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A Diversity-Oriented Approach to Spirocyclic and Fused Hydantoins via Olefin Metathesis

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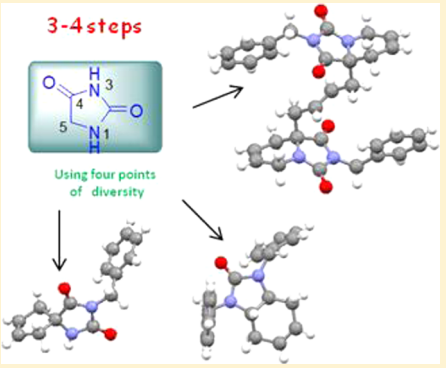
Supporting Information

ABSTRACT: An efficient and general method is reported to prepare a diverse series of 5,5-spirocyclic and 1,5-, 4,5-, and 3,4-fused bicyclic imidazolidinone derivatives based on selective alkylation and ring closing metathesis (RCM) by exploiting the four possible points of diversity in the hydantoin ring. Hydantoins containing trienes and tetraenes undergo selective RCM and cross metathesis to afford functionalized spirohydantoins. A tandem metathesis sequence involving ring closing−ring opening−ring closing and cross metathesis (RC−RO−RC−CM) occurred with a hydantoin triene to give a bicyclic hydantoin dimer in high yield. The fused bicylic dimer could participate in cross metathesis to produce a functionalized fused hydantoin derivative. The methodology establishes novel routes to unnatural amino acids, proline homologues, and cyclic vicinal diamines.



INTRODUCTION

Imidazolidine-2,4-dione derivatives, generally called hydantoins, represent an important class of biologically active scaffolds that have broad applications in medicinal chemistry.[1,2] Several derivatives exhibit antidiabetic, antitumor, antiviral, antiulcer, antiarrythmic and antimuscarinic activities.[2] In most cases, the biological activities arise from the different substituents that have been appended to the hydantoins.[1−5] In particular, spirohydantoins[3−6] and fused[7,8] bicyclic hydantoin derivatives have recently attracted much attention because they exhibit various biological activities. Some of these biologically active compounds are shown in Figure 1, which include naturally occurring spironucleoside[5] hydantocidin (X = O) and its carbocyclic analogue[4] (X = CH_2), spirocyclic core of biologically active alkaloids palau'amine and axinellamines,[9] tetrantoin,[10] tetrahydroisoquinoline-hydantoins.[8] Hydantoin derivatives have also been used as synthons for supramolecular chemistry[10] and β-strand mimetics.[11]

The synthesis of spiro-cyclopentane and cyclohexane hydantoin derivatives has been accomplished by cycloaddition using hydantoin dienophiles.[6] There exists very few methods[1−12] for the synthesis of spirohydantoins and fused bicyclic hydantoin derivatives. Therefore the development of efficient and elegant synthetic strategies for the preparation of new functionalized hydantoin derivatives would be highly desirable due to their similarity with drug-like molecules. Although ring-closing metathesis has emerged as one of the most powerful methods in organic synthesis,[13−16] there have been no reports on synthesis of spirocyclic hydantoins by using ring closing metathesis. Only few examples have dealt with the construction of six membered fused hydantoins using RCM, where amino acids have been used as the starting materials to prepare the hydantoin precursors.[17] On our efforts aimed at diversity oriented synthesis[18] of functionalized thiazole derivatives,[19] we recently reported ring-closing and cross metathesis of thiazolidinedione derivatives to generate a quick access to spirocyclic thiazolidinediones.[20] We describe here a ring-closing metathesis approach by utilizing the four possible points of diversity in hydantoin **1** to produce a diverse series of spirocyclic and 1,5-, 4,5- and 3,4-fused bicyclic imidazolidinone derivatives (Figure 2).

RESULTS AND DISCUSSION

Synthesis of Metathesis Precursors. For this purpose, a series of metathesis precursors were constructed from the commercially available hydantoin **1** by using 2−3 step procedures involving selective *N* and C(5) alkylation.[21] The results obtained with various combinations of alkyl and alkenyl halides and the hydantoin derivatives are summarized in Tables 1−4 and Scheme 1.

