1002 [M+Li]. HRMS (ESI) Calcd for $C_{50}H_{69}N_3O_{12}S_2SiLi$ [M+Li]: 1002.4252. Found: 1002.4262.

4.1.58. Spirocycle 78. A slurry of alkene **43** (500 mg, 0.44 mmol) and magnesium sulfate (100 mg) in 40 mL of dichloromethane was cooled to −50 °C and treated with dimethyldioxirane (~0.06 M in acetone, 8.1 mL, 0.48 mmol). After 3 h, the reaction was quenched with 100 μL of methyl sulfide at −50 °C, filtered through a pad of Celite® and concentrated in vacuo to afford crude allylic alcohol **77** (500 mg, 99%) as a colorless foam. The crude allylic alcohol **77** was redissolved in 40 mL of dichloromethane and cooled to −50 °C. Addition of cyclohexene (223 μL, 2.20 mmol) and magnesium sulfate (100 mg) was followed by treatment with chloramine-T (200 mg, 0.88 mmol). The reaction mixture was allowed to warm to 25 °C, and then stirred for a total of 12 h. The reaction was quenched with 20 mL of water and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo, and the crude oil was purified by flash chromatography on SiO_2, eluting with EtOAc/hexanes (1:3) to afford cyclopentane **78** (339 mg, 65%) as a colorless foam: R_f=0.35 (EtOAc/hexanes, 1:2); IR (film) 1773, 1718 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 8.26 (d, J=8.5 Hz, 2H), 7.96–7.94 (m, 2H), 7.88 (d, J=8.5 Hz, 2H), 7.81–7.79 (m, 2H), 7.46 (d, J=2.0 Hz, 1H), 7.39 (dd, J=8.0, 2.0 Hz, 1H), 7.28–7.20 (m, 6H), 6.84 (d, J=8.5 Hz, 2H), 6.77 (d, J=8.5 Hz, 2H), 6.39 (d, J=8.0 Hz, 1H), 5.87 (d, J=16.0 Hz, 1H), 4.90 (s, 1H), 4.74 (d, J=16.0 Hz, 1H), 4.55 (t, J=10.0 Hz, 1H), 4.50 (d, J=12.5 Hz, 1H), 4.23 (dd, J=10.0, 2.0 Hz, 1H), 4.11 (m, 2H), 3.96 (t, J=8.0 Hz, 1H), 3.80 (d, J=8.0 Hz, 1H), 3.79–3.73 (m, 1H), 3.62 (s, 3H), 3.58–3.53 (ddd, J=15.0, 9.0, 3.0 Hz, 1H), 3.39–3.34 (ddd, J=15.5, 7.0, 3.0 Hz, 1H), 3.27 (s, 3H) 3.26–3.21 (ddd, J=15.0, 9.0, 3.0 Hz, 1H), 2.95–2.90 (ddd, J=15.5, 7.0, 3.0 Hz, 1H), 1.87 (s, 3H), 1.84 (s, 3H), 1.20 (s, 9H), 0.98–0.90 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.3, 171.8, 156.8, 150.3, 149.9, 145.0, 144.8, 136.5, 136.3, 136.0, 135.9, 133.9, 133.7, 129.91, 129.88, 129.8, 129.6, 129.14, 129.12, 128.0, 121.5, 113.1, 112.2, 76.8, 65.5, 61.2, 60.6, 60.0, 55.8, 55.3, 50.6, 49.1, 48.6, 47.2, 46.0, 33.4, 27.1, 21.2, 21.1, 19.5, 18.18, 18.15, 18.11, 12.2; HRMS (ESI) Calcd for $C_{61}H_{78}N_3O_{11}S_2Si_2ClLi$ [M+Li]: 1190.4465. Found: 1190.4366.

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References and notes

1. Firn, R. D.; Jones, C. G. *Nat. Prod. Rep.* **2003**, *20*, 382.
2. (a) Jacquot, D.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551; (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, *12*, 1753.
3. (a) Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159; (b) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Org. Chem. Soc.* **2002**, *67*, 7780.
4. Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793–8794.
5. (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319; (b) Lovely, C. J.; Du, H.; Dias, H. V. R. *Heterocycles* **2003**, *60*, 1; (c) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623.
6. Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Lowe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203.
7. Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, O. Y.; Doundoulaskis, T.; Harran, P. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 765–769.
8. (a) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376–3377; (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281–3286.
9. Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.
10. Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 2674.
11. (a) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzio, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147; (b) Pelligrini, C.; Weber, M.; Borschberg, H.-J. *Helv. Chem. Acta* **1996**, *79*, 151; (c) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557.
12. Poullennec, K.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344.
13. Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3188.
14. Gassman, P. G.; Singleton, D. A. *J. Org. Chem.* **1986**, *51*, 3075.
15. (a) Romo, D.; Choi, N. S.; Buchler, I. P.; Shi, Z.; Liu, J. O. *J. Am. Chem. Soc.* **2004**, *126*, 10582; (b) Low, W.-K.; Dang,

Y.; Schneider-Poetsch, T.; Shi, Z.; Choi, N. S.; Merrick, W. C.; Romo, D.; Liu, J. O. *Mol. Cell* **2005**, *20*, 709.
16. (a) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535; (b) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679.
17. (a) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511; (b) Ackermann, J.; Matthes, M.; Tamm, C. *Helv. Chem. Acta* **1990**, *73*, 122.
18. Baxter, R. L.; Camp, D. J.; Coutts, A.; Shaw, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 225.
19. Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594.
20. (a) Ackermann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122; (b) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 507.
21. Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937.
22. (a) Arjona, O.; Medel, R.; Rojas, J.; Costa, A. M.; Vilarrasa, J. *Tetrahedron Lett.* **2003**, *44*, 6369; (b) Arjona, O.; Iradier, F.; Medel, R.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 6090.
23. (a) Snyder, H. R.; Hallada, D. P. *J. Am. Chem. Soc.* **1952**, *74*, 5; (b) Cossu, S.; De Lucchi, O.; Durr, R.; Fabris, F. *Synth. Commun.* **1996**, *26*, 211.
24. (a) Howell, S. J.; Spencer, N.; Philip, D. *Tetrahedron* **2001**, *57*, 4945; (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403; (c) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250 and references therein.
25. Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4340.
26. Ager, D. J.; Fleming, I. *J. Chem. Res.* **1977**, 6–7.
27. Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2000**, *2*, 1717.
28. Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.
29. Hong, T. W.; Jimenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158.
30. Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3891.
31. Lovely and co-workers also observed similar aromatic byproduct in related reactions, see Ref. 4b.
32. The use of cyclohexene as an alkene buffer was first described to us by T.R. Hoye during a seminar at Texas A&M.