Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 2685

www.rsc.org/obc

PAPER

Intramolecular Diels–Alder chemistry of 4-vinylimidazoles†

Yong He, Pasupathy Krishnamoorthy, Heather M. Lima, Yingzhong Chen, Haiyan Wu, Rasapalli Sivappa,‡ H. V. Rasika Dias* and Carl J. Lovely*

Received 1st September 2010, Accepted 13th December 2010
DOI: 10.1039/c0ob00657b

An investigation of 4-vinylimidazoles as diene components in the intramolecular Diels–Alder reaction is described. In the course of these studies several parameters affecting the cycloaddition were evaluated including the nature of the imidazole protecting group, the type of dienophile and the linking group. These investigations established that amino linkers were generally more effective than either ethers or esters. In most cases, the cycloadditions were highly stereoselective, resulting in the formation of products derived from an *anti* transition state. The polysubstituted tetrahydrobenzimidazole core of the pyrrole-imidazole alkaloid ageliferin can be constructed through the use of pseudo dimeric 4-vinylimidazoles.

Our group has been interested for some time in the development of new synthetic methods for the elaboration of simple imidazoles into more complex derivatives.[1] The primary motivation for this effort has been to apply these methods in the total synthesis of imidazole-containing alkaloids, in particular for approaches to the oroidin family of pyrrole-imidazole marine alkaloids[1,2] and the *Leucetta* family of aminoimidazole alkaloids (Fig. 1).[3,4] We also anticipated these efforts would provide useful methods in a general sense for the construction of polysubstituted imidazoles. In connection with an approach to the originally reported structure of palau'amine (**2**)[5] and related congeners,[5–7] we have developed the intermolecular Diels–Alder (DA) reaction of 4-vinylimidazoles[8] and subsequent oxidative functionalization[9] of these adducts to construct the DEF-ring fragment based on a biosynthetic proposal.[5] An obvious and important extension of the initial cycloaddition chemistry was its application in an intramolecular variant.[10] Although we perceived that this reaction may be valuable in its own right for the construction of polycyclic imidazole derivatives,[11] we were particularly interested in determining its utility in the context of approaches to several pyrrole-imidazole alkaloids, *e.g.*, ageliferin (**3**),[12,13] axinellamine A (**4**),[14,15] massadine (**5**),[16,17] and the recently-revised structures of the palau'amine family,[18,19] *e.g.*, **6** as a means to enforce, *inter alia*, the correct regiochemistry ("head-to-head") of the building blocks. In general terms, the intramolecular variant of the DA reaction is well known, and widely used in synthetic approaches to natural products,[20] however at the outset of this study, there were few examples of vinylimidazoles as ***4π-components*** in the DA reaction.[21] Similarly, there were only limited examples of intramolecular DA (IMDA) reactions involving imidazoles.[22] Wuonola and Smallheer have reported one example of an IMDA reaction involving the

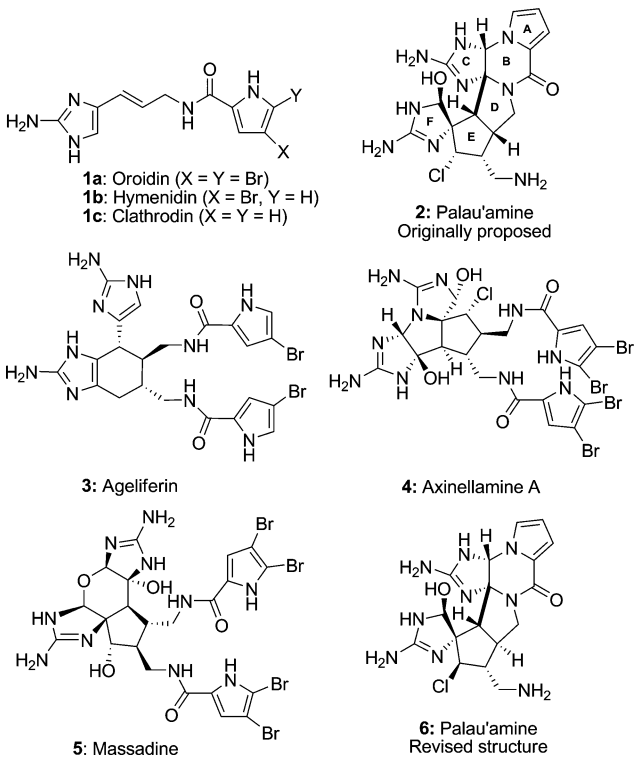


Fig. 1 Structures of some oroidin alkaloids.

Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas, USA. E-mail: lovely@uta.edu, dias@uta.edu; Fax: +1 817-272-3808; Tel: +1 817-272-5446; +1 817-272-3813

† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for new compounds not described in the main manuscript. Plots of X-ray structures for compounds **20a**, **62**, and **68**. CCDC reference numbers 791657–791659. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00657b

‡ Current address: Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, North Dartmouth, MA02747–2300, USA.

imidazole moiety as a diene, although the imidazole fragment was not found in the product due to a retro DA reaction leading to the expulsion of HCN.[22] Snyder and co-workers have examined several 2-aminoimidazole derivatives as 2π-components in intramolecular variants of inverse electron demand DA reactions, which provided efficient access to a variety of fused heterocyclic systems.[23] As a result of the paucity of reports,[24] the general parameters to successfully execute this reaction had to be ascertained prior to application of this chemistry in total synthesis efforts. For example, the nature of the imidazole nitrogen protecting group and the range of dienophile substituents needed to be established, along with the identification of suitable linking moieties.[25] Further, as was found in the intermolecular variant, there is the possibility of the formation of two possible products, the initial adduct *cf.* **8** and the aromatized adduct **9** (Fig. 2);[8] raising the question of whether this can be controlled by the substrate structural features (*e.g.*, the N-protecting group, the nature of the dienophile *etc.*) or the reaction conditions. Finally, issues pertaining to stereocontrol in these DA reactions and the utility of the cycloadducts for further elaboration towards natural product targets, such as those depicted in Fig. 1 needed to be determined.

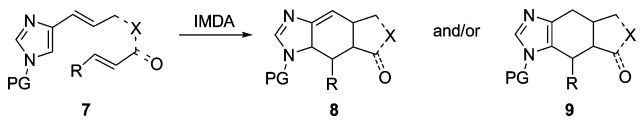
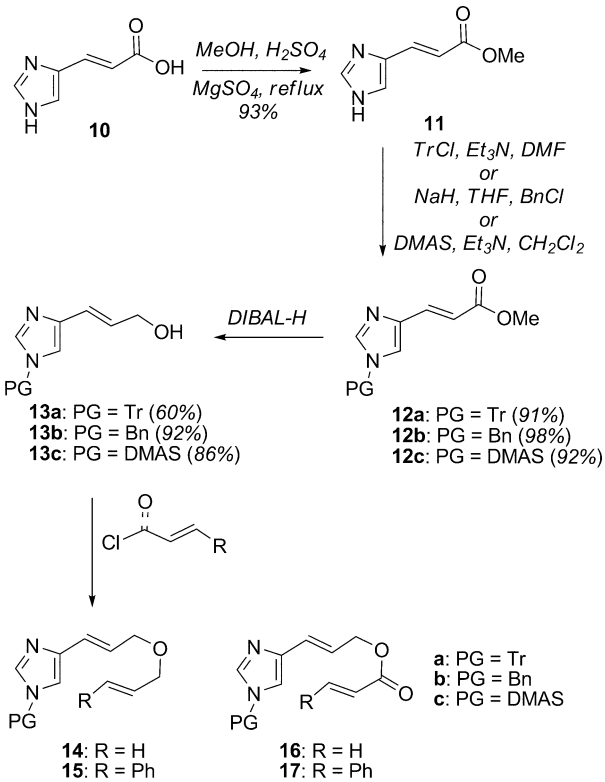


Fig. 2 Overview of the current study.

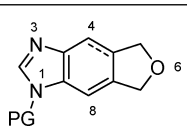
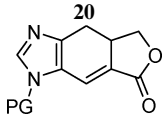


Scheme 1

Results and discussion

Urocanic acid (**10**) serves as a convenient starting material for this investigation as this unsaturated imidazole derivative is commercially available, or can be readily prepared from histidine.[26] Conversion of **10** to the corresponding methyl ester **11** *via* a simple Fischer esterification protocol can be conveniently accomplished on large scales using Pirrung's modification of the original Wunack procedure (Scheme 1).[27] Initial experiments were conducted using a trityl-protecting group on nitrogen as compounds **12a** and **13a** were not only described in the literature, but the protection occurs selectively at the least hindered nitrogen atom, providing the 4-vinylimidazole derivative **12a** efficiently (Scheme 1), thus permitting direct comparison with the previously reported intermolecular studies.[28,29] Reduction of ester **12a** with DIBAL-H gave the corresponding allyl alcohol **13a** (Scheme 1).[30] With quantities of the allyl alcohol in hand, a variety of simple ethers and esters **14a–19a** were prepared *via* standard methods,[31] and subjected to DA reactions under thermal activation. In most cases, the heating bath temperature was increased (temperature range 60–180 °C) until cycloaddition was observed or alternatively decomposition occurred. As can be seen from Table 1, only two of the six substrates, the propargylic derivative **18a** (145 °C, PhH, 26 h) and the propiolate derivative **19a** (140 °C, PhH, 24 h), engaged in the cycloaddition reaction forming dihydrobenzimidazoles **20a** (and the aromatized derivative) and **21a**, respectively. The remaining substrates underwent decomposition on extended heating at 150 °C (typically through loss of the trityl moiety). In the absence of other information, we concluded from these results that terminal substituents were not tolerated, which in turn suggested that there most likely were unfavorable steric interactions between the bulky trityl protecting group and the terminal substituent. An X-ray crystal structure (see the ESI†) obtained on **20a** strongly supports this notion, as there is very little free space between the trityl moiety and H8. The fact that the allyl substrate **14a** did not engage in a DA reaction was not difficult to rationalize, based on (presumably) unfavorable electronic factors, the acrylate substrate **16a** was somewhat more difficult to understand considering we knew that intermolecular DA reactions occur with electron deficient dienophiles, including

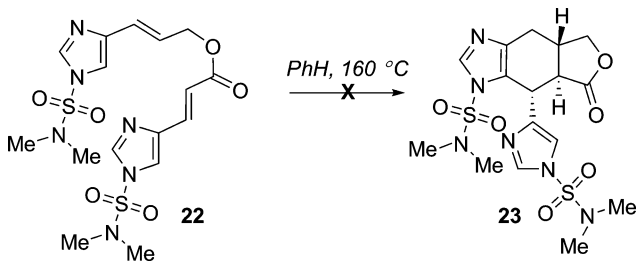
Table 1 Cyclization products and yields from intramolecular DA reactions of alkynyl substrates

Substrate	Product	PG = Tr/%	PG = Bn/%	PG = DMAS/%
		10[a] (34)[b]	76	65 (1)[b]
18	**20**	**a**	**b**	**c**
		30	0[c]	30
19	**21**	**a**	**b**	**c**

[a] Structure was confirmed by X-ray crystallography. [b] Yield in parenthesis corresponds to the oxidized product. [c] The propiolate derivative was not stable to chromatographic purification, and attempts to cyclize the crude product derived from the acylation of the alcohol were unsuccessful.

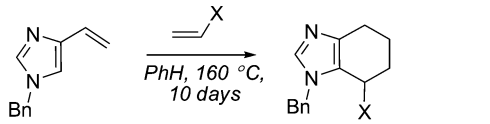
methyl acrylate, although the intrinsic regioselectivity of this reaction is in the opposite sense (see Scheme 3 below).[8] Initially, guided by the notion that steric factors due to the bulky nature of the trityl protecting group were playing a dominant role, we turned our attention to the preparation and evaluation of substrates with smaller imidazole protecting groups.

By the time these initial results with the Tr-systems were in hand, our experience in imidazole chemistry had evolved substantially, and thus we were able to prepare selectively two other 4-vinylimidazole derivatives from urocanic acid (**10**) containing smaller,[8] and more robust, protecting groups, with complementary electronic properties; the electron rich benzyl group and the electron withdrawing dimethylaminosulfonyl (Me_2NSO_2–, DMAS) group leading to the preparation of alcohols **13b** and **13c**, respectively (Scheme 1). Similar series of dienes **14b–19b** and **14c–19c** were prepared from each alcohol ranging from simple unactivated olefins to electron deficient olefins, and each diene was subjected to a DA reaction under thermal activation. In addition to the systems depicted in Scheme 1 and in Table 1, we were eager to push our chemistry towards natural product applications and so the pseudo dimeric substrate **22** (Scheme 2) was prepared and evaluated in the DA reaction. Essentially the same pattern of results was observed for these new derivatives **14b–19b** and **14c–19c** as for the Tr-protected series **14a–19a** with only the acetylenic substrates undergoing cycloaddition. In addition ester **22** failed to undergo cycloaddition to produce the expected lactone **23** (Scheme 2).



Scheme 2

Only the propargyl substrates **18a–c**, and in the cases of the Tr- and DMAS-derivatives, the propiolate systems **19a** and **c** successfully participate in the cycloaddition chemistry. These results clearly demonstrate that steric interactions between the nitrogen protecting group and the terminal dienophile substituent are not the primary (or perhaps even the major) cause for these cycloaddition reactions to fail, as presumably the Bn and DMAS groups can largely avoid unfavorable non-bonded interactions by rotating the majority of their steric bulk out of the way of an approaching dienophile. Again, for unactivated systems (allyl and cinnamyl), the failure still could be rationalized, at least qualitatively, in terms of mismatched HOMO–LUMO energies, whereas the activated systems (acryloyl[32] and cinnamoyl) were a little more puzzling to understand from this perspective. Around this time, results were emerging from parallel studies in the intermolecular reaction, which provided a possible clue to the cause of the failure of these systems to react in a general sense. For example, when the Bn-protected vinylimidazole **24** was reacted with methyl acrylate (Scheme 3) two notable observations were made: (1) the reaction was significantly slower (days *vs.*



24

25: X = CO_2Me, *65%* (X-ray)
26: X = CN, *57%*

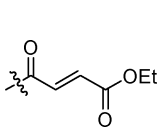
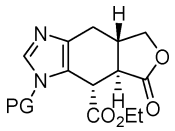
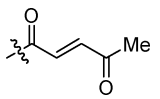
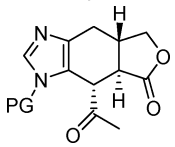
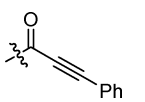
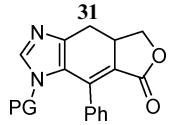
Scheme 3

h) compared to the reactions with *N*-phenylmaleimide, and (2) the reaction was regioselective, placing the carboxymethyl moiety proximal to the imidazole (Scheme 3, **24**→**25**).[8] Similar results were obtained with **24** and acrylonitrile (Scheme 3, **24**→**26**). In other words, mono activated dienophiles are substantially less reactive in this chemistry and they react with the **opposite** regiochemistry to that enforced by intramolecularity in the present study. Clearly, the entropic gain from the intramolecularity of the reaction with these *O*-linked substrates was not sufficient to overcome the intrinsic and unfavorable reactivity and electronic factors.

It is known in the literature that attainment of the transition state in cycloadditions with substrates related to **16a–c** and **17a–c** is accompanied by a twisting of the C–C bond between the olefin and carbonyl unit, which reduces the effectiveness of the conjugation between the π-bonds and thus raises the activation energy of the process.[33] Taking this factor into account suggested that the use of doubly activated dienophiles may provide substrates that would engage more readily in an intramolecular reaction.[34]

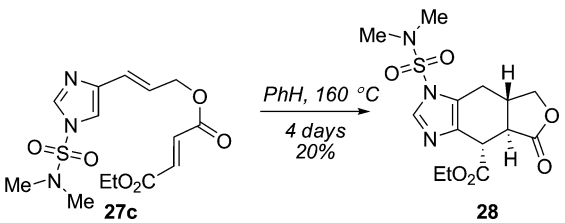
Accordingly, the fumarates **27b–c**, the acetylpropenoates **30b–c**, and the phenylpropiolates **32b–c** were prepared by condensing the half acid chloride or the corresponding acid (activated *in situ* with DCC) with the two allylic alcohols **13b** and **13c** (Table 2).[35] Both fumarate derivatives participated in an intramolecular DA reaction in benzene at 145 °C (bath temperature), providing cycloadducts,

Table 2 Intramolecular DA reactions of bis-activated substrates

			Product	
Entry	*R*		PG = Bn (%)	PG = DMAS (%)
1	 **27**	 **29**	70 **b**	20[a] **c**
2	 **30**	 **31**	59 **b**	68 **c**
3	 **32**	 **33**	85 **b**	65 **c**

[a] 51% of unreacted starting material was recovered.

in modest to good yield. In the case of the Bn-protected derivative **27b**, all of the spectroscopic data were consistent with formation of an all *trans* substituted adduct **29b**. Similarly with the DMAS-protected derivative, the spectroscopic data was consistent with the formation of a cycloadduct with the same all *trans* configuration. However, X-ray crystallographic analysis of this cycloadduct,§ performed to confirm the relative stereochemistry, revealed a surprise; although the stereochemistry was determined to be all *trans* as expected, the nitrogen protecting group had migrated to the less sterically congested nitrogen (**28**, Scheme 4).[36] This type of migration has been observed previously with the DMAS group on an imidazole system.[37] Subsequently it was found that by conducting the reaction at lower temperatures, the migration could be avoided and the expected cycloadduct **29c** was obtained in relatively low yield (entry 1, Table 2), although it should be noted that the migration started to occur on extended reaction times. We also evaluated the corresponding unsaturated keto ester derivatives **30b** and **30c**, which were being considered as substrates for approaches to several of the oroidin dimers.[13] We found that these substrates also participated in the cycloaddition reactions providing **31b** and **31c**, respectively, although the efficiencies were still relatively modest. Similarly, the phenylpropiolate derivatives **32b** and **32c** were prepared and subjected to the IMDA reaction, leading in both cases to a successful cycloaddition, providing **33b** and **33c** in reasonable yields.