Hydantoin **1** was reacted with three different alkyl halides and allyl bromide in the presence of K_2CO_3 in DMF at 60 °C for 12 h. As shown in Table 1, this reaction afforded the corresponding 1,3-disubstituted hydantoin derivatives **2a−d** in good to high yields (54−75%). To prepare spirocyclic imidazolidinone ring systems it was decided to introduce diallyl groups at C(5) position. Diallylation was successfully carried out at C(5) position by reacting compounds **2** with base

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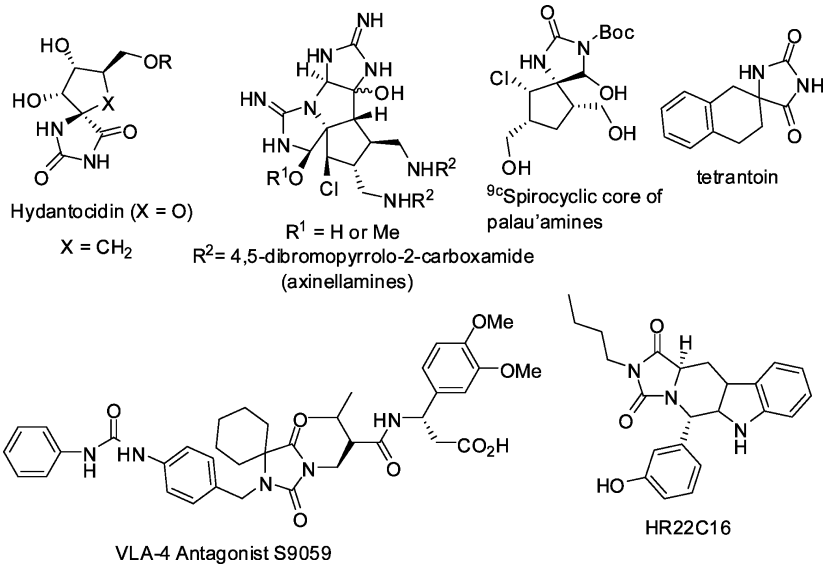


Figure 1. Bioactive molecules containing spiro and fused imidazalodinones.

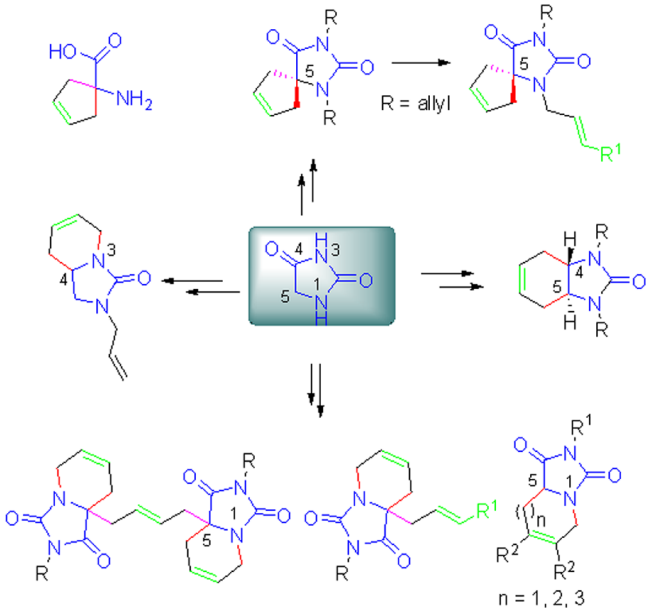


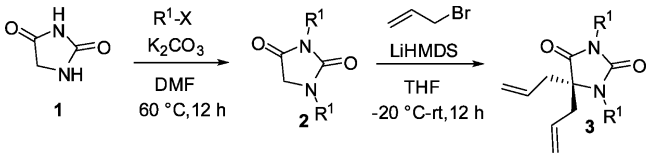
Figure 2. Hydantoin as a scaffold for diversity oriented synthesis of bicyclic and spirocyclic ring systems by RCM and CM.

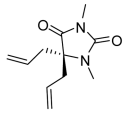
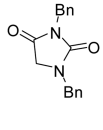
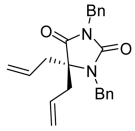
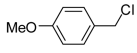
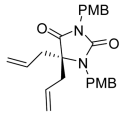
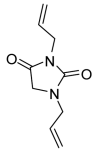
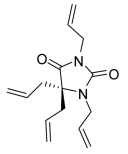
such as LiHMDS in THF. The reactions were stirred at −20 °C to rt for 12 h to afford diallyl imidazolidinedione derivatives **3a**−**3d** in 51−70% yields (Table 1, entries 1−4). The reaction did not proceed using other bases such as $K_2CO_3$and KO^{t}Bu.

In order to increase structural variation in the starting materials for our study, we have incorporated two different *N*-substituents in the hydantoin unit. First a selective *N*-protection of **1** was carried out at *N* (3) position using K_2CO_3 in DMF at rt to prepare **4a** and **4b**. Reacting **4** with 1 equiv of allyl bromide in the presence of K_2CO_3 at 50 °C afforded the corresponding 1,3-disubstituted hydantoins **5a,b** in 70−73% yields (Scheme 1). Hydantoin derivatives **4** were treated with excess allyl bromide in the presence of LiHMDS at −40 °C to rt for 12 h to give selectively the diallyl derivatives **6a,b** in 75−81% yields.

The disubstituted hydantoins **2d** and **5** were then treated with four different alkenyl bromides using LiHMDS as the base

Table 1. Preparation of 5,5-Diallyl-1,3-Disubstituted Imidazolidine-2,4-dione 3



Entry	R^1-X	product **2** yield (%)[a]	product **3** yield (%)[a]
1	MeI	 **2a** (54)	 **3a** (65)
2		 **2b** (75)	 **3b** (62)
3		 **2c** (75)	 **3c** (70)
4		 **2d** (70)	 **3d** (51)

[a]Yields are of isolated products after chromatography. Bn = benzyl, PMB = *p*-methoxy benzyl.

(Table 2). These alkylation reactions proceeded well to give the corresponding 1,3,5-trisubstituted hydantoin derivatives **7a**−**e** in yields ranging from 46 to 78%. Thus, we have an easy access to five different substrates with double bonds suitably

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Scheme 1. Synthesis of N-Protected Imidazolidine-2,4-diones

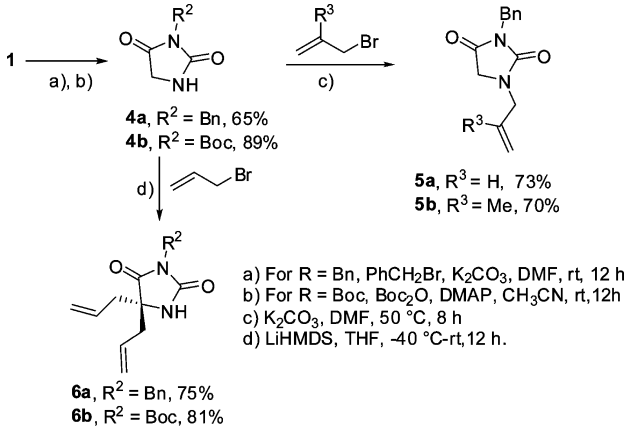
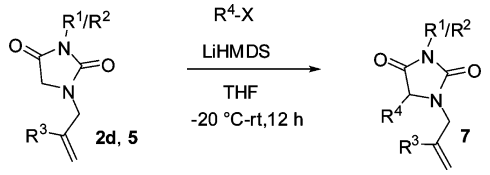
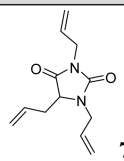
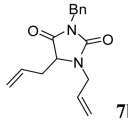
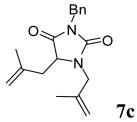
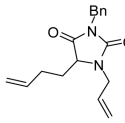
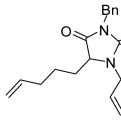