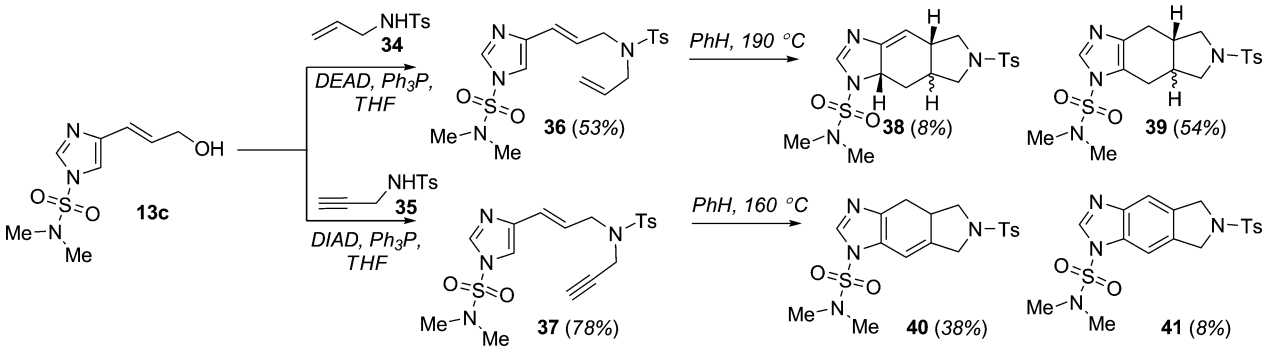
Scheme 4

Despite the fact that these cyclizations can be considered successful, based on the relatively modest efficiencies in some cases, we suspected that in addition to electronic effects, conformational issues were playing a significant role. Specifically, in order for cycloaddition to occur, an appropriate reactive conformation must be achieved, therefore structural features in the cyclization precursor that increase the population of the reactive conformation should lead to an increase in the cycloaddition rate.[38] It is well-known that substituted amines and amides can behave in this manner, and so the next logical step was to prepare and evaluate such substrates.

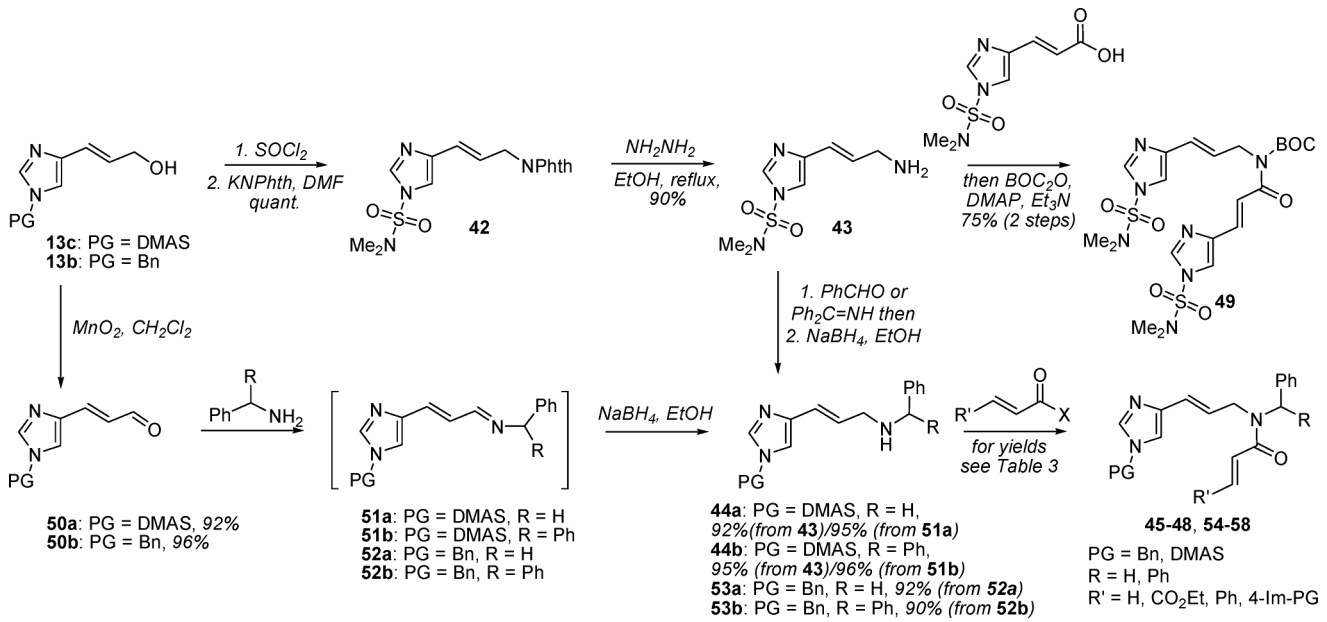
Initially, the *N*-tosyl protected derivatives **36** and **37** were prepared *via* a Mitsunobu reaction of the corresponding *N*-tosyl allyl amine **34**[39] and *N*-tosyl propargyl amine **35**[40] with allylic alcohol **13c**. This route was successful only for the DMAS-protected series (Scheme 5). It was found that the Bn-protected series did not participate in Mitsunobu reactions cleanly, in fact under these reaction conditions S_N2' products were formed as the major product in addition to the desired product, and these two adducts often proved difficult to separate chromatographically, leading to very poor yields. In subsequent studies it was found that the S_N2' pathway could be circumvented through the use of reductive amination (see Scheme 6 below) or by Pd-catalyzed π–allyl nucleophilic substitution,[41] but this was not determined until much later in the investigation, and thus the Bn-derivatives corresponding to **36** and **37** were not prepared. However, when the two sulfonyl urea substrates **36** and **37** were subjected to the DA reaction at elevated temperature, we were delighted to observe that cycloaddition occurred providing the expected cycloadducts, albeit in relatively moderate efficiency and under harsh reaction conditions (Scheme 5) leading to the formation of **39** (and **38**) and **40** (and **41**). Presumably, the high reaction temperatures result in some decomposition leading to modest yields. In the case of the allyl substrate **36**, both the initial adduct **38** and aromatized adducts **39** were obtained, each as inseparable 1 : 1 mixtures of stereoisomers. The propargyl substrate **37** led to the formation of two cycloadducts; the expected aromatized adduct **40**, along with a very small amount of the oxidized adduct **41**. The key observation from these experiments was the fact that even the non-activated allyl system **36** underwent cycloaddition in contrast to the corresponding ethers **14a–c**, suggesting that conformational issues do in fact play a major role in the facility of these cycloadditions. Extrapolating these findings suggested that combining more activated dienophiles with an amino linker should further facilitate the cycloaddition, and therefore we turned our attention to the preparation of related amides.

Our initial investigations were conducted with the DMAS series, in part due to the accessibility of the requisite substrates, as the S_N2' problems discussed above initially precluded the use of the corresponding Bn-protected system.

§ The X-ray structures and CIFs were reported in the preliminary account of this work (see ref. 10) and have been deposited at the Cambridge Crystallographic Data Center (compound **28** = CCDC 222234; compound **60** = CCDC 222235).



Scheme 5



Scheme 6

It was found that the *N*-alkyl phthalimide **42** was readily obtained through a Mitsunobu reaction of the allylic alcohol **13c** with phthalimide, although later it was determined that a more traditional Gabriel-type of reaction with K-phthalimide *via* the allyl chloride was more efficient (Scheme 6). Hydrazinolysis of **42** to **43**, conversion to the imine with benzaldehyde and then reduction with $NaBH_4$ provided the corresponding benzylamine **44a**. Subsequently an improved second generation route was developed whereby the same benzylamine **44a** can be obtained *via* oxidation of the allylic alcohol **13c** to aldehyde **50a**, and reductive amination with benzylamine affords **44a** (Scheme 6). Critically, this new route also permitted the construction of the corresponding Bn-protected substrates **53a** and **53b** (see below). With **44a** in hand, the preparation of the corresponding fumaramide **45**, cinnamide **46**, acrylamide **47**, and urocanamide **48** (Table 3) was easily accomplished *via* treatment with the appropriate acid chlorides (**45**–**47**) or the activated carboxylic acid (**48**). That these substrates were more reactive was immediately evident during the preparation of **45**, as it was found that some cycloaddition occurred during the process of preparation and work-up. Subsequent thermal activation of the purified amide at 68 °C provided the anticipated initial adduct **59** in an excellent 95% yield as a single stereoisomer (no other isomer detected by ^{1}H NMR spectroscopy of the crude reaction mixture). After the initial preparation, where cycloaddition occurred during the work-up, it was decided to subject the crude reaction mixture to the conditions employed above. In this case the cycloaddition occurred readily; however, the initial adduct **59** was only obtained in 10% yield, the major product was in fact the aromatized adduct **60**, again obtained as a single stereoisomer. Presumably traces of either acid or base remaining from the preparation of the substrate catalyze the aromatization process.[8] This aromatized cycloadduct was highly crystalline, providing material suitable for an X-ray crystal structure determination,§ which confirmed that the ring junction was *trans*, as was the relationship between the ester and amido moiety. It is also of note that under these mild reaction conditions, migration of the DMAS group was not observed. Similarly, the cinnamide derivative **46** underwent cycloaddition, providing a separable mixture of the initial adduct **61** and the aromatized congener **62**. Unlike with the fumaramide **45**, we were unable to find conditions which led to the exclusive production of the initial cycloadduct **61**. Access to the initial adduct would be useful as it permits oxidative functionalization of the olefin and ultimately would serve as a handle for the introduction of heteroatoms in targets such as palau'amine (**6**), axinellamine A (**4**) and massadine (**5**). The aromatized adduct **62** provided good quality crystals, which were evaluated by X-ray crystallography (see the ESI†), indicating that the relative stereochemistry was all *trans*. As expected, the acrylamide derivative **47** was much less reactive, but a cycloadduct **63** could be obtained in low yield and in this case as a nearly equimolar mixture of stereoisomers.

Most gratifyingly, the "dimeric" substrate **48** also undergoes cycloaddition in good yield (82% combined), but surprisingly two cycloadducts were obtained in these experiments. Initially, we suspected that these adducts were *cis* and *trans* stereoisomers, presumably at the ring junction, however proving this was difficult as we had some trouble in separating the two adducts. Eventually, however, preparative TLC permitted their separation and characterization. Extensive NMR analysis indicated that rather than being stereoisomers, these cycloadducts were in fact constitutional isomers, in which the major isomer was the normal (and expected) DA adduct **64**, and the minor isomer **65** results from an inverse electron demand DA reaction through the alternate pairing of the vinylimidazoles (**48**→**75** + **76**→**64** + **65**, Scheme 7). Interestingly, both cycloadducts had the same all *trans* relative stereochemistry (determined from the magnitudes of the appropriate vicinal coupling constants), and thus both cycloadducts, in principle, could be employed en route to the ageliferin group of natural products.

Table 3 Intramolecular DA products from amide-containing substrates

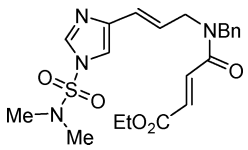
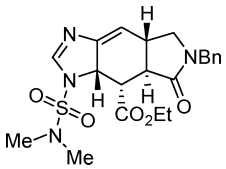
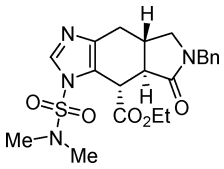
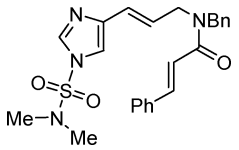
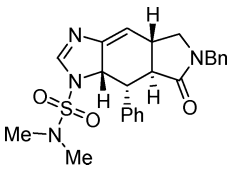
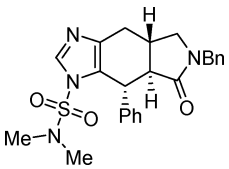
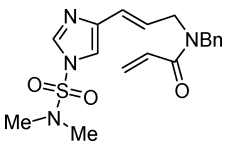
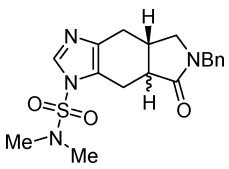
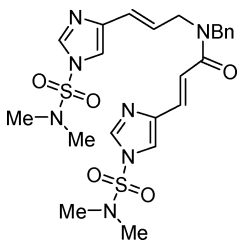
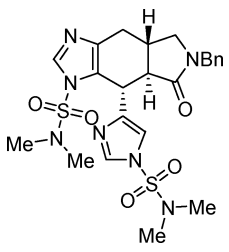
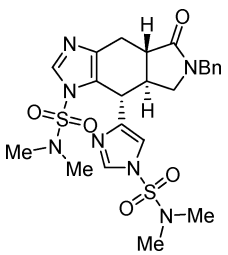
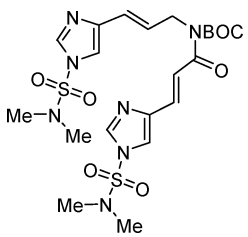
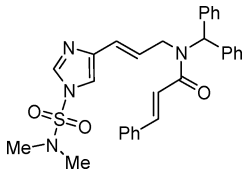
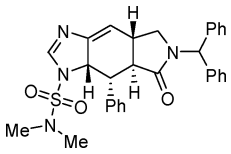
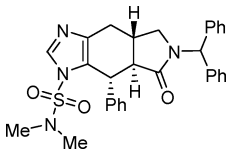
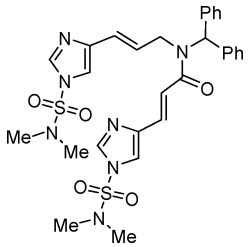
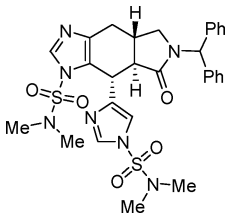
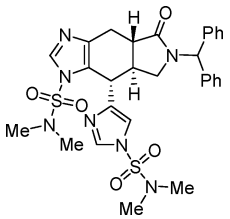
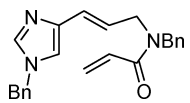
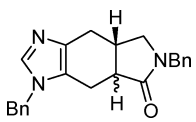
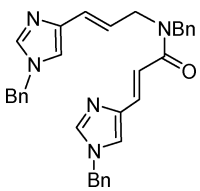
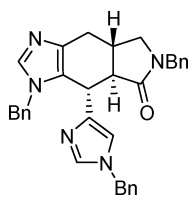
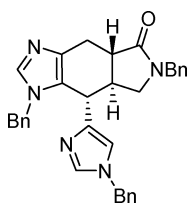
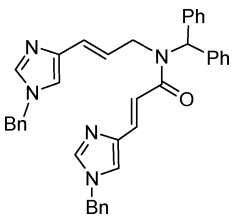
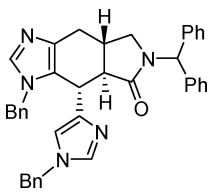
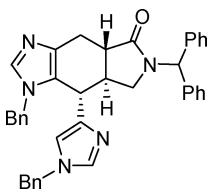
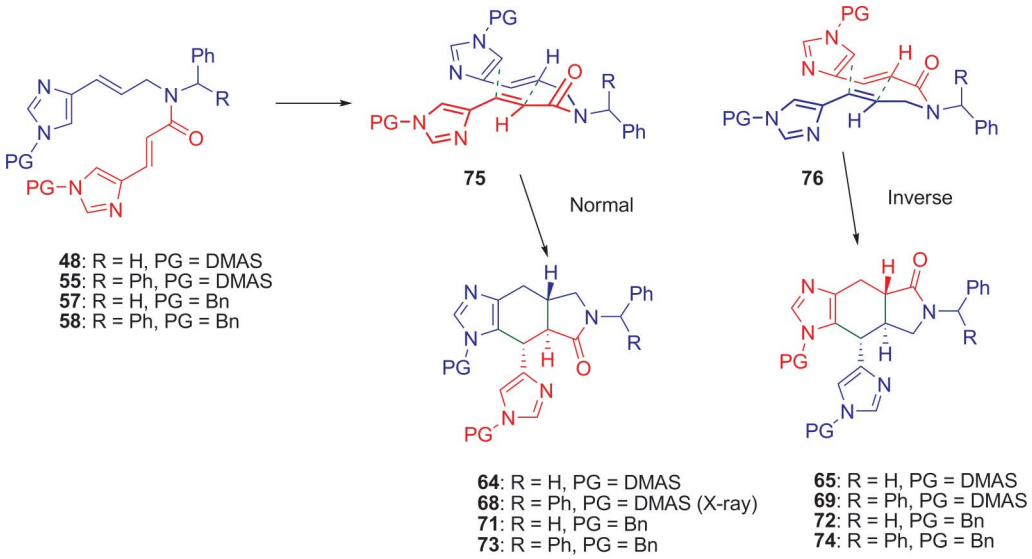
Substrate (yield/%)[a]/conditions[b]	PG	*R′*	*R*	Initial adduct (%)	Aromatized product (%)	
						