Table 2. Preparation of Trisubstituted Imidazolidine-2,4-dione 7



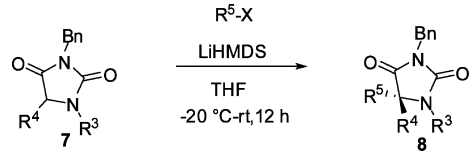
entry	substrate	R^4-X	Product	yield (%)[a]
1	**2d**		 **7a**	65
1	**5a**		 **7b**	78
2	**5b**		 **7c**	55
3	**5a**		 **7d**	48
4	**5a**		 **7e**	46

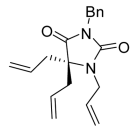
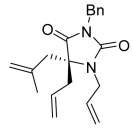
[a]Yields are of isolated products after chromatography.

positioned to carry out ring-closing metathesis. The hydantoin derivative **7b** was then alkylated with allyl bromides under similar conditions using LiHMDS to give the corresponding tetrasubstituted hydantoin derivatives **8a** and **8b** (Table 3). The products were obtained in high yields (68−85%).

Spirocyclic Hydantoins Using RCM. With the imdazolidinone derivatives **3**, **6** and **8** in our hands, we examined the

Table 3. Preparation of 5,5-Dialkenyl-1,3-Disubstituted Imidazolidine-2,4-dione 8



entry	substrate	R^5-X	product	yield (%)[a]
1	**7b**		 **8a**	68
2	**7b**		 **8b**	85

[a]Yields are of isolated products after chromatography.

RCM reaction utilizing the standard metathesis condition. Thus these compounds were treated with 2 mol % Grubbs' second-generation catalyst (**G-II**) in dichloromethane at rt for 8 h (Table 4). The desired 1,3-diazaspiro[4.4]non-7-ene-2,4-dione ring systems **9a**−**g** were obtained in excellent yields (entries 1−8, Table 4). Spirocyclic compounds are important synthetic targets that exhibit significant pharmacological activities due to their conformational rigidity. The diallyl hydantoin starting material **6a** containing a free NH group could be effectively used in RCM to give the corresponding spirocyclic compounds **9e** (entries 5, Table 4). The crystal structure[22] analysis of **9e** shows a dimeric structure that is held together by H-bonding between imide hydrogen donor and carbonyl oxygen acceptor (see Figure S1a, Supporting Information (SI).

It is interesting to note that RCM of tetraene **3d** afforded exclusively the spirocyclic compounds **9d** and none of the fused six membered or bridged bicyclic alternatives (entry 4, Table 4). Similarly, the RCM of trienes **8a** and **8b** resulted in highly selective generation of spirocyclic compounds **9f** and **9g**, respectively, in excellent yields (Table 4, entries 6−7). In these cases, spirocyclic compounds prevailed over the formation of corresponding fused ring systems.

Preparation of Cyclic Amino Acid. Since substituted hydantoins are important building blocks for the synthesis of non-natural amino acids by alkaline degradation, several rare cyclic quaternary amino acids can be easily available using our protocol.[23,24] Cyclic amino acids can control peptide conformations[24] and act as ligand for glutamate receptors.[25] RCM has been used for the synthesis of several amino acid derivatives.[13,26] We have exemplified that cyclic amino acid **10** can be efficiently prepared in high overall yield from the hydantoin **1** in four steps (Schemes and 2). The diallyl hydantoin **6b** was treated with 2 mol % Grubbs' second-generation catalyst (**G-II**) in dichloromethane at rt for 8 h to give the corresponding *N*-Boc spiro hydantoin **9h** in near quantitative yield (Scheme 2). Treatment of the *N*-Boc hydantoin derivative **9h** with $Ba(OH)_2$ in THF−H_2O at 180 °C for 72 h afforded the cyclopentene amino acid **10** in 93% yield (Scheme 2).[27]