45 (92)[c] PhH, 68 °C, 12 h PhH, 68 °C, 10 h	DMAS	CO_2Et	Bn	**59** 95[d] 10[e]	**60**[f] — 80	
						
46 (82) PhH, 130 °C, 25 h PhH, 130 °C, 45 h	DMAS	Ph	Bn	**61** 61 27	**62**[f] 32 51	
						
47 (41) PhH, 145 °C, 60 h	DMAS	H	Bn		**63** 21 (3 : 2)[g]	
						
48 (78) PhH, 95 °C, 70 h PhH, 135 °C, 25 h	DMAS		Bn		**64** 50 56	**65** 32 43
						
49 PhH, 95 °C, 14 days	DMAS		BOC		[h]	

Table 3 *(Contd.)*

Substrate (yield/%)[a]/conditions[b]	PG	*R′*	*R*	Initial adduct (%)	Aromatized product (%)	
						
54 (75) PhH, 95 °C, 44 h	DMAS	Ph	Bzh	**66** 38	**67** 52	
						
55 (98) PhH, 95 °C, 46 h MeOH, 95 °C, 42 h CH_2Cl_2, 95 °C, 72 h	DMAS		Bzh		**68**[c] 56 53 60	**69** 39 42 30
						
56 (28) PhMe, 145 °C, 98 h	Bn	H	Bn		**70** 71 (3 : 2)[g]	
						
57 (80) PhH, 130 °C, 36 h	Bn		Bn		**71** 31	**72** 35
						
58 (80) PhH, 95 °C, 30 h	Bn		Bzh		**73** 45	**74** 45

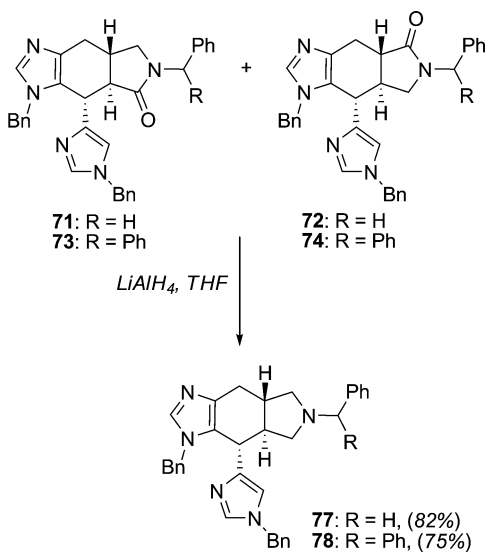
[a] Yields correspond to the acylation of the allylic amines to produce DA substrates. For details of their preparation see Experimental and the ESI.† [b] Conditions correspond to those employed in the DA cycloaddition. [c] In addition, 5% of initial cycloadduct. [d] The substrate was purified by column chromatography prior to cycloaddition. [e] The crude substrate was used in the cycloaddition. [f] The structure was confirmed by X-ray crystallography. [g] The stereochemistry of the major adduct was not determined. [h] Cycloaddition occurred, but a complex mixture of products was obtained from which no characterizable products were isolated.



Scheme 7

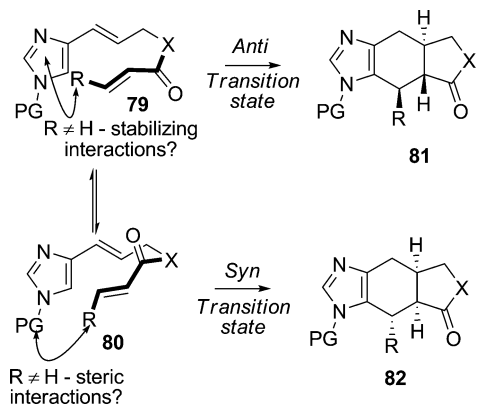
In an attempt to improve the cycloaddition selectivity both in terms of isolation of the initial adduct, chemoselectivity (normal *versus* inverse electron demand DA) and ease of subsequent elaboration, we became interested in the use of other substituents on the linking amino group with an aim of lowering the reaction temperature and potentially increasing selectivity. In particular, the use of bulky *N*-substituents has been shown to be beneficial in accelerating sluggish cycloaddition reactions by increasing the "reactive conformer" concentration,[42] therefore derivatives were prepared which contained either a *N*-BOC moiety **49** or a *N*-benzhydryl moiety, **54** and **55**, *via* standard chemistry. These substrates were then subjected to DA reactions. In the case of the *N*-BOC system **49**, a very slow reaction took place, with only approximately 40% conversion (estimated by ^{1}H NMR spectroscopy of the crude reaction mixture) after 14 days at 95 °C, increasing the temperature did not lead to an appreciable improvement in the situation. A fairly complex mixture of products was obtained containing what appear to be several cycloadducts judging from the complexity of the NMR spectrum, presumably the normal and inverse products and their corresponding initial adducts. Unfortunately, attempted purification of these products to rigorously establish their identity was not successful. On the other hand, substrates containing the benzhydryl group **54** and **55** underwent cycloaddition at a somewhat increased rate and reasonable temperatures. Fortuitously, with the DMAS-protected pseudo dimeric system **55**, it was found that the major product **68** crystallized out selectively from the partially concentrated reaction mixture and provided crystals suitable for X-ray crystallography (see the ESI†). This analysis not only confirmed the connectivity of the major adduct, but the all *trans* stereochemistry, which, as indicated above, was required in several of the natural products targeted in this program. Attempts were made to improve the selectivities by conducting the reaction in different solvents, but this only led to incremental improvements. Although the formation of constitutional isomers was not considered to be fatal to this approach to several natural product targets, *e.g.*, ageliferin, the situation was exacerbated by our inability to elaborate the lactam moiety under sufficiently mild conditions that did not lead to deprotection of the imidazoles or decomposition.

Therefore we looked at the preparation of the corresponding Bn-protected derivative, which we hoped may display improved selectivities in the cycloaddition due to the different electronic properties conferred on the imidazoles and, as the protecting groups are more robust, would permit the elaboration of the amide. Unfortunately, however, when either the N_{amide}-benzyl **57** or N_{amide}-benzhydryl **58** substituted derivatives were subjected to cycloaddition, an inseparable, essentially 1 : 1 mixture, of the two isomers **71** and **72** was obtained in 66% yield, and **73** and **74** in 90% yield. For characterization purposes and to demonstrate that these two cycloadducts were in fact regioisomeric rather than stereoisomers, the lactam moiety was reduced with $LiAlH_4$, leading to the formation of single compounds (**77** and **78**, respectively, Scheme 8) in both the benzyl series and the benzyhydryl series.



Scheme 8

A common trend observed among these doubly activated derivatives is that they all proceed to give the all *trans* isomer (irrespective of the connectivity in the cases where competitive inverse electron demand DA reaction occurred), whereas the acrylamide derivatives provide mixtures of *cis* and *trans* cycloadducts. The putative transition states for these *trans* selective cycloadditions place the terminal substituents in an *anti* orientation¶ (**79**→**81**, Scheme 9), *i.e.*, tucked under the imidazole moiety of the diene, and thus there is a possibility of stabilizing secondary orbital or π/π-interactions.[43] However, since many of these reactions occur at elevated temperature it is highly likely that the stereochemistry in these cycloadditions is a result of steric interactions, as in the alternate transition state leading to the *cis* fused product there appears to be a steric clash between the imidazole protecting group and the dienophile substituent (**80**→**82**, Scheme 9). In the case of the acrylamide derivatives this steric interaction is absent, and there are no other apparent secondary stabilizing interactions and therefore both *cis* and *trans* cycloadducts are more or less equally feasible.



Scheme 9

A second trend that emerges is that the initial adduct is only observed with the certain substrates in the DMAS series (*e.g.*, **49**→**63**), this observation is consistent with the intermolecular variants where lower reaction temperatures and electron withdrawing *N*-substituents favor the formation of stable initial adducts.[8] Thus at lower reaction temperatures at which the fumaramide, and to a lesser extent the cinnamide derivatives react, the re-aromatization pathway is less favorable, this is augmented by the *N*-sulfamoyl moiety reducing the electron density on the N1 of imidazole, which in turn reduces the driving force for rearomatization. For other analogs, either a higher reaction temperature is employed which facilitates aromatization, or the N1-substituent is electron rich, favoring aromatization.

In summary, we have investigated the preparation and intramolecular DA chemistry of several 4-vinylimidazole derivatives. In general, we have found that nitrogen-linked systems engage in cycloaddition with better efficiencies than the corresponding oxygen-linked systems. It was found, however, that propiolate, aryl-substituted propiolate, and bis activated derivatives linked *via* an ester do participate in cycloaddition. Based on this study, we are now investigating second generation systems and employing this chemistry in a number of approaches to imidazole-containing natural products and we will report our endeavors in due course.

¶ *Syn* and *anti* denote the orientation of the terminal dienophile substituent relative to the diene and used to avoid confusion with *endo* and *exo*, using terms suggested by Ciganek (see ref. 20).

Experimental

General considerations

All reactions were conducted in oven-dried glassware under an inert atmosphere of either nitrogen or argon. All reaction solvents were dried prior to use, either by standard methods or using alumina columns. NMR spectra were recorded in $CDCl_3$ solutions at 500 MHz for ^1H NMR or 125 MHz for ^{13}C NMR unless indicated otherwise. Experimental descriptions are provided for the DMAS-containing series, the remaining Tr- and Bn-derivatives are described in the ESI.†

General procedure A for alkylation (and some acylation) reactions (GP-A). A THF (5 mL) solution of alcohol (0.50 mmol) was cooled in an ice bath for 20 min. NaH (34 mg, 60% suspension in mineral oil, ~0.85 mmol) was added to the flask in two portions, and the flask was purged with nitrogen after the addition was completed. The solution was held in the ice bath for 1 h. The neat alkyl halide (0.50 mmol) was then added *via* syringe dropwise. The ice bath was removed after 10 min and the reaction flask was allowed warm up to room temperature.[44] Tetrabutylammonium iodide (50 mg, 0.13 mmol) was added and stirring was continued until the reaction was deemed complete by TLC analysis (12–36 h). Water (5 mL) was added to quench the reaction with the flask in an ice bath. After the mixture was stirred for 20 min, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with water (2 × 6 mL) then dried ($MgSO_4$) and concentrated. The EtOAc solution was concentrated and the residue was purified by flash column chromatography.

General procedure B for *N*-acylation reactions with acid chlorides (GP-B). The appropriate acyl chloride (1.05 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a mixture of the amine (1.00 mmol) and sodium bicarbonate (101 mg, 1.20 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After the completion of addition, the reaction was allowed to warm up to room temperature and stirred for several hours until completion (TLC). The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with water (2 × 5 mL), brine, dried (Na_2SO_4) and concentrated. Purification of the crude sample by chromatography gave the corresponding *N*-acylated product.

General procedure C for EDCI coupling reactions (GP-C). The alcohol or amine (1.00 mmol), EDCI (287 mg, 1.50 mmol) and acid (1.50 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL). The solution was cooled to 0 °C and DMAP (183 mg, 1.50 mmol) was added in one portion. The solution was allowed to warm to room temperature and stirred overnight. On completion of the reaction (TLC), the reaction mixture was diluted with CH_2Cl_2, washed with water (3 × 5 mL), brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography to afford the pure ester or amide.

General procedure D for DCC coupling reactions (GP-D). Allylic alcohol (2.0 mmol), DMAP (10 mg) and acid (3.0 mmol) were dissolved in CH_2Cl_2 (3 mL). The solution was cooled to −78 °C and DCC (500 mg, 2.4 mmol) in CH_2Cl_2 (1.5 mL)

was added by cannula. The solution was allowed to warm to room temperature over a period of 3–4 h. On completion of the reaction (TLC), the reaction mixture was filtered through Celite and washed with CH_2Cl_2. The combined filtrates were evaporated under vacuum and the residue purified by chromatography to afford the pure ester.

General procedure for thermal Diels–Alder reactions. The Diels–Alder substrate was dissolved in the appropriate solvent (usually benzene) to prepare a ~0.1 M solution in a thick-walled pressure tube with a Teflon screw-cap. The solution was degassed by bubbling N_2 or Ar gas through it for a few minutes and then the tube was sealed. The mixture was heated at the indicated temperature and the reaction was monitored by TLC or ^{1}H NMR spectroscopy of the crude reaction mixture. On completion of the reaction, the solvent was removed by rotary evaporation followed by purification of the residue by chromatography to afford the cycloadducts.

1-Dimethylsulfamoyl-4-[(1*E*)-3-(prop-2-ynyloxy)prop-1-enyl]-1*H*-imidazole (18c). Compound **18c** was prepared by GP-A from **13c**[45] (464 mg, 2.01 mmol) and propargyl bromide. Flash chromatography (EtOAc–hexane, 4 : 1) afforded **18c** (326 mg, 60%) as a pale yellow liquid: ^{1}H NMR: δ = 7.79 (s, 1H), 7.09 (s, 1H), 6.46 (m, 2H), 4.18 (d, J = 4.0 Hz, 2H), 4.15 (d, J = 2.6 Hz, 2H), 2.80 (s, 6H), 2.42 (t, J = 2.6 Hz, 1H);^{13}C NMR: δ = 141.03, 137.0, 127.0, 123.0, 114.5, 79.7, 74.7, 69.6, 57.2, 8.3; IR ($CHCl_3$, cm^{-1}): 3290, 3133, 2854, 2115, 1669, 1479, 1419, 1394, 1264, 1176, 1085, 1008, 966, 730, 601; EIMS (*m*/*z*): 270 (100%, M$^+$ + 1), 214, 161, 125, 108; Anal. Calcd for $C_{11}H_{15}N_3O_3S$: C, 49.06; H, 5.61; N, 15.60. Found: C, 49.16; H, 5.82; N, 15.51.

(2*E*)-3-(1-Dimethylsulfamoyl-1*H*-imidazol-4-yl)prop-2-enyl propynoate (19c). Compound **19c** was prepared by GP-C from **13c**[45] (347 mg, 1.50 mmol) and propiolic acid. Flash chromatography (EtOAc–hexane, 4 : 1) afforded product **19c** (331 mg, 79%) as colorless solid: mp: 67.0–67.5 °C; ^{1}H NMR: δ = 7.83 (s, 1H), 7.16 (s, 1H), 6.55 (d, J = 15.8 Hz, 1H), 6.50 (dt, J = 15.8, 4.8 Hz, 1H), 4.82 (d, J = 4.8 Hz, 2H), 2.90 (s, 1H), 2.85 (s, 6H); ^{13}C NMR: δ = 152.5, 140.4, 137.1, 125.1, 123.5, 115.2, 75.1, 74.6, 66.2, 38.3; IR (KBr, cm^{-1}): 3274, 2119, 1714, 1392, 1221, 1175, 1077, 1008, 966, 728, 598; EIMS (*m*/*z*): 65, 71, 98, 108, 125, 153, 214 (100%), 284 (M$^+$); Anal. Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.63; N, 14.83. Found: C, 46.76; H, 4.94; N, 14.45.

4,4a,5,7-Tetrahydro-1-dimethylsulfamoyl-1*H*-furo[3,4-*f*]benzimidazole (20c). Compound **20c** was prepared from the Diels–Alder reaction of compound **18c** (277 mg, 1.03 mmol) in benzene. Flash chromatography (EtOAc) afforded product **21c** (181 mg, 65%) as colorless solid: mp: 171.0–171.5 °C; ^{1}H NMR: δ = 7.70 (s, 1H), 6.43 (d, J = 2.6 Hz, 1H), 4.59 (dd, J = 15.0, 1.5 Hz, 1H), 4.42 (d, J = 15.0 Hz, 1H), 4.33 (dd, J = 8.1, 7.7 Hz, 1H), 3.53 (dd, J = 10.3, 8.4 Hz, 1H), 3.28 (m, 1H), 2.93 (dd, J = 15.8, 9.2 Hz, 1H), 2.82 (s, 6H), 2.53 (dd, J = 16.3, 16.3 Hz, 1H); ^{13}C NMR: δ = 143.7, 138.0, 135.9, 127.2, 105.5, 73.9, 69.4, 42.1, 38.3, 25.2; IR (KBr, cm^{-1}): 3104, 2860, 1382, 1169, 1122, 1040, 962, 912, 726, 593; EIMS (*m*/*z*): 270 (100%, M$^+$ + 1), 269 (M$^+$),202, 163, 131, 65; Anal. Calcd for $C_{11}H_{15}N_3O_3S$: C, 49.06; H, 5.61; N, 15.60. Found: C, 49.11; H, 5.82; N, 15.57. In addition a very small quantity (1.4 mg, ~1%) of the oxidized cycloadduct was obtained

5,7-Dihydro-1-dimethylsulfamoyl-1*H*-furo[3,4-*f*]benzimidazole. Only NMR data is available for this compound: ^{1}H NMR: δ = 8.22 (s, 1H), 7.69 (s, 1H), 7.61 (s, 1H), 5.20 (s, 4H), 2.90 (s, 6H); ^{13}C NMR: δ = 143.7, 142.1, 137.4, 136.3, 131.6, 113.1, 105.3, 73.2, 73.1, 38.4.

3,7,7a,8-Tetrahydro-3-dimethylsulfamoyl-5*H*-furo[3,4-*f*]benzimidazol-5-one (21c). Compound **21c** was prepared from the Diels–Alder reaction of compound **19c** (391 mg, 1.38 mmol) in benzene. Flash chromatography (EtOAc) afforded **21c** (117 mg, 30%) as colorless solid: mp: 171.5–172.0 °C; ^{1}H NMR: δ = 7.87 (s, 1H), 7.56 (d, 1H, J = 3.7 Hz), 4.75 (dd, 1H, J = 8.8, 8.8 Hz), 4.04 (dd, 1H, J = 9.2, 8.8 Hz), 3.52 (ddddd, 1H, J = 17.2, 9.5, 9.2, 8.8, 3.7 Hz), 3.11 (dd, 1H, J = 9.5, 17.2 Hz), 2.86 (s, 6H), 2.65 (dd, 1H, J = 17.2, 17.2 Hz); ^{13}C NMR: δ = 168.8, 143.6, 139.1, 126.2, 125.4, 121.2, 72.0, 38.3, 36.3, 26.9; IR (KBr, cm^{-1}): 3123, 2924, 1748, 1638, 1393, 1187, 1044, 968, 727, 598, 567; EIMS (*m*/*z*): 65, 89, 108, 177, 283 (M$^+$), 284 (100%, M$^+$ + 1); Anal. Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.63; N, 14.83. Found: C, 47.01; H, 4.89; N, 14.46.

Ethyl (2*E*)-3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-2-propenyl (2*E*)-2-butenedioate (27c). Compound **27c** was prepared by GP-C from **13c** (463 mg, 2.00 mmol) and the half ethyl ester of fumaric acid. Chromatography (Et_2O–hexane: 85/15) afforded **27c** (695 mg, 97%) as a colorless oil which solidified on standing. mp: 61–62 °C. ^{1}H NMR: δ = 7.84 (d, J = 1.4 Hz, 1H), 7.15 (d, J = 1.4 Hz, 1H), 6.86 (s, 2H), 6.52 (m, 2H), 4.83 (dd, J = 2.3, 2.3 Hz, 2H), 4.24 (q, J = 6.9 Hz, 2H), 2.85 (s, 6H), 1.30 (t, J = 6.9 Hz, 3H); ^{13}C NMR: δ = 165.0, 164.8, 140.5, 137.1, 134.2, 133.3, 124.3, 115.0, 65.3, 61.5, 38.3, 14.2; IR (KBr, cm^{-1}): 3138, 2984, 2942, 1731, 1715, 1480, 1420, 1394, 1308, 1178, 1225, 1079, 1007, 970, 729, 603; EI-MS (*m*/*z*): 357 (M$^+$, 10%), 229 (100%). Anal. Calcd for $C_{14}H_{19}N_3O_6S$: C, 47.05; H, 5.36; N, 11.76. Found: C, 46.98; H, 5.19; N, 11.40.

Ethyl (4*S,4a*R**,7a*S**)-1-dimethylsulfamoyl-5-oxo-4,4a,7a,8-tetrahydro-1*H*-furo-[3,4-*f*]benzimidazole-4-carboxylate (28).** Compound **28** was prepared by the general Diels–Alder reaction procedure from **27c** (300 mg, 0.84 mmol) in benzene at 160 °C for 4 days. Chromatographic purification of the crude residue (EtOAc) provided **28** (60 mg, 20%) as a colorless solid. mp: 180–181 °C. ^{1}H NMR: δ = 7.82 (s, 1H), 4.56 (dd, J = 8.8, 6.4 Hz, 1H), 4.36 (dq, J = 7.1, 3.6 Hz, 1H), 4.31 (dq, J = 7.1, 3.6 Hz, 1H), 4.10 (dd, J = 10.3, 8.8 Hz, 1H), 3.80 (d, J = 10.8 Hz, 1H), 3.20 (dd, J = 11.2, 10.4 Hz, 1H), 3.07 (dd, J = 13.3, 10.8 Hz, 1H), 2.90 (s, 6H), 2.69–2.66 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR: δ = 174.1, 170.9, 138.0, 137.0, 125.5, 71.1, 62.1, 44.7, 42.3, 38.7, 38.2, 24.6, 14.3; IR (KBr, cm^{-1}): 2982, 1782, 1734, 1469, 1390, 1178, 1150, 1091, 992, 720, 588; EI-MS (*m*/*z*): 358.7 (M$^+$+1, 5%), 356.5 (M$^+$, 45%), 283.5 (100%), 106.9 (65%). Anal. Calcd for $C_{14}H_{19}N_3O_6S$: C, 47.05; H, 5.36; N, 11.76. Found: C, 47.14; H, 5.57; N, 11.89.

Ethyl (4a*S,7a*R**,8*S**)-1-dimethylsulfamoyl-7-oxo-4,4a,7a,8-tetrahydro-1*H*-furo[3,4-*f*]benzimidazole-8-carboxylate (29c).** Compound **29c** was prepared by the general Diels–Alder reaction procedure from **27c** (197 mg, 0.55 mmol) in benzene at 135 °C for 72 h. Flash chromatography (EtOAc–hexane, 80/20) provided the unreacted starting material **27c** (100 mg, 51%) and the cycloadduct **29c** (40 mg, 20%) as a colorless solid. mp: 135–136 °C. ^{1}H NMR:

δ = 7.86 (s, 1H), 4.53 (dd, J = 8.8, 6.9 Hz, 1H), 4.28 (dq, J = 7.2, 3.6 Hz, 1H), 4.23 (dq, J = 7.2, 3.6 Hz, 1H), 4.06 (dd, J = 10.7, 8.8 Hz, 1H), 3.94 (d, J = 10.6 Hz, 1H), 2.90 (m, 1H), 2.88 (s, 6H), 2.82 (dd, J = 13.6, 10.6 Hz, 1H), 2.71 (ddd, J = 15.1, 11.2, 2.8 Hz, 1H), 2.62 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR: δ = 173.4, 171.1, 141.1, 139.1, 123.3, 70.8, 60.2, 46.7, 41.1, 39.6, 38.2, 27.5, 14.0; IR (KBr, cm^{-1}): 2984, 2933, 1783, 1732, 1474, 1392, 1233, 1186, 1149, 1082, 1011, 760, 595; EI-MS (m/z): 357 (M$^+$, 100%), 283. Anal. Calcd for $C_{14}H_{19}N_3O_6S$: C, 47.05; H, 5.36; N, 11.76. Found: C, 47.09; H, 5.30; N, 11.53.

(2*E*)-3-(1-Dimethylsulfamoyl-1*H*-imidazol-4-yl)-2-propenyl (*E*)-3-acetylpropenoate (30c). To a solution of (*E*)-3-acetylpropenoic acid (518 mg, 4.54 mmol) and alcohol **13c** (700 mg, 3.03 mmol) in CH_2Cl_2 (40 mL), DCC (937 mg, 4.54 mmol) and DMAP (37 mg) were added and stirred for 30 h at room temperature. The precipitated *N*,*N*-dicyclohexylurea was removed by filtration and the filtrate was washed with EtOAc. The organic layer was concentrated and to the resulting residue was added EtOAc (50 mL). The insoluble *N*,*N*-dicyclohexylurea obtained was removed by filtration. The EtOAc layer was washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried (Na_2SO_4), filtered, and concentrated. Column chromatography (EtOAc–hexane, 1 : 1) afforded **30c** as a white solid (580 mg, 59%). mp: 105–107 °C; ^{1}H NMR (300 MHz): δ = 7.84 (s, 1H), 7.16 (s, 1H), 7.04 (d, J = 16.2 Hz, 1H), 6.67 (d, J = 15.9, 1H) 6.54 (s, 2H), 4.86 (s, 2H), 2.86 (s, 6H), 2.36 (s, 3H); ^{13}C NMR (75 MHz): δ = 197.6, 165.2, 140.4, 140.3, 137.1, 131.2, 124.5, 124.2, 115.0, 65.4, 38.2, 28.2; IR (neat, cm^{-1}): = 2927, 1715, 1674, 1542, 1479. HRMS (ESI): calcd for $C_{13}H_{18}N_3O_5S$ (M+H)$^+$ 328.0962, found 328.0971.

(4a*S,7a*R**,8*S**)-8-Acetyl-1-dimethylsulfamoyl-7-oxo-4,4a,7a,8-tetrahydro-1*H*-furo[3,4-*f*]benzimidazole (31c).** Compound **31c** was prepared by the general Diels–Alder reaction procedure from **30c** (200 mg, 0.610 mmol) at 135 °C for 86 h in benzene. Chromatography ($CHCl_3$–MeOH, 24 : 1) provided **31c** (135 mg, 68%) as a white solid. mp: 84–86 °C; ^{1}H NMR (C_6D_6 + $CDCl_3$): δ = 7.54 (s, 1H), 3.93 (d, J = 10.6 Hz, 1H), 3.58 (dd, J = 8.7, 6.9, Hz, 1H), 3.02 (dd, J = 11.0, 8.7 Hz, 1H), 2.67 (s, 3H), 2.33 (dd, J = 15.1, 4.6 Hz, 1H), 2.02 (ddd, J = 15.7, 11.3, 2.8 Hz, 1H), 1.99 (dd, J = 13.8, 10.6 Hz, 1H), 2.16 (s, 6H), 1.65 (m, 1H) ^{13}C NMR (75 MHz): δ = 208.6, 174.5, 140.8, 138.0, 125.2, 71.1, 47.6, 46.4, 40.3, 38.3, 32.5, 27.3; IR (neat, cm^{-1}): = 2924, 1774, 1716 and 1473; HRMS (ESI): calcd for $C_{13}H_{17}N_3O_5SNa$ (M+Na)$^+$ 350.0781, found 350.0806.

(2*E*)-3-(1-Dimethylsulfamoyl-1*H*-imidazol-4-yl)prop-2-enyl 3-phenylpropynoate (32c). The allylic alcohol **13c** (2.55 g, 11.0 mmol), phenyl propiolic acid (2.43 g, 16.6 mmol) and DMAP (0.055 g, 0.45 mmol) were dissolved in CH_2Cl_2 (35 mL), and the mixture was cooled to −78 °C under N_2. DCC (2.77 g, 13.4 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise. The solution was allowed to warm to rt and stir overnight. The solids were filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and purified by column chromatography (EtOAc–hexane, 2 : 3) to afford **32c** (3.43 g, 83%) as an off-white solid. mp: 83–85 °C; ^{1}H NMR: δ = 7.84 (s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.37 (t, J = 6.9 Hz, 2H), 7.16 (s, 1H), 6.57 (s, 2H), 4.88 (d, J = 3.2 Hz, 2H), 2.85 (s, 6H); ^{13}C NMR (75 MHz): δ = 153.8, 140.5, 137.1, 133.1, 130.9, 128.7, 124.8, 124.0, 119.6, 115.1, 86.7, 80.5, 65.9, 38.3; IR (NaCl disk, cm^{-1}): 3138, 2934, 2221, 1708, 1489, 1393, 1286, 1173, 1077, 966, 728, 599; HRMS (ESI) calcd for $C_{17}H_{18}N_3O_4S$ (M+H)$^+$ 360.1013; found 360.1034; calcd for $C_{17}H_{17}N_3O_4SNa$ (M+Na)$^+$ 382.0832, found 382.0835.

3,7,7a,8-Tetrahydro-3-dimethylsulfamoyl-4-phenyl-5*H*-furo[3,4-*f*]benzimidazol-5-one (33c). The substrate **32c** (1.00 g, 2.77 mmol) was dissolved in benzene (150 mL) in a pressure tube and bubbled with N_2 for 5 min. The tube was then sealed and heated to 130 °C for 48 h. The solvent was removed under reduced pressure and the resulting solid was washed repeatedly with CH_2Cl_2 to afford the product **33c** (0.73 g, 73%) as an off-white solid. mp: 180–184 °C; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.17 (s, 1H), 7.20–7.28 (m, 5H), 4.60 (t, J = 8.7 Hz, 1H), 4.00 (t, J = 8.7 Hz, 1H), 3.55–3.70 (m, 1H), 2.95 (dd, J = 15.9, 16.5 Hz, 1H), 2.70 (t, J = 17.1 Hz, 1H), 2.58 (s, 6H); ^{13}C NMR (300 MHz, DMSO-d$_6$): δ = 167.6, 146.9, 142.9, 139.1, 133.3, 130.7, 130.3, 128.8, 127.4, 121.0, 70.2, 37.9, 37.2, 27.5; IR (KBr, cm^{-1}): 3105, 2966, 2900, 1737, 1619, 1447, 1378, 1263, 1168, 1103, 1070, 1028, 1004, 980, 762, 726, 590, 564; HRMS (ESI) calcd for $C_{17}H_{18}N_3O_4S$ (M+H)$^+$ 360.1013, found 360.1011.

***N*-Allyl-*N*-[(2*E*)-3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-prop-2-enyl]-*N*-tosylamine (36).** Allyl tosyl amine **34**[39] (2.11 g, 10.0 mmol) and PPh_3 (3.90 g, 15.0 mmol) was dissolved in THF (70 mL). The allylic alcohol **13c** (1.16 g, 5.00 mmol) was added followed by DEAD (1.9 mL, 12.3 mmol). The mixture was stirred at room temperature for 2 h. The solvent was removed by rotary evaporation and the residue was subjected to column chromatography (EtOAc–hexane, 3 : 2) to give product **36** (1.12 g, 53%) as a sticky colorless solid: ^{1}H NMR: δ = 7.78 (s, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.06 (s, 1H), 6.31 (d, J = 15.8 Hz, 1H), 6.19 (dt, J = 15.8, 5.9 Hz, 1H), 5.57 (m, 1H), 5.12 (d, J = 6.2 Hz, 1H), 5.09 (s, 1H), 3.89 (d, J = 5.9 Hz, 2H), 3.79 (d, J = 6.2 Hz, 2H), 2.81 (s, 6H), 2.37 (s, 3H); ^{13}C NMR: δ = 143.4, 140.8, 137.4, 136.9, 132.7, 129.8, 127.3, 125.8, 123.9, 119.3, 114.4, 49.8, 48.4, 38.3, 21.6; IR ($CHCl_3$, cm^{-1}): 3313, 2984, 1731, 1393, 1339, 1225, 1176, 1159, 1080, 967, 729, 600; EIMS (m/z): 425 (M$^+$), 269, 243, 214 (100%), 177, 157, 139, 125, 108, 65; Anal. Calcd for $C_{18}H_{24}N_4O_4S_2$: C, 50.92; H, 5.70; N, 13.20. Found: C, 50.90; H, 6.06; N, 12.87.