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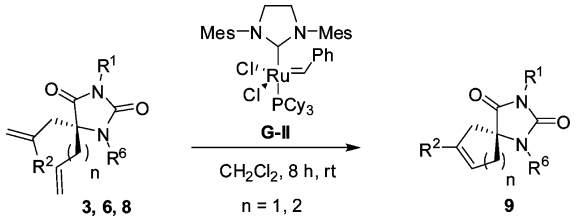
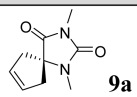
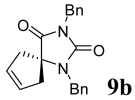
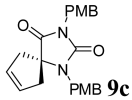
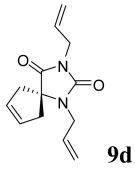
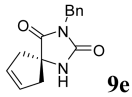
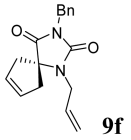
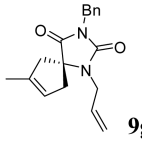
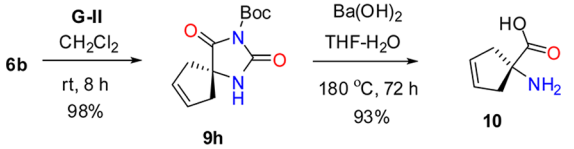
Table 4. Synthesis of Spirocylic Hydantoin Derivatives by RCM[a]



entry	substrate	product	yield (%)[b]
1	**3a**	 **9a**	95
2	**3b**	 **9b**	97
3	**3c**	 **9c**	89
4	**3d**	 **9d**	95
5	**6a**	 **9e**	99
6	**8a**	 **9f**	97
7	**8b**	 **9g**	96

[a]All reactions were carried out using (0.2 mmol, 1.0 equiv) of **3**, **6**, or **8** and in CH_2Cl_2 (4 mL) with 2 mol % of **G-II** catalyst at rt for 8 h. [b]Yields are of isolated products after chromatography.

Scheme 2. Preparation of Cyclopentene Amino Acid 10



Tandem Metathesis. Unlike RCM, the synthetic applications of ring-opening metathesis (ROM)[15] and cross metathesis (CM)[16] have been relatively less explored. We envisioned that the hydantoin containing triene derivative such as **8a** could serve as precursors for skeletal diversity using a domino/tandem[28] metathesis sequence. Tandem processes involving a series of organic transformations are of high importance for the rapid access of structural complexity.[28] It is interesting to note that refluxing the triene **8a** with 5 mol % Hoveyda–Grubbs' second-generation catalyst (**HG-II**) in dichloromethane at 45 °C, self-metathesis dimer of fused bicyclic hydantoin **11** was obtained together with the spirocyclic compound **9f** (Table 5).

The formation of dimer could occur by a simultaneous *ab*-mode RCM followed by a self-metathesis of the intermediate monomeric fused hydantoin. However, the highly selective formation of the spiro compound **9f** (entry 6, Table 4) suggests that the *aa*-mode RCM reaction is much faster than the *ab*-mode. To investigate the possibility of conversion of the spiro product **9f** to **11**, the progress of the reaction was monitored with time (entries 1–4, Table 5). Treatment of **8a** in the presence of 5 mol % with **HG-II** for 7 h at 45 °C for 12 h afforded the corresponding products with a ratio of spiro compound **9f** and fused bicyclic dimer **11** as a ratio of 69:31 in a combined yield of 93% (entry 1, Table 5). Under prolonged reaction (ca. 6 days), the reaction afforded a mixture of spiro compound **9f** and the dimer **11** in a ratio of 20:80 in 85% combined yields (entry 4, Table 5). However, the compound **8a** was treated with the Grubbs' second-generation catalyst (**G-II**) in refluxing CH_2Cl_2 at 45 °C for 36 h to give exclusively the spirocyclic compound **9f**, with no trace of the dimer **11** in the reaction (entries 5–6, Table 5).

These results indicate that the spiro compound **9f** underwent ring rearrangement metathesis[13] in the presence of **HG-II** to produce the thermodynamically preferred dimer **11**. To confirm these results, the spiro compound **9f** was treated with 5 mol % **HG-II** for 72 h in refluxing CH_2Cl_2 to provide the dimer **11** in 73% isolated yield following a sequence of tandem ROM–RCM–CM (Scheme 3). The structure of the bicyclic hydantoin dimer **11** was unambiguously confirmed by single crystal X-ray analysis[22] (Figure S1b, SI).