***N*-[(2*E*)-3-(1-Dimethylsulfamoyl-1*H*-imidazol-4-yl)prop-2-enyl]-*N*-prop-2-ynyl-*N*-tosylamine (37).** *N*-Propargyl toluenesulfonamide **35**[46] (419 mg, 2.00 mmol) and PPh_3 (781 mg, 3.00 mmol) was dissolved in THF (14 mL). The allylic alcohol **13c** (231 mg, 1.00 mmol) was added followed by DIAD (0.5 ml, 2.5 mmol). The mixture was stirred at room temperature for 2 h. The solvent was removed by rotary evaporation and the residue was subjected to column chromatography (EtOAc–hexane, 3 : 2) to give compound **37** (329 mg, 78%) as a sticky colorless solid: mp: 110–112 °C; ^{1}H NMR: δ = 7.81 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.11 (s, 1H), 6.47 (d, J = 15.8 Hz, 1H), 6.31 (dt, J = 15.8, 6.6 Hz, 1H), 4.11 (d, J = 2.4 Hz, 2H), 3.96 (d, J = 6.6 Hz, 2H), 2.85 (s, 6H), 2.41 (s, 3H), 2.02 (t, J = 2.4 Hz, 1H); ^{13}C NMR: δ = 143.7, 140.7, 137.0, 136.0, 129.6, 127.9, 124.85, 124.80, 114.7, 76.6, 74.0, 48.0, 38.3, 36.0, 21.6; IR ($CHCl_3$, cm^{-1}): 3245, 3040, 2990, 1753, 1697, 1534, 1392, 1260, 1161, 1075, 966, 899, 729, 659, 598; EIMS (m/z): 423 (M$^+$), 316, 214, 177, 153 (100%),

125, 108, 65; Anal. Calcd for $C_{18}H_{22}N_4O_4S_2$: C, 51.17; H, 5.25; N, 13.26. Found: C, 51.39; H, 5.57; N, 12.94.

1-Dimethylsulfamoyl-6-tosyl-1,4,4a,5,6,7,7a,8-octahydroimidazo[4,5-*f*]isoindole (39) and 1-dimethylsulfamoyl-6-tosyl-1,4a,5,6,7,7a,8,8a-octahydroimidazo[4,5-*f*]isoindole (38). Compounds **38** and **39** were obtained from the Diels–Alder reaction of compound **36** (566 mg, 1.33 mmol) in benzene at 160 °C. Flash chromatography (EtOAc) afforded **39** (308 mg, 54%), as a colorless solid as a 1 : 1 mixture of two diastereomers (*trans* and *cis*), and **38** (45 mg, 8%):

Data for compound **39**: mp: 125–126 °C; ^{1}H NMR: δ = 7.68–7.76 (m, 3H), 7.28–7.34 (m, 2H), 3.72 (dd, J = 9.5, 6.6 Hz, 1H), 3.46 (ddd, J = 9.5, 6.6, 3.7 Hz, 1H), 2.55–3.20 (m, 10H), 2.24–2.50 (m, 7H), 1.92 (m, 1H),; ^{13}C NMR: δ = 143.72, 143.66, 137.4, 137.23, 137.17, 135.7, 134.4, 134.3, 129.9, 127,4, 127.3, 124.7, 122.6, 52.48, 54.41, 52.37, 51.8, 41.2, 41.1, 38.15, 38.12, 35.8, 35.7, 29.8, 27.4, 25.2, 23.6, 21.8, 21.6; IR (KBr, cm^{-1}): 3025, 2946, 1716, 1598, 1472, 1390, 1340, 1164, 967, 759, 665, 591, 549; EIMS (*m*/*z*): 425 (M$^+$), 307, 279, 201, 180, 153 (100%), 125, 108, 89, 74, 65; Anal. Calcd for $C_{18}H_{24}N_4O_4S_2$: C, 50.92; H, 5.70; N, 13.20. Found: C, 50.86; H, 5.94; N, 13.02.

Data for compound **38**: this compound is quite sensitive to column chromatography (EtOAc),‖ only ^{1}H NMR and IR data are available for this compound: ^{1}H NMR: δ = 8.27 (s, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.59 (d, J = 5.1 Hz, 1H), 4.75 (d, J = 9.2 Hz, 1H), 3.87 (m, 1H), 3.48 (dd, J = 9.5, 9.2 Hz, 1H), 3.30 (dd, J = 10.3, 6.2, Hz, 1H), 3.21 (d, J = 10.3 Hz, 1H), 3.05 (dd, J = 9.2, 9.5 Hz, 1H), 2.82 (s, 6H), 2.44 (s, 3H), 2.34 (m, 1H), 1.96 (ddd, J = 12.8, 5.1, 4.8 Hz, 1H), 1.50 (dd, J = 23.1, 12.8 Hz, 1H); IR ($CHCl_3$, cm^{-1}): 3280, 3022, 2924, 2887, 1691, 1516, 1457, 1337, 1155, 1092, 959, 757, 710, 669, 592, 549.

1-Dimethylsulfamoyl-6-tosyl-1,4,4a,5,6,7-hexahydroimidazo-[4,5-*f*]isoindole (40) and 1-dimethylsulfamoyl-6-tosyl-1,5,6,7-tetrahydroimidazo[4,5-*f*]isoindole (41). These compounds were prepared from the Diels–Alder reaction of compound **37** (329 mg, 0.78 mmol) in benzene at 160 °C. Flash chromatography (EtOAc) afforded **40** (124 mg, 38%) and **41** (27 mg, 8%) as colorless solids:

Data for compound **40**: mp: 172–173 °C; ^{1}H NMR: δ = 7.72 (d, J = 8.1 Hz, 2H), 7.66 (s, 1H), 7.35 (d, J = 8.1 Hz, 2H), 6.43 (s, 1H), 4.23 (d, J = 15.8 Hz, 1H), 3.95 (dd, J = 8.6, 8.6 Hz, 1H), 3.78 (d, J = 15.8 Hz, 1H), 3.25 (m, 1H), 2.90 (dd, J = 15.8, 9.2 Hz, 1H), 2.81 (s, 6H), 2.77 (m, 1H), 2.44 (m, 1H), 2.43 (s, 3H), ^{13}C NMR: δ = 144.1, 138.9, 137.8, 136.1, 132.5, 129.9, 127.9, 126.3, 108.3, 53.8, 50.5, 40.6, 38.3, 26.3, 21.7; IR (KBr, cm^{-1}): 3125, 3025, 2945, 2852, 1598, 1558, 1454, 1391, 1346, 1165, 1094, 1049, 965, 816, 755, 726, 665, 594, 550, 497; EIMS (*m*/*z*): 423 (M$^+$), 316, 279, 180, 157 (100%),139, 125, 108, 93, 65; Anal. Calcd for $C_{18}H_{22}N_4O_4S_2$: C, 51.17; H, 5.25; N, 13.26. Found: C, 51.31; H, 5.46; N, 12.91.

Data for compound **41**: mp: 184–185 °C; ^{1}H NMR: δ = 8.18 (s, 1H), 7.78 (d, 2H, J = 8.1 Hz), 7.62 (s, 1H), 7.57 (s, 1H), 7.31 (d, 2H, J = 8.1 Hz), 4.70 (br s, 4H), 2.89 (s, 6H), 2.39 (s, 3H); ^{13}C NMR: δ = 144.0, 143.8, 142.4, 134.0, 133.5, 133.1, 131.7, 130.0, 127.8, 115.0, 107.1, 53.5, 53.3, 38.4, 21.6; IR (KBr, cm^{-1}): 2925, 1700, 1597, 1497, 1453, 1392, 1344, 1165, 1096, 967, 759, 667, 591, 549; EIMS (*m*/*z*): 152, 108, 91, 64 (100%); Anal. Calcd for $C_{18}H_{20}N_4O_4S_2$: C, 51.41; H, 4.79; N, 13.32. Found: C, 51.70; H, 5.16; N, 13.12.

4-[(1*E*)-3-Chloroprop-1-enyl]-1-dimethylsulfamoyl-1*H*-imidazole. Allylic alcohol **13c** (231 mg, 1.00 mmol) was dissolved in CH_2Cl_2 (6 mL). The mixture was cooled to 0 °C and thionyl chloride (0.08 mL, 1.1 mmol) was added. The mixture was allowed to warm up to room temperature and stirred for 2 h. The organic solvent was removed by distillation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The solution was washed with saturated $NaHCO_3$ aqueous solution and the organic solvent was dried over $MgSO_4$ and concentrated under reduced pressure to afford the chloride (250 mg, 100%) as a colorless solid. mp: 76.0–76.5 °C. ^{1}H NMR: δ = 7.80 (s, 1H), 7.13 (s, 1H), 6.53 (dt, J = 15.4, 6.6 Hz, 1H), 6.47 (d, J = 15.4 Hz, 1H), 4.18 (d, J = 6.2 Hz, 2H), 2.81 (s, 6H); ^{13}C NMR: δ = 140.3, 137.1, 126.6, 124.2, 115.1, 45.0, 38.2; IR (KBr, cm^{-1}): 3137, 2936, 1486, 1382, 1265, 1167, 1088, 1012, 951, 803, 738, 603, 515; EIMS (*m*/*z*): 250 (55%, M$^+$), 228, 214, 97, 73, 65, 55 (100%). Anal. Calcd for $C_8H_{12}ClN_3O_2S$: C, 38.48; H, 4.84; N, 16.83. Found: C, 38.63; H, 5.07; N, 16.47.

4-[(1*E*)-3-Phthalimidoylprop-1-enyl]-1-dimethylsulfamoyl-1*H*-imidazole (42). The chloride (350 mg, 1.40 mmol) was dissolved in dry DMF (3 mL) at room temperature, potassium phthalimide (623 mg, 3.36 mmol) in dry DMF (7 mL) was added dropwise. The mixture was stirred at room temperature overnight then the DMF was removed by vacuum distillation. The residue was subjected to chromatography (EtOAc) to give **42** (505 mg, 100%) as a colorless solid. mp: 180–181 °C. ^{1}H NMR: δ = 7.84 (dd, J = 5.1, 2.9 Hz, 2H), 7.79 (s, 1H), 7.71 (dd, J = 5.1, 2.9 Hz, 2H), 7.09 (s, 1H), 6.51–6.44 (m, 2H), 4.43 (d, J = 4.2 Hz, 2H), 2.82 (s, 6H); ^{13}C NMR: δ = 168.0, 140.7, 136.9, 134.1, 132.2, 124.8, 123.5, 123.4, 114.6, 39.3, 38.3; IR (KBr, cm^{-1}): 3132, 1773, 1708, 1482, 1388, 1262, 1171, 1075, 955, 723, 603; EI-MS (*m*/*z*): 361 (20%, M$^+$), 181, 165, 148, 125, 111, 101 (100%). Anal. Calcd for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.47; N, 15.55. Found: C, 53.09; H, 4.71; N, 15.22.

(2*E*)-3-(1-Dimethylsulfamoyl-1*H*-imidazol-4-yl)prop-2-en-1-amine (43). Compound **42** (505 mg, 1.4 mmol) was dissolved in absolute ethanol (14 mL) at room temperature and hydrazine monohydrate (0.4 mL, 7 mmol) was added and the mixture was heated at reflux for 3 h, then cooled to room temperature. The precipitated solid was removed by filtration and the resulting solid was washed with ethanol. The ethanolic solutions were combined and concentrated. CH_2Cl_2 (15 mL) was added to the residue and the precipitate formed was removed by filtration and this process was repeated one more time. The solvent was removed to provide crude amine **47** as a brown oil (290 mg, 90%) which was not purified further and was used directly in for the next step: ^{1}H NMR: δ = 7.82 (s, 1H), 7.07 (s, 1H), 6.56 (dt, J = 15.7, 5.7 Hz, 1H), 6.36 (d, J = 15.7 Hz, 1H), 3.46 (d, J = 5.7 Hz, 2H), 2.84 (s, 6H), 1.44 (brs, 2H); ^{13}C NMR: δ = 141.5, 136.9, 133.2, 119.5, 113.7, 43.9, 38.3; IR (neat, cm^{-1}): 3300, 2922, 1477, 1389, 1174, 1080, 964, 728, 600; EI-MS (*m*/*z*): 230 (26%, M$^+$), 213, 121 (100%), 94.

(2*E*)-3-(1-Dimethylsulfamoyl-1*H*-imidazol-4-yl)propenal (50a). *General Procedure for MnO_2 Oxidation*: The alcohol **13c** (200 mg, 0.86 mmol) was dissolved in dry CH_2Cl_2 (6 mL), then MnO_2 (216 mg, 85% activated from Aldrich, 2.59 mmol) was added and the resulting mixture was stirred at room temperature overnight, or under reflux for 6 h, until TLC analysis indicated complete

‖ These initial adducts tend to aromatize on purification by silica-gel chromatography.

consumption of starting material. The reaction mixture was filtered and washed thoroughly with CH_2Cl_2. The combined filtrates were washed with brine and concentrated to provide the aldehyde (181 mg, 92%) as a beige solid, which was used without further purification. mp: 143–145 °C. ^{1}H NMR: δ = 9.67 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 7.50 (s, 1H), 7.33 (d, J = 15.6 Hz, 1H), 6.88 (dd, J = 15.6, 7.8 Hz, 1H), 2.91 (s, 6H); ^{13}C NMR: δ = 193.3, 141.7, 139.1, 137.9, 129.7, 119.6, 38.3; IR (neat, cm^{-1}): 3121, 2961, 1673, 1386, 1174, 1085, 1007, 972, 859, 776, 739, 609; ESI-MS (m/z), positive mode: 413 (100%), 252 (M+Na$^+$, 10%), 230 (M+H$^+$, 3%); negative mode: 264 (M+Cl$^-$, 54%), 257 (100%), 228 ([M − H]$^-$, 53%). Anal. Calcd for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 41.82; H, 4.47; N, 18.35.

***N*-Benzyl-*N*-[(2*E*)-3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-2-propenyl]amine (44a).** Method A: Benzaldehyde (484 mg, 4.56 mmol) was added to a solution of allylamine **43** (1.00 g, 4.34 mmol) in anhydrous ethanol (40 mL) and stirred at room temperature for 2 h. The reaction was then cooled to 0 °C and $NaBH_4$ (330 mg, 8.72 mmol) was added. After stirring for several hours at room temperature, the reaction was quenched carefully with H_2O and extracted with CH_2Cl_2 (3×). The combined organics were dried (Na_2SO_4) and concentrated to afford **44a** (1.28 g, 92%) as a beige oil, which was used in the next step without further purification.

Method B: aldehyde **50a** (56 mg, 0.24 mmol), molecular sieves (4 Å, 132 mg) and benzylamine (31 mg, 0.032 mL, 0.29 mmol) were dissolved in anhydrous MeOH (1.5 mL) at room temperature and stirred for 3 h, then $NaBH_4$ (14 mg, 0.37 mmol) was added in one portion and stirred for an additional 5 h. The reaction mixture was diluted with CH_2Cl_2, filtered through Celite, and rinsed with a small amount of CH_2Cl_2. Sat. NH_4Cl was added and the organic layer was separated, washed with H_2O (2×), brine, dried (Na_2SO_4) and concentrated to provide the pure amine **44a** (74 mg, 95%) as a beige solid, which was used directly in the next step. mp: 141–143 °C ^{1}H NMR: δ = 7.82 (s, 1H), 7.34–7.30 (m, 4H), 7.25–7.23 (m, 1H), 7.08 (s, 1H), 6.54 (dt, J = 15.6, 6.0 Hz, 1H), 6.42 (dt, J = 15.6, 0.9 Hz, 1H), 3.83 (s, 2H), 3.43 (dd, J = 6.0, 0.9 Hz, 2H), 2.84 (s, 6H), 1.94 (brs, 1H); ^{13}C NMR: δ = 141.5, 140.2, 136.9, 130.3, 128.5, 128.3, 127.1, 121.6, 113.8, 53.2, 50.7, 38.3; IR (neat, cm^{-1}): 3153, 3056, 2944, 2847, 1653, 1639, 1457, 1390, 1262, 1175, 1078, 998, 966, 727, 599; EI-MS (m/z): 320 (16%, M$^+$), 211 (100%), 90.

***N*-Benzhydryl-*N*-((2*E*)-3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-2-propenyl) amine (44b).** Method A: A mixture of allyl amine **43** (100 mg, 0.43 mmol) and benzophenone imine (73 µL, 0.43 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature overnight. The solvent was then completely removed under vacuum to provide the pure imine intermediate (170 mg, 100%) which was directly used in the next step without purification. Data for the imine intermediate: mp: 136–137 °C. ^{1}H NMR: δ = 7.83 (s, 1H), 7.67–7.64 (m, 2H), 7.48–7.32 (m, 6H), 7.20–7.17 (m, 2H), 7.09 (s, 1H), 6.65 (dt, J = 15.6, 5.5 Hz, 1H), 6.44 (dt, J = 15.6, 1.8 Hz, 1H), 4.19 (dd, J = 5.5, 1.8 Hz, 2H), 2.84 (s, 6H); ^{13}C NMR: δ = 169.4, 141.9, 139.8, 136.8, 136.6, 130.4, 130.2, 128.63, 128.60, 128.2, 127.7, 120.4, 113.6, 55.2, 38.3; IR (KBr, cm^{-1}): 1659, 1392, 1175, 1078, 966; EI-MS (m/z): 179.1 (20%), 285.5 (100%), 394.5 (M$^+$, 21%). The crude imine from the previous step was suspended in anhydrous MeOH (4 mL) at 0 °C, and then $NaBH_4$ (40 mg, 1.05 mmol) was added in one portion. Then the reaction mixture was stirred at room temperature for 3 h. H_2O (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organics were dried (Na_2SO_4), concentrated and dried to afford **44b** (158 mg, 95%) as a colorless solid.