The spirocyclic compound **9f** was functionalized by a selective cross-metathesis (CM)[16] with methyl acrylate to give exclusively the *E*-olefin **12** in 62% yield (Scheme 3). The reaction was carried out using 5 mol % of **HG-II** in CH_2Cl_2 at 45 °C. The crude NMR analysis of the reaction shows the formation of a trace amount (<10%) of dimer **11**. We could establish a highly selective "one-pot" sequential RCM and CM to yield the spirohydantoin derivative **12** in 53% yields from the triene **8a** (Scheme 3). It is intriguing to note that the dimer **11** could be efficiently used as cross metathesis partner with methyl acrylate to give the corresponding *E*-olefin **13** in 79% yields (Scheme 3). This method would allow synthesis of several fused hydantoin derivatives, which are otherwise difficult to prepare by standard protocols. To our knowledge, the aforementioned transformations are the first examples of the ring-closing and cross metathesis to prepare spirocyclic hydantoin derivatives and the functionalized spiro and fused compounds.

Synthesis of Fused Hydantoin Derivarives. In the next step of this work, we have examined the feasibility of RCM precursors **7** to prepare the bicyclic imidazolidinediones **14**, *n* = 1–3. The 1,5-dialkenyl substituted hydantoin precursors **7** were treated using Grubbs catalyst (**G-II**) in toluene at 80 °C (Table 6). Precursors **7a,b** with allyl substituents at 1 and 3 positions afforded dihydroimidazo[1,5-a]pyridine-1,3(2*H*,5*H*)-dione **14a,b** in high yield (entries 1–2, Table 6). Similarly the dimethyl analogue of diazabicyclic compound **14c** was synthesized in 51% yield from the precursor **7c** (entry 3, Table 6). Thus, we have an easy access to azabicyclic compounds bearing nitrogen at the fusion of six-membered rings, which are key building blocks in many multistep alkaloids and drug syntheses.

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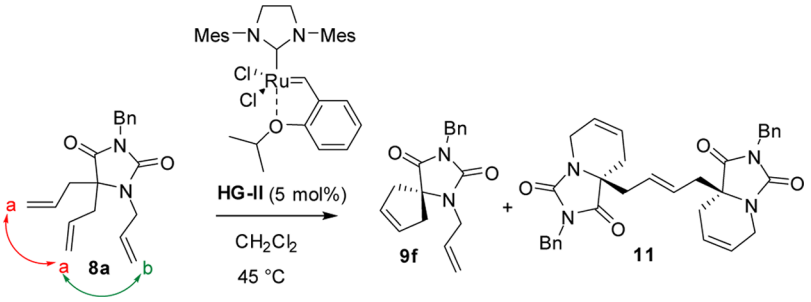
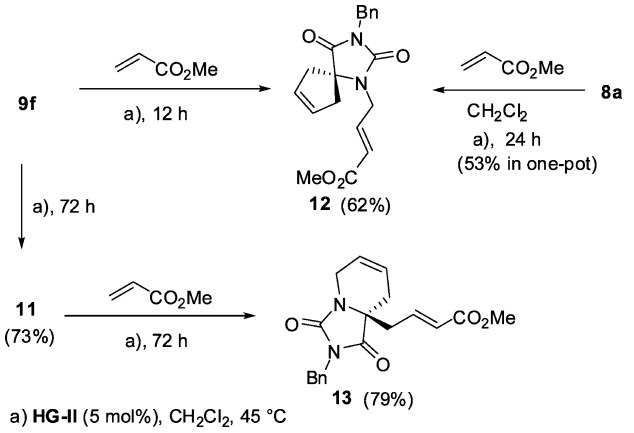
Table 5. One-Pot RCM−ROM−CM



entry	time	conv[a]	ratio (**9f**/**11**)[a]	yield (%)[b]
1	12 h	>99	69:31	93
2	29 h	>99	33:67	91
3	66 h	>99	23:77	87
4	6 d	>99	20:80	85
5[c]	12 h	>99	100:0[c]	98
6[c]	36 h	>99	100:0[c]	98

[a]The conv and ratios were determined by ^{1}H NMR analysis of the crude mixture. [b]Combined yields of isolated products after chromatography. [c]Using 5 mol % **G-II**.