Method B: Aldehyde **50a** (60 mg, 0.26 mmol) and diphenylmethylamine (53 mg, 0.05 mL, 0.29 mmol) were dissolved in anhydrous MeOH (1.3 mL) at room temperature and stirred for 3 h, then $NaBH_4$ (20 mg, 0.52 mmol) was added in one portion and stirred for an additional 5 h. Following the same work-up procedures as in Method A, the pure product **44b** (99 mg, 96%) was obtained after trituration with ether as a colorless solid. mp: 124–125 °C. ^{1}H NMR: δ = 7.84 (s, 1H), 7.43–7.41 (m, 4H), 7.32–7.28 (m, 4H), 7.22–7.19 (m, 2H), 7.09 (s, 1H), 6.58 (dt, J = 15.6, 6.0 Hz, 1H), 6.41 (dt, J = 15.6, 1.4 Hz, 1H), 4.92 (s, 1H), 3.37 (dd, J = 6.0, 1.4 Hz, 2H), 2.84 (s, 6H), 1.73 (brs, 1H); ^{13}C NMR: δ = 144.0, 141.6, 136.9, 130.6, 128.6, 127.4, 127.1, 121.2, 113.7, 66.5, 49.3, 38.3; IR (KBr, cm^{-1}): 1454, 1418, 1390, 1175, 1077, 966; EI-MS (m/z): 396.8 (M$^+$, 15%), 166.1 (100%), 228.2 (77%), 287.6 (32%). Anal. Calcd for $C_{21}H_{24}N_4O_2S$: C, 63.61; H, 6.10; N, 14.13. Found: C, 63.42; H, 6.14; N, 13.84.

(*E*,*E*)-4-[[3-(1-Dimethylsulfamoyl-1*H*-imidazol-4-yl)-2-propenyl]benzylamino]-4-oxo-2-butenoic acid, ethyl ester (45). Compound **45** was prepared by procedure GP-B from **44a** (320 mg, 1.00 mmol) and fumaric acid chloride ethyl ester[47] (171 mg, 1.05 mmol). Chromatography (EtOAc–hexane, 3 : 1) afforded **45** (410 mg, 92%) as an oil and the Diels–Alder adduct **59** (22 mg, 5%) as a colorless waxy solid. ^{1}H NMR of a 60 : 40 mixture of two rotamers: δ = 7.83, 7.82 (s, total 1H), 7.40–7.24 (m, 5H), 7.23–7.21, 7.18–7.16 (m, total 1H), 7.103, 7.096 (s, total 1H), 6.90, 6.87 (d, J = 12.4, 12.4 Hz, total 1H), 6.44–6.37 (m, 1H), 6.37–6.29 (m, 1H), 4.69, 4.63 (s, total 2H), 4.25–4.16 (m, 2H), 4.06 (d, J = 3.9 Hz, 2H), 2.87, 2.84 (s, total 6H), 1.29 (t, J = 7.3 Hz, 3H); ^{13}C NMR of a 60 : 40 mixture of two rotamers: δ = 165.75, 165.66, 165.24, 165.11, 140.9, 140.4, 137.1, 136.9, 136.80, 136.3, 136.1, 133.7, 132.3, 129.1, 128.9, 128.8, 128.4, 127.9, 127.8, 126.7, 125.5, 123.6, 122.4, 114.8, 114.4, 61.3, 48.8, 48.4, 47.2, 47.0, 38.32, 38.27, 14.2; IR (neat, cm^{-1}): 3056, 3028, 2980, 2941, 1721, 1698, 1654, 1627, 1556, 1420, 1391, 1287, 1175, 1079, 969, 763, 599; EI-MS (m/z): 446 (100%, M$^+$), 293, 52. Anal. Calcd for $C_{21}H_{26}N_4O_5S{\cdot}1/2H_2O$: C, 55.37; H, 5.97; N, 12.30. Found: C, 55.73; H, 5.65; N, 12.31.

(*E*,*E*)-*N*-Benzyl-*N*-[3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-2-propenyl]-3-phenyl-2-propenamide (46). Compound **46** was prepared by procedure GP-B from **44a** (250 mg, 0.78 mmol) and cinnamoyl chloride (136 mg, 0.82 mmol). Chromatography (EtOAc–hexane, 3 : 1) afforded **46** (287 mg, 82%) as a colorless solid. mp: 129–130 °C. ^{1}H NMR of a 57 : 43 mixture of two rotamers: δ = 7.85, 7.83 (s, total 1H), 7.79, 7.71 (d, J = 16.0, 16.0 Hz, total 1H), 7.51–7.50, 7.44–7.43 (m, total 2H), 7.38–7.23 (m, 8H), 7.11, 7.09 (s, total 1H), 6.88, 6.84 (d, J = 5.3, 5.0 Hz, total 1H), 6.52–6.43 (m, 1H), 6.36 (dd, J = 16.0, 3.4 Hz, 1H), 4.75, 4.71 (s, total 2H), 4.25, 4.15 (d, J = 5.7, 3.7 Hz, total 1H), 2.85, 2.84 (s, total 6H); ^{13}C NMR of a 57 : 43 mixture of two rotamers: δ = 167.14, 167.08, 143.82, 143.78, 141.1, 140.6, 137.5, 137.2, 137.1, 137.02, 136.96, 136.90, 135.3, 135.2, 129.8, 129.1, 128.9, 128.7, 128.4, 128.0, 127.9, 127.6, 126.6, 126.4, 126.1, 123.0, 121.8, 117.3, 114.7, 114.6, 114.2, 114.1, 50.6, 49.1, 48.3, 47.6, 38.31, 38.27; IR (KBr, cm^{-1}): 3121, 2926, 1650, 1609, 1458, 1419, 1392, 1175, 1078, 967, 729, 598; EI-MS (m/z): 450 (17%, M$^+$), 342 (100%), 90. Anal.

Calcd for $C_{24}H_{26}N_4O_3S$: C, 63.98; H, 5.82; N, 12.44. Found: C, 63.93; H, 5.73; N, 12.28.

(*E*)-*N*-Benzyl-*N*-[3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-2-propenyl]propenamide (47). To the allyl amine **44b** (300 mg, 0.936 mmol) and triethylamine (127 mg, 1.40 mmol) in dry CH_2Cl_2 at 0 °C was added acryloyl chloride (170 mg, 1.70 mmol) dropwise and stirred at room temperature for 3 h, after which water was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The solution was concentrated and the residue was purified by flash chromatography (hexane–EtOAc, 4 : 1), yielding **47** as a white solid (40% yield, 140 mg). mp: 86–88 °C. ^{1}H NMR (300 MHz) of 56 : 44 mixture of two rotamers: δ = 7.83, 7.82 (s, total 1H), 7.38–7.17 (m, 5H), 7.09 (s, 1H), 6.63–6.52 (m, 1H), 6.48–6.38 (m, 2H), 6.36–6.27 (m, 1H), 5.71 (td, J = 9.9, 2.1 Hz, 1H), 4.69, 4.61 (s, 2H), 4.19, 4.04 (d, J = 5.4 Hz, 3.9 Hz, total 2H), 2.86, 2.84 (s, total 6H); ^{13}C NMR (75 MHz): δ = 141.0, 140.5, 137.3, 137.0, 136.8, 136.7, 129.0, 128.7, 128.3, 127.8, 127.6, 127.5, 126.5, 126.1, 125.9, 123.1, 121.9, 114.5, 114.1, 50.3, 48.8, 48.2, 47.3, 38.2; IR (neat, cm^{-1}) = 2927, 1647, 1612, 1450, 1421; HRMS (ESI): calcd for $C_{18}H_{23}N_4O_3S$ (M+H)$^+$ 375.1485, found 375.1485.

(*E*,*E*)-*N*-Benzyl-3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-*N*-[3-(1-dimethyl-sulfamoyl-1*H*-imidazol-4-yl)-2-propenyl]-2-propenamide (48). Following GP-D using benzylamine **51a** (320 mg, 1.00 mmol) and the imidazolyl acid (368 mg, 1.50 mmol) afforded the corresponding amide **48** (427 mg, 78%) as a colorless solid after flash chromatography (EtOAc–MeOH, 9 : 1). mp: 131–132 °C. ^{1}H NMR of a 59 : 41 mixture of two rotamers: δ = 7.86, 7.83 (s, total 1H), 7.824, 7.819 (s, total 1H), 7.64, 7.61 (d, J = 5.7, 5.7 Hz, total 1H), 7.36–7.27 (m, 5H), 7.22–7.21, 7.17–7.14 (m, total 2H), 7.09, 7.07 (s, total 1H), 6.48–6.41 (m, 1H), 6.35–6.32 (m, 1H), 4.73, 4.71 (s, total 2H), 4.21, 4.15 (d, J = 5.7, 4.1 Hz, total 2H), 2.87, 2.863, 2.860, 2.84 (s, total 12H); ^{13}C NMR of a 59 : 41 the mixture of two rotamers: δ = 166.9, 166.8, 141.1, 140.8, 140.1, 140.0, 137.50, 137.47, 137.0, 136.9, 136.7, 133.3, 133.2, 129.0, 128.7, 128.3, 127.8, 127.5, 126.8, 126.2, 123.0, 121.9, 118.5, 118.4, 118.33, 118.30, 114.5, 114.1, 60.5, 50.4, 48.9, 48.2, 47.2, 38.3; IR (KBr, cm^{-1}): 3126, 2926, 1655, 1611, 1460, 1420, 1391, 1263, 1175, 1078, 1007, 967, 729, 598; EI-MS (m/z): 439 (32%, M$^+$), 90 (100%). Anal. Calcd for $C_{23}H_{29}N_7O_5S_2 \cdot 1/2H_2O$: C, 49.63; H, 5.43; N, 17.61. Found: C, 49.58; H, 5.39; N, 17.24.

(*E*,*E*)-*N*-Benzhydryl-*N*-[3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-2-propenyl]-3-phenyl-2-propenamide (54). To amine **44b** (312 mg, 0.79 mmol) in anhydrous THF (6 mL) at 0 °C was added NaH (60% oil dispersion, 42 mg, 1.06 mmol) and stirred at 0 °C for 30 min. Cinnamoyl chloride (181 mg, 1.06 mmol) in THF (1.5 mL) was added to the above anion solution at 0 °C dropwise. Then the reaction mixture was allowed to warm up to room temperature and stirred overnight. After being quenched carefully with a small amount of water, the reaction mixture was diluted with CH_2Cl_2, washed with H_2O (2×), brine, dried (Na_2SO_4) and concentrated. The crude oil was purified by chromatography (hexane–EtOAc, 3 : 1) to afford the title product as a colorless solid (312 mg, 75%). mp: 88–89 °C. ^{1}H NMR of the 65 : 35 mixture of two rotamers: δ = 7.82, 7.70 (d, J = 15.4, 15.6 Hz, total 1H), 7.73 (s, 1H), 7.52–7.48, 7.38–7.24 (m, total 15H), 6.92, 6.80 (d, J = 15.4, 15.6 Hz, total 1H), 6.84, 6.51 (s, total 1H), 6.10–5.83 (m, total 2H), 4.29, 4.19 (s, total 2H), 2.80 (s, 6H); ^{13}C NMR of a 65 : 35 mixture of two rotamers: δ = 167.7, 167.3, 143.9, 143.1, 141.4, 140.7, 139.3, 136.8, 136.7, 135.3, 129.8, 129.2, 129.0, 128.9, 128.6, 128.1, 127.9, 127.6, 127.2, 122.4, 121.7, 118.5, 118.2, 114.1, 113.7, 65.5, 61.6, 47.1, 38.2; IR (KBr, cm^{-1}): 3028, 1648, 1605, 1455, 1392, 1175, 1077, 966; EI-MS (m/z): 526.3 (M$^+$, 25%), 418.4 (100%); HRMS (ESI) calcd for $C_{17}H_{19}N_2O_3S$ (M+H)$^+$ 527.2111, found 527.2127.

(*E*,*E*)-*N*-Benzhydryl-3-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-*N*-[3-(1-dimethyl-sulfamoyl-1*H*-imidazol-4-yl)-2-propenyl]-2-propenamide (55). **55** was prepared from amine **44b** (2.50 g, 6.31 mmol) and acid (2.32 g, 9.46 mmol) according to GP-D. The crude sample was purified through a short plug of SiO_2 (EtOAc–MeOH, 4 : 0.15) to provide the title compound (3.87 g, 98%) as a colorless solid. mp: 151–152 °C. ^{1}H NMR of a 65 : 35 mixture of two rotamers: δ = 7.83, 7.81 (s, total 1H), 7.70 (s, 1H), 7.61, 7.56 (d, J = 14.9, 14.7 Hz, total 1H), 7.38–7.20 (m, total 11H), 7.18, 6.88 (s, total 1H), 6.83, 6.61 (s, total 1H), 5.96–5.91 (m, 1H), 5.84–5.79 (m, 1H), 4.26, 4.15 (d, J = 4.2, 4.6 Hz, total 2H), 2.83 (s, 6H), 2.78 (s, 6H); ^{13}C NMR of a 65 : 35 mixture of two rotamers: δ = 167.3, 167.1, 141.4, 140.8, 140.2, 140.0, 139.4, 139.2, 137.4, 136.7, 133.3,133.0, 129.1, 128.7, 128.5, 128.0, 127.6, 127.1, 127.0, 122.0, 121.8, 122.0, 121.8, 119.4, 119.0, 118.3, 114.1, 113.6, 65.1, 61.7, 47.1, 46.8, 38.3, 38.2; IR (KBr, cm^{-1}): 3137, 2928, 1654, 1610, 1392, 1264, 1175, 1077, 966, 728, 597; EI-MS (m/z): 624.2 (M$^+$+1, 28%), 593.5 (15%), 514.6 (34%), 430.0 (100%), 228.2 (83%). Anal. Calcd for $C_{29}H_{33}N_7O_5S_2 \cdot H_2O$: C, 54.27; H, 5.50; N, 15.28. Found: C, 54.01; H, 5.17; N, 14.73.

(3a*S,4*S**,4a*R**,7a*S**)-6-Benzyl-3-dimethylsulfamoyl-3a,4a,5,6,7,7a-hexahydro-5-oxo-5*H*-imidazo[4,5-*f*]isoindole-4-carboxylic acid, ethyl ester (59).** Compound **59** was prepared by the general Diels–Alder reaction procedure from purified **45** (60 mg, 0.13 mmol) at 68 °C in benzene for 12 h. Flash chromatography (hexane–EtOAc, 15 : 85) afforded the product **59** (57 mg, 95%) as a colorless solid. mp: 64–66 °C. ^{1}H NMR: δ = 7.52 (s, 1H), 7.34–7.27 (m, 3H), 7.23–7.21 (m, 2H), 6.03 (dd, J = 3.7, 3.7 Hz, 1H), 4.49 (d, J = 14.7 Hz, 1H), 4.45 (ddd, J = 9.0, 3.7, 1.6 Hz, 1H), 4.42 (d, J = 14.7 Hz, 1H), 4.16 (dq, J = 7.1, 3.7 Hz, 1H), 4.12 (dq, J = 7.1, 3.7 Hz, 1H), 3.63 (dd, J = 9.0, 8.2 Hz, 1H), 3.45 (dd, J = 9.5, 6.6 Hz, 1H), 3.26 (dd, J = 9.9, 9.5 Hz, 1H), 2.91 (s, 6H), 2.35 (m, 1H), 2.30 (dd, J = 12.6, 8.2 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR: δ = 171.5, 153.9, 153.6, 136.3, 128.9, 128.2, 127.9, 111.6, 61.5, 58.6, 48.2, 47.9, 47.0, 40.4, 39.3, 38.1, 14.2; IR (KBr, cm^{-1}): 3053, 3013, 2987, 2939, 1731, 1696, 1556, 1377, 1258, 1157, 970, 719, 595; EI-MS (m/z): 446 (51%, M$^+$), 338, 293 (100%), 265. Anal. Calcd for $C_{21}H_{26}N_4O_5S \cdot 1/2H_2O$: C, 55.37; H, 5.97; N, 12.30. Found: C, 55.81; H, 5.77; N, 12.34.

(4*S,4a*R**,7a*S**)-6-Benzyl-3-dimethylsulfamoyl-4a,5,6,7,7a,8-hexahydro-5-oxo-5*H*-imidazo[4,5-*f*]isoindole-4-carboxylic acid, ethyl ester (60).** Compound **60** was prepared by the general Diels–Alder reaction procedure from the crude sample **45** (180 mg, 0.56 mmol) at 68 °C in benzene for 10 h. Chromatography (hexane–EtOAc: 20/80) afforded the initial adduct **59** (18 mg, 10%) and the aromatized product **60** (144 mg, 80%) as a colorless solid. mp: 155–156 °C. ^{1}H NMR (benzene-d6): δ = 7.70 (s, 1H), 7.06–6.98 (m, 5H), 4.43 (dq, J = 7.1, 3.6 Hz, 1H), 4.30 (d, J = 14.7 Hz, 1H), 4.24 (dq, J = 7.1, 3.6 Hz, 1H), 3.93 (d, J = 10.8 Hz,

1H), 3.91 (d, J = 14.7 Hz, 1H), 2.57 (dd, J = 12.9, 10.8 Hz, 1H), 2.39 (m, 1H), 2.35 (dd, J = 9.4, 7.1 Hz, 1H), 2.10 (m, 1H), 2.09 (s, 6H), 2.04 (dd, J = 9.6, 9.4 Hz, 1H), 1.37 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR: δ = 171.9, 141.9, 139.1, 136.2, 128.9, 128.3, 127.9, 123.5, 61.8, 49.5, 49.4, 46.7, 42.0, 38.2, 37.4, 28.5, 14.1; IR (KBr, cm^{-1}): 3132, 3056, 3028, 2982, 2933, 1731, 1698, 1474, 1421, 1392, 1329, 1275, 1251, 1186, 1028, 967, 762, 730, 579; EI-MS (m/z): 446 (16%, M$^+$), 203, 107 (100%). Anal. Calcd for $C_{21}H_{26}N_4O_5S{\cdot}1/2H_2O$: C, 55.37; H, 5.97; N, 12.30. Found: C, 55.44; H, 5.77; N, 12.41.

(3a*S,4*S**,4a*R**,7a*S**)-6-Benzyl-3-dimethylsulfamoyl-3a,4a,5,6,7,7a-hexahydro-5-oxo-4-phenyl-5*H*-imidazo[4,5-*f*]isoindole (61) and (4*S**,4a*R**,7a*S**)-6-benzyl-3-dimethylsulfamoyl-4a,5,6,7,7a,8-hexahydro-5-oxo-4-phenyl-5*H*-imidazo[4,5-*f*] isoindole (62).** Compounds **61** and **62** were prepared by the general Diels–Alder reaction procedure from **46** (200 mg, 0.44 mmol) at 130 °C in benzene for 45 h. Chromatography (EtOAc–hexane, 85 : 15) afforded the initial adduct **61** (54 mg, 27%) and the aromatized adduct **62** (102 mg, 51%).

Data for **61**: A colorless solid. mp: 163–164 °C. ^{1}H NMR: δ = 7.49 (s, 1H), 7.33–7.15 (m, 8H), 7.08–7.06 (m, 2H), 6.11 (dd, J = 3.9, 3.7 Hz, 1H), 4.73 (ddd, J = 9.5, 3.7, 2.3 Hz, 1H), 4.48 (d, J = 14.9 Hz, 1H), 4.37 (d, J = 14.9 Hz, 1H), 3.88 (dd, J = 9.5, 8.7 Hz, 1H), 3.47 (dd, J = 9.4, 6.9 Hz, 1H), 3.21 (dd, J = 10.3, 9.4 Hz, 1H), 2.46 (m, 1H), 2.39 (s, 6H), 2.13 (dd, J = 13.1, 8.7 Hz, 1H); ^{13}C NMR: δ = 172.8, 154.9, 154.7, 142.0, 136.5, 128.9, 128.7, 128.4, 128.2, 127.8, 127.1, 112.1, 60.4, 54.2, 48.2, 46.9, 40.3, 39.8, 37.0; IR (KBr, cm^{-1}): 3061, 3039, 2928, 2861, 1689, 1551, 1360, 1157, 1076, 971, 702, 591; EI-MS (m/z): 450 (100%, M$^+$), 342. Anal. Calcd for $C_{24}H_{26}N_4O_3S$: C, 63.98; H, 5.82; N, 12.44. Found: C, 64.06; H, 5.88; N, 12.38.

Data for **62**: A colorless solid. mp: 177.0–177.5 °C. ^{1}H NMR: δ = 7.85 (s, 1H), 7.38–7.21 (m, 7H), 7.20–7.16 (m, 3H), 4.53 (d, J = 10.1 Hz, 1H), 4.48 (d, J = 14.7 Hz, 1H), 4.31 (d, J = 14.7 Hz, 1H), 3.27 (dd, J = 9.4, 7.3 Hz, 1H), 3.00 (dd, J = 10.1, 9.4 Hz, 1H), 2.85 (dd, J = 14.9, 4.1 Hz, 1H), 2.69 (ddd, J = 14.9, 11.9, 1.8 Hz, 1H), 2.49 (dd, J = 12.8, 10.1 Hz, 1H), 2.39–2.31 (m, 1H), 2.36 (s, 6H); ^{13}C NMR: δ = 173.2, 143.1, 141.3, 139.4, 136.5, 128.9, 128.8, 128.3, 127.7, 127.1, 54.6, 48.8, 46.6, 40.8, 39.3, 37.1, 28.8; IR (KBr, cm^{-1}): 3057, 3027, 2919, 2851, 1693, 1420, 1387, 1144, 970, 757, 726, 699, 587; EI-MS (m/z): 450 (32%, M$^+$), 342 (100%), 90. Anal. Calcd for $C_{24}H_{26}N_4O_3S$: C, 63.98; H, 5.82; N, 12.44. Found: C, 64.18; H, 5.93; N, 12.27.

(4a*R/*S**,7a*S**)-6-Benzyl-3-dimethylsulfamoyl-4a,5,6,7,7a,8-hexahydro-5-oxo-5*H*-imidazo[4,5-*f*]isoindole (63).** Compound **63** was prepared by the general Diels–Alder reaction procedure from **47** (75.0 mg, 0.20 mmol) at 145 °C in benzene for 60 h. The solution was concentrated and the residue was purified by flash chromatography (EtOAc–methanol, 49 : 1), yielding **63** as an inseparable mixture of *cis* and *trans* isomers (ratio = 3 : 2) as a white solid (16 mg, 21% yield). mp: 105–107 °C; ^{1}H NMR (300 MHz): δ = 7.97, 7.94 (s, total 1H), 7.51–7.43 (m, 3H), 7.41–7.37 (m, 2H), 4.64, 4.63 (d, J = 8.7 and 9.6 Hz, total 2H), 3.61, 3.53 (dd, m, J = 9.6, 4.8 Hz, total 2H), 3.26 (t, J = 9.6 Hz, 1H), 3.09, 3.07 (2xs, total 6H), 2.97 (m, 2H), 2.84 (m, 1H), 2.71–2.57 (m, 1H), 2.48–2.37 (m, 1H); ^{13}C NMR (75 MHz): δ = 174.6, 174.0, 139.1, 137.7, 137.2, 136.6, 136.3, 129.0, 128.4, 128.3, 128.0, 127.9, 125.2, 123.4, 52.0, 50.3, 47.4, 46.9, 45.3, 41.2, 38.4, 38.3, 30.8, 29.9, 28.1, 26.2, 23.1, 19.6; IR (neat, cm^{-1}): = 2924, 1687, 1443, 1389; HRMS (ESI): calcd for $C_{18}H_{23}N_4O_3S$ (M+H)$^+$ 375.1485, found 375.1485.

(4*S,4a*R**,7a*S**)-6-Benzyl-3-dimethylsulfamoyl-4-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-4a,5,6,7,7a,8-hexahydro-5-oxo-5*H*-imidazo[4,5-*f*]isoindole (64) and (4*S**,4a*R**,7a*S**)-6-benzyl-3-dimethylsulfamoyl-4-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-4a,5,6,7,7a,8-hexahydro-7-oxo-5*H*-imidazo[4,5-*f*]isoindole (65).** Compounds **64** and **65** were prepared by the general Diels–Alder reaction procedure from **48** (62 mg, 0.11 mmol) at 95 °C in benzene for 72 h. Purification by preparative TLC ($CHCl_3$–MeOH, 95 : 5) afforded adduct **64** (31 mg, 50%) and adduct **65** (20 mg, 32%).

Data for **64**: A colorless solid mp: 174.5–175 °C. ^{1}H NMR (benzene-d6): δ = 7.80 (s, 1H), 7.74 (s, 1H), 7.58 (s, 1H), 7.12–6.98 (m, 5H), 4.48 (d, J = 10.5 Hz, 1H), 4.35 (d, J = 14.9 Hz, 1H), 3.89 (d, J = 14.9 Hz, 1H), 2.83 (dd, J = 12.8, 10.5 Hz, 1H), 2.55 (dd, J = 14.6, 3.8 Hz, 1H), 2.40–2.32 (m, 2H), 2.29 (s, 6H), 2.12 (dd, J = 9.7, 9.7 Hz, 1H), 1.95 (s, 6H), 1.48 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 173.2, 142.5, 141.0, 138.3, 136.4, 135.9, 128.9, 128.1, 127.8, 127.4, 117.2, 50.3, 48.9, 46.6, 38.5, 38.4, 37.8, 34.5, 28.6; IR (KBr, cm^{-1}): 2928, 1693, 1389, 1274, 1175, 1076, 964, 725, 600; EI-MS (m/z): 547 (M$^+$, 5%), 152, 107, 90 (100%). Anal. Calcd for $C_{23}H_{29}N_7O_5S_2{\cdot}H_2O$: C, 48.84; H, 5.52; N, 17.33. Found: C, 48.75; H, 5.32; N, 17.12.

Data for **65**: A colorless solid. mp: 177.5–178.5 °C. ^{1}H NMR: δ = 7.76 (d, J = 1.4 Hz, 1H), 7.73 (s, 1H), 7.33–7.27 (m, 3H), 7.22–7.20 (m, 2H), 6.93 (d, J = 1.4 Hz, 1H), 4.59 (d, J = 14.9 Hz, 1H), 4.33 (d, J = 14.9 Hz, 1H), 4.06 (d, J = 10.1 Hz, 1H), 3.19–3.17 (m, 2H), 3.15 (ddd, J = 16.0, 4.7, 1.4 Hz, 1H), 2.87–2.83 (m, 1H), 2.833 (s, 6H), 2.827 (s, 6H), 2.57 (ddd, J = 12.8, 11.5, 4.7 Hz, 1H), 2.49–2.43 (m, 1H); ^{13}C NMR: δ = 173.4, 143.4, 141.7, 137.5, 136.4, 136.3, 128.9, 128.3, 127.8, 127.2, 114.7, 49.4, 46.9, 46.2, 44.7, 38.2, 26.1; IR (KBr, cm^{-1}): 3113, 2927, 1692, 1390, 1268, 1175, 1075, 965, 729, 599, 584; EI-MS (m/z): 547 (40%, M$^{+)}$, 440, 406, 357, 151 (100%).

(3a*S,4*S**,4a*R**,7a*S**)-6-Benzhydryl-3-dimethylsulfamoyl-3a,4a,5,6,7,7a-hexahydro-5-oxo-4-phenyl-5*H*-imidazo[4,5-*f*]isoindole (66) and (4*S**,4a*R**,7a*S**)-6-benzhydryl-3-dimethylsulfamoyl-4a,5,6,7,7a,8-hexahydro-5-oxo-4-phenyl-5*H*-imidazo[4,5-*f*]isoindole (67).** Compounds **66** and **67** were prepared by the general Diels–Alder reaction procedure from **54** (66 mg, 0.12 mmol) at 95 °C for 44 h. Chromatography (hexane–EtOAc, 1 : 4) afforded the initial adduct **66** (25 mg, 38%) and the aromatized adduct **67** (34 mg, 52%).

Data for the initial cycloadduct **66**: A colorless semi-solid. ^{1}H NMR: δ = 7.50 (s, 1H), 7.39–7.22 (m, 8H), 7.07–7.05 (m, 2H), 6.53 (s, 1H), 6.10 (dd, J = 3.9, 3.9 Hz, 1H), 4.77 (ddd, J = 9.3, 3.9, 2.3 Hz, 1H), 3.92 (dd, J = 9.3, 8.6 Hz, 1H), 3.56 (dd, J = 9.8, 6.6 Hz, 1H), 3.06 (dd, J = 10.1, 9.8 Hz, 1H), 2.54 (m, 1H), 2.40 (s, 6H), 2.14 (dd, J = 13.1, 8.6 Hz, 1H); ^{13}C NMR: δ = 172.8, 154.9, 154.8, 141.9, 138.9, 138.6, 129.1, 128.8, 128.7, 128.3, 127.9, 127.8, 127.7, 127.1, 111.9, 60.5, 58.6, 54.3, 46.2, 40.3, 39.9, 37.0; IR (KBr, cm^{-1}): 1694, 1553, 1495, 1455, 1400, 1361, 1158,1076; EI-MS (m/z): 526.4 (M$^+$, 79%), 438.7 (78%), 413.9 (100%). Anal. Calcd for $C_{30}H_{30}N_4O_3S{\cdot}1/2H_2O$: C, 67.27; H, 5.83; N, 10.46. Found: C, 67.37; H, 5.54; N, 10.45.

Data for aromatized cycloadduct **67**: A colorless solid. mp: 171–172. ^{1}H NMR: δ = 7.86 (s, 1H), 7.35–7.27 (m, 10H), 7.19–7.17 (m, 1H), 7.14–7.12 (m, 4H), 6.51 (s, 1H), 4.59 (d, J = 10.1 Hz, 1H), 3.39 (dd, J = 9.6, 6.4 Hz, 1H), 2.89–2.83 (m, 2H), 2.68 (ddd, J = 15.1, 10.8, 2.5 Hz, 1H), 2.52 (dd, J = 13.1, 10.1 Hz, 1H), 2.49–2.45 (m, 1H), 2.36 (s, 6H); ^{13}C NMR: δ = 173.3, 143.1, 141.3, 139.4, 138.9, 138.7, 129.2, 128.9, 128.7, 128.3, 127.9, 127.7, 127.5, 127.1, 58.4, 54.7, 47.0, 40.8, 39.5, 37.1, 29.8, 28.7; IR (KBr, cm^{-1}): 2923, 2853, 1694, 1411, 1390, 1271, 1244, 1179, 1145, 970; EI-MS (m/z): 526.3 (M$^+$, 100%), 166.2 (25%). Anal. Calcd for $C_{30}H_{30}N_4O_3S\cdot1/2H_2O$: C, 67.27; H, 5.83; N, 10.46. Found: C, 67.70; H, 5.65; N, 10.54.

(4*S,4a*R**,7a*S**)-6-Benzhydryl-3-dimethylsulfamoyl-4-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-4a,5,6,7,7a,8-hexahydro-5-oxo-5*H*-imidazo[4,5-*f*]isoindole (68) and (4*S**,4a*R**,7a*S**)-6-benzhydryl-3-dimethylsulfamoyl-4-(1-dimethylsulfamoyl-1*H*-imidazol-4-yl)-4a,5,6,7,7a,8-hexahydro-7-oxo-5*H*-imidazo[4,5-*f*]-isoindole (69).** Compounds **68** and **69** were prepared by the general Diels–Alder reaction procedure from **55**. On a small scale: **55** (62 mg, 0.1 mmol) was heated in benzene (1.0 mL) at 95 °C for 42 h. Chromatography (EtOAc–MeOH, 4 : 0.5) afforded the normal Diels–Alder adduct **68** (35 mg, 56%) and the inverse electron demand adduct **69** (24 mg, 39%). On a larger scale: **55** (1.25 g, 2.00 mmol) was heated in benzene (20.0 mL) at 95 °C for 51 h. The solution was then cooled to room temperature and the resulting white precipitate was collected and rinsed with a small amount of benzene (2×) to afford the pure **68** (579 mg, 46%). The benzene rinsings were combined with the previous benzene filtrate and concentrated under vacuum to afford an oily product (~700 mg), which ^{1}H NMR indicated contained mainly **69** with some impurities and a trace amount of **72**. The crude oil was then passed through a short plug of SiO_2 (EtOAc–MeOH, 5 : 1) to afford pure **69** (424 mg, 34%).

Data for adduct **68**: A colorless solid. mp: 149–150 °C. ^{1}H NMR (benzene-d6): δ = 7.81 (s, 1H), 7.72 (s, 1H), 7.55 (s, 1H), 7.19–7.00 (m, 8H), 6.99–6.92 (m, 2H), 6.72 (s, 1H), 4.52 (d, J = 10.5 Hz, 1H), 2.94 (dd, J = 13.1, 10.5 Hz, 1H), 2.75 (dd, J = 9.6, 7.1 Hz, 1H), 2.52 (dd, J = 15.0, 4.2 Hz, 1H), 2.33 (dd, J = 10.1, 9.6 Hz, 1H), 2.29–2.26 (m, 1H), 2.28 (s, 6H), 1.96 (s, 6H), 1.67 (m, 1H);^{13}C NMR: δ = 173.2, 142.4, 141.0, 138.9, 138.7, 138.2, 136.0, 129.1, 128.71, 128.68, 127.9, 127.8, 127.6, 127.4, 117.2, 58.4, 50.4, 47.1, 38.7, 38.3, 37.8, 34.5, 28.5; IR (KBr, cm^{-1}): 2929, 1686, 1474, 1416, 1388, 1272, 1175, 1075, 964; EI-MS (m/z): 623.6 (M$^+$, 43%), 430.1 (74%), 82.8 (100%). Anal. Calcd for $C_{29}H_{33}N_7O_5S_2\cdot1/2H_2O$: C, 55.05; H, 5.42; N, 15.50. Found: C, 54.87; H, 5.03; N, 15.20.

Data for adduct **69**: A colorless solid. mp: 167–169 °C. ^{1}H NMR (benzene-d6): δ = 7.62 (s, 1H), 7.60 (s, 1H), 7.14–7.07 (m, 7H), 7.03–6.96 (m, 3H), 6.95 (s, 1H), 6.80 (s, 1H), 3.88 (d, J = 10.1 Hz, 1H), 3.44 (dd, J = 9.6, 6.9 Hz, 1H), 3.40 (dd, J = 11.2, 4.8 Hz, 1H), 2.98 (dd, J = 9.9, 9.9 Hz, 1H), 2.94 (m, 1H), 2.58 (m, 1H), 2.21 (s, 6H), 2.09 (ddd, J = 12.3, 12.0, 5.0 Hz, 1H), 1.99 (s, 6H); ^{13}C NMR: δ = 173.6, 143.2, 141.5, 138.4, 137.4, 136.4, 129.3, 128.8, 128.7, 128.0, 127.7, 127.5, 127.2, 114.9, 58.53, 58.48, 47.0, 45.9, 44.9, 38.3, 38.1, 26.0; IR (KBr, cm^{-1}): 2922, 1689, 1475, 1417, 1390, 1266, 1175, 1077, 965; EI-MS (m/z): 624.1 (M$^+$+1, 74%), 516.8 (34%), 166.7 (100%), 150.7 (61%); HRMS (ESI) calcd for $C_{28}H_{34}N_7O_5S_2$ (M+H)$^+$ 624.2057, found 624.2086.

Acknowledgements

We are grateful to the Robert A. Welch Foundation (Y-1362 (CJL) and Y-1289 (HVRD)), National Institutes of Health (GM065503) and the NSF (CHE-0234811, CHE-9601771) for supporting our efforts in this area.

Notes and references

1 Y. He, H. Du, R. Sivappa and C. J. Lovely, *Synlett*, 2006, 965.
2 H. Hoffmann and T. Lindel, *Synthesis*, 2003, 1753; S. M. Weinreb, *Nat. Prod. Rep.*, 2007, **24**, 931; B. Forte, B. Malgesini, C. Piutti, F. Quartieri, A. Scolaro and G. Papeo, *Mar. Drugs*, 2009, **7**, 705.
3 J. D. Sullivan, R. L. Giles and R. E. Looper, *Curr. Bioact. Comp*, 2009, **5**, 39; P. B. Koswatta and C. J. Lovely, *Nat. Prod. Rep.*, 2011, DOI: 10.1039/c0np00001a.
4 P. B. Koswatta, R. Sivappa, H. V. R. Dias and C. J. Lovely, *Org. Lett.*, 2008, **10**, 5055; P. B. Koswatta and C. J. Lovely, *Tetrahedron Lett.*, 2009, **50**, 4998; P. B. Koswatta, R. Sivappa, H. V. R. Dias and C. J. Lovely, *Synthesis*, 2009, 2970; P. B. Koswatta and C. J. Lovely, *Tetrahedron Lett.*, 2010, **51**, 164; P. B. Koswatta and C. J. Lovely, *Chem. Commun.*, 2010, **46**, 2148.
5 R. B. Kinnel, H. P. Gehrken and P. J. Scheuer, *J. Am. Chem. Soc.*, 1993, **115**, 3376; R. B. Kinnel, H.-P. Gehrken, R. Swali, G. Skoropowski and P. J. Scheuer, *J. Org. Chem.*, 1998, **63**, 3281.
6 T. Kato, Y. Shizuri, H. Izumida, A. Yokoyama and M. Endo, *Tetrahedron Lett.*, 1995, **36**, 2133.
7 J. Kobayashi, M. Suzuki and M. Tsuda, *Tetrahedron*, 1997, **53**, 15681.
8 C. J. Lovely, H. Du, R. Sivappa, M. K. Bhandari, Y. He and H. V. R. Dias, *J. Org. Chem.*, 2007, **72**, 3741; C. J. Lovely, H. Du and H. V. R. Dias, *Org. Lett.*, 2001, **3**, 1319; C. J. Lovely, H. Du and H. V. R. Dias, *Heterocycles*, 2003, **60**, 1; Y. He, Y. Chen, H. Du, L. A. Schmid and C. J. Lovely, *Tetrahedron Lett.*, 2004, **45**, 5529.
9 C. J. Lovely, H. Du, Y. He and H. V. R. Dias, *Org. Lett.*, 2004, **6**, 735; R. Sivappa, P. Koswatta and C. J. Lovely, *Tetrahedron Lett.*, 2007, **48**, 5771.
10 Y. He, Y. Chen, H. Wu and C. J. Lovely, *Org. Lett.*, 2003, **5**, 3623; R. Sivappa, N. M. Hernandez, Y. He and C. J. Lovely, *Org. Lett.*, 2007, **9**, 3861; R. Sivappa, S. Mukherjee, H. V. R. Dias and C. J. Lovely, *Org. Biomol. Chem.*, 2009, **7**, 3215.
11 L. De Luca, *Curr. Med. Chem.*, 2006, **13**, 1.
12 J. Kobayashi, M. Tsuda, T. Murayama, H. Nakamura, Y. Ohizumi, M. Ishibashi, M. Iwamura, T. Ohta and S. Nozoe, *Tetrahedron*, 1990, **46**, 5579; P. A. Keifer, R. E. Schwartz, M. E. S. Koker, R. G. Hughes, Jr. D. Rittschof and K. L. Rinehart, *J. Org. Chem.*, 1991, **56**, 2965; D. H. Williams and D. J. Faulkner, *Tetrahedron*, 1996, **52**, 5381.
13 D. P. O'Malley, K. Li, M. Maue, A. L. Zografos and P. S. Baran, *J. Am. Chem. Soc.*, 2007, **129**, 4762; B. H. Northrop, D. P. O'Malley, A. L. Zografos, P. S. Baran and K. N. Houk, *Angew. Chem., Int. Ed.*, 2006, **45**, 4126; P. S. Baran, K. Li, D. P. O'Malley and C. Mitsos, *Angew. Chem., Int. Ed.*, 2006, **45**, 249; P. S. Baran, D. P. O'Malley and A. L. Zografos, *Angew. Chem., Int. Ed.*, 2004, **43**, 2674.
14 S. Urban, P. d. A. Leone, A. R. Carroll, G. A. Fechner, J. Smith, J. N. A. Hooper and R. J. Quinn, *J. Org. Chem.*, 1999, **64**, 731.
15 D. P. O'Malley, J. Yamaguchi, I. S. Young, I. B. Seiple and P. S. Baran, *Angew. Chem., Int. Ed.*, 2008, **47**, 3581; D. P. O'Malley, J. Yamaguchi, I. S. Young, I. B. Seiple and P. S. Baran, *Angew. Chem., Int. Ed.*, 2008, **47**, 3581; M. A. Zancanella and D. Romo, *Org. Lett.*, 2008, **10**, 3685.
16 S. Nishimura, S. Matsunaga, M. Shibazaki, K. Suzuki, K. Furihata, R. W. M. Van Soest and N. Fusetani, *Org. Lett.*, 2003, **5**, 2255.
17 S. Su, I. B. Seiple, I. S. Young and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 16490; A. Breder, G. M. Chinigo, A. W. Waltman and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 8514.
18 A. Grube and M. Köck, *Angew. Chem., Int. Ed.*, 2007, **46**, 2320; M. S. Buchanan, A. R. Carroll and R. J. Quinn, *Tetrahedron Lett.*, 2007, **48**, 4573; H. Kobayashi, K. Kitamura, K. Nagai, Y. Nakao, N. Fusetani, R. W. M. van Soest and S. Matsunaga, *Tetrahedron Lett.*, 2007, **48**, 2127.
19 I. J. McAlpine and R. W. Armstrong, *J. Org. Chem.*, 1996, **61**, 5674; L. E. Overman, B. N. Rogers, J. E. Tellew and W. C. Trenkle, *J. Am. Chem. Soc.*, 1997, **119**, 7159; G. Belanger, F.-T. Hong, L. E. Overman, B. N. Rogers, J. E. Tellew and W. C. Trenkle, *J. Org. Chem.*, 2002, **67**, 7880; J. D. Katz and L. E. Overman, *Tetrahedron*, 2004, **60**, 9559; S. G.

Koenig, S. M. Miller, K. A. Leonard, R. S. Lowe, B. C. Chen and D. J. Austin, *Org. Lett.*, 2003, **5**, 2203; H. Garrido-Hernandez, M. Nakadai, M. Vimolratana, Q. Li, T. Doundoulakis and P. G. Harran, *Angew. Chem., Int. Ed.*, 2005, **44**, 765; X. Tan and C. Chen, *Angew. Chem., Int. Ed.*, 2006, **45**, 4345; M. Nakadai and P. G. Harran, *Tetrahedron Lett.*, 2006, **47**, 3933; B. A. Lanman, L. E. Overman, R. Paulini and N. S. White, *J. Am. Chem. Soc.*, 2007, **129**, 12896; M. S. Bultman, J. Ma and D. Y. Gin, *Angew. Chem., Int. Ed.*, 2008, **47**, 6821; J. Hudon, T. A. Cernak, J. A. Ashenhurst and J. L. Gleason, *Angew. Chem., Int. Ed.*, 2008, **47**, 8885; T. A. Cernak and J. L. Gleason, *J. Org. Chem.*, 2008, **73**, 102; Q. Li, P. Hurley, H. Ding, A. G. Roberts, R. Akella and P. G. Harran, *J. Org. Chem.*, 2009, **74**, 5909; K. Namba, Y. Kaihara, H. Yamamoto, H. Imagawa, K. Tanino, R. M. Williams and M. Nishizawa, *Chem.–Eur. J.*, 2009, **15**, 6560; I. B. Seiple, S. Su, I. S. Young, C. A. Lewis, J. Yamaguchi and P. S. Baran, *Angew. Chem., Int. Ed.*, 2010, **49**, 1095; K. Namba, M. Inai, U. Sundermeier, T. J. Greshock and R. M. Williams, *Tetrahedron Lett.*, 2010, **51**, 6557; K. S. Feldman and A. Y. Nuriye, *Org. Lett.*, 2010, **12**, 4532–4535. For reviews see: D. E. N. Jacquot and T. Lindel, *Curr. Org. Chem.*, 2005, **9**, 1551; M. Köck, A. Grube, I. B. Seiple and P. S. Baran, *Angew. Chem., Int. Ed.*, 2007, **46**, 6586; H.-D. Arndt and M. Riedrich, *Angew. Chem., Int. Ed.*, 2008, **47**, 4785; B. Heasley, *Eur. J. Org. Chem.*, 2009, 1477; H. J. Jessen and K. Gademann, *Angew. Chem., Int. Ed.*, 2010, **49**, 2972.

20 K. Takao, R. Munakata and K. Tadano, *Chem. Rev.*, 2005, **105**, 4779; E. Ciganek, *Org. React. (N.Y.)*, 1984, **32**, 1.

21 For other examples of vinylimidazoles as dienes in the Diels–Alder reaction see: M. A. Walters and M. D. Lee, *Tetrahedron Lett.*, 1994, **35**, 8307; I. R. Greig, M. J. Tozer and P. T. Wright, *Org. Lett.*, 2001, **3**, 369; I. Kawasaki, N. Sakaguchi, N. Fukushima, N. Fujioka, F. Nikaido, M. Yamashita and S. Ohta, *Tetrahedron Lett.*, 2002, **43**, 4377; I. Kawasaki, N. Sakaguchi, A. Khadeer, M. Yamashita and S. Ohta, *Tetrahedron*, 2006, **62**, 10182 See also ref. 24 and 29.

22 M. A. Wuonola and J. M. Smallheer, *Tetrahedron Lett.*, 1992, **33**, 5697.

23 B. R. Lahue, S.-M. Lo, Z. K. Wan, G. H. C. Woo and J. K. Snyder, *J. Org. Chem.*, 2004, **69**, 7171; B. R. Lahue, S.-M. Lo, Z. K. Wan, G. H. C. Woo and J. K. Snyder, *J. Org. Chem.*, 2004, **69**, 7171.

24 The Lindel lab has reported one unsuccessful attempt to perform an intramolecular Diels–Alder reaction of a bis vinylimidazole substrate, in which the two units were linked *via* an urea. C. Poverlein, G. Breckle and T. Lindel, *Org. Lett.*, 2006, **8**, 819.

25 For a description of the motivation behind using 4-vinylimidazoles see ref. 8.

26 C. J. Lovely, R. Sivappa, S. Mukherjee, T. Doundoulakis, H. M. Fenton and Y. Muhammed, *Heterocycles*, 2010, **80**, 1353.

27 M. C. Pirrung and T. Pei, *J. Org. Chem.*, 2000, **65**, 2229.

28 This study was conducted in parallel with the intermolecular study, and we had experienced some initial success with trityl-protected vinylimidazoles, thus it appeared reasonable to evaluate this family of derivatives. Further, the preparation of the requisite allylic alcohol was known in the literature.

29 L. J. Cotterill, R. W. Harrington, W. Clegg and M. J. Hall, *J. Org. Chem.*, 2010, **75**, 4604–4607.

30 C. Sellier, A. Buschauer, S. Elz and W. Schunack, *Liebigs Ann. Chem.*, 1992, 317.

31 Most substrate preparations were not optimized, and in several cases the reactions were only conducted one time.

32 Similar results for intramolecular Diels–Alder reactions were obtained with vinyl furans: H. Kotsuki, M. Kawamura, M. Ochi and T. Tokoroyama, *Chem. Lett.*, 1981, 917.

33 T. N. Cayzer, M. N. Paddon-Row, D. Moran, A. D. Payne, M. S. Sherburn and P. Turner, *J. Org. Chem.*, 2005, **70**, 5561; T. N. Cayzer, M. N. Paddon-Row, D. Moran, A. D. Payne, M. S. Sherburn and P. Turner, *J. Org. Chem.*, 2005, **70**, 5561.

34 Attempts to react fumarates in an intermolecular sense have not been successful.

35 The corresponding Tr-protected derivatives were not evaluated as it was believed that there would be insufficient space for a terminal substituent to be accommodated. Furthermore, we and others (see ref. 29) have noted some thermal lability with this substituent.

36 J.-W. Kim, S. M. Adbdelaal, L. Bauer and N. E. Heimer, *J. Heterocycl. Chem.*, 1995, **32**, 611.

37 L. Bhagavatula, R. H. Premchandran, D. J. Plata, S. A. King and H. E. Morton, *Heterocycles*, 2000, **53**, 729. For similar protecting group migration see ref. 29.

38 M. E. Jung and G. Piizzi, *Chem. Rev.*, 2005, **105**, 1735.

39 M. C. Patel, T. Livinghouse and B. L. Pagenkopf, *Org. Synth*, 2003, **80**, 93.

40 J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. D. Harris and S. M. Weinreb, *Tetrahedron Lett.*, 1989, **30**, 5709.

41 P. Krishnamoorthy, R. Sivappa, H. Du and C. J. Lovely, *Tetrahedron*, 2006, **62**, 10555.

42 H. W. Gschwend, A. O. Lee and H. P. Meier, *J. Org. Chem.*, 1973, **38**, 2169; M. E. Jung and J Gervay, *J. Am. Chem. Soc.*, 1991, **113**, 224; M. E. Jung, *Synlett*, 1990, 186; M. E Jung, *Synlett*, 1999, 843; S. K. Bur, S. M. Lynch and A Padwa, *Org. Lett.*, 2002, **4**, 473.

43 A. M. Sarotti, I. Fernandez, R. A. Spanevello, M. A. Sierra and A. G. Suarez, *Org. Lett.*, 2008, **10**, 3389.

44 J. I. Levin, E. Turos and S. M. Weinreb, *Synth. Commun.*, 1982, **12**, 989.

45 I. R. Greig, M. J. Tozer and P. T. Wright, *Org. Lett.*, 2001, **3**, 369.

46 W. Oppolzer and J. Ruiz-Montes, *Helv. Chim. Acta*, 1993, **76**, 1266.

47 S. E. Denmark and T. K. Jones, *J. Org. Chem.*, 1982, **47**, 4595.