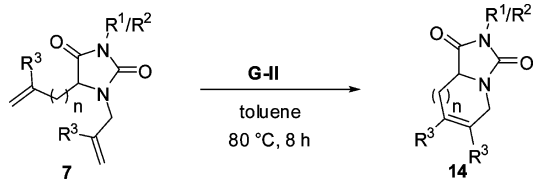
Scheme 3. One-Pot RCM−CM

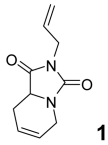
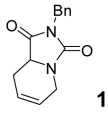
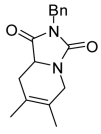
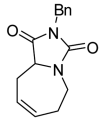
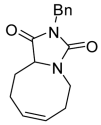


This methodology was extended to access seven and eight membered ring systems. (*Z*)-2-benzyl-5,6,9,9a-tetrahydro-1*H*-imidazo[1,5-a]azepine-1,3(2*H*)-dione **14d** and (*Z*)-2-benzyl-5,6,10,10a-tetrahydroimidazo[1,5-a]azocine-1,3(2*H*,9*H*)-dione **14e** were obtained in moderate yields under similar conditions (entries 4−5, Table 6). Since hydantoins can give the corresponding amino acids, these medium ring systems **14a**−**e** can serve as precursors for proline homologues and can be used as the replacement for proline in polypeptides and antibiotics.[29]

Synthesis of Fused Imidazolone Derivatives. Finally, we have incorporated alkene substituents at C(4)−C(5) and N(3)−C(4) positions of imidazolidinone (Scheme 4). The dibenzyl hydantoin **2b** was monoallylated at C(5) position to give compound **15** in 70% yield. The C(4) lactam carbonyl groups of **15** were then reduced with DIBAL-H, followed by reaction of the crude resulting mixture with allyltrimethylsilane in the presence of BF_3·OEt_2, furnishing the 4,5-diallylimidazolidinone **16** in 78% yield (Scheme 4).[30] Ring-closing metathesis of the diene **16** with the catalyst **G-II** afforded diazabicyclic compound **17** in near quantitative yield. The relative configuration of the bicyclic urea **17** was confirmed to be trans from single crystal X-ray analysis (Figure S2, SI).[22] The

Table 6. Synthesis of Bicyclohydantoin Derivatives by RCM[a]



entry	substrate	product	yield (%)[b]
1	**7a**	 **14a**	85
2	**7b**	 **14b**	84
3	**7c**	 **14c**	51 (81)[c]
4	**7d**	 **14d**	45 (74)[c]
5	**7e**	 **14e**	47 (79)[c]

[a]All reactions were carried out using (0.2 mmol, 1.0 equiv) of **8** and in toluene (3 mL) with 2 mol % of **G-II** catalyst at rt for 8 h. [b]Yields are of isolated products after chromatography. [c]Yields based on starting material recovery.

compound **17** can serve as the immediate precursor for stereoselective synthesis of cyclic vicinal diamines,[31] ligand for

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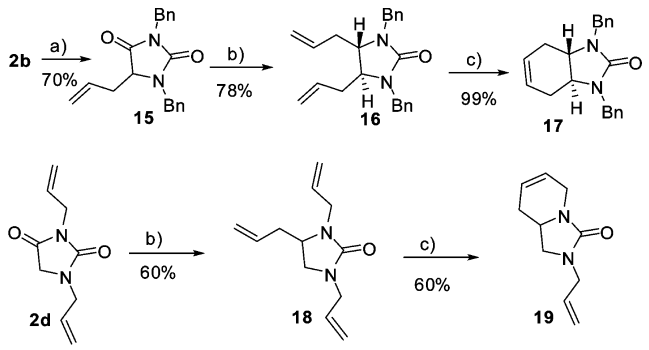
Scheme 4. Synthesis of Tetrahydrobenzoimidazolone 17 and Tetrahydroimidazopyridinone 19 Derivatives



a) LiHMDS, THF, -20 °C-rt,12 h.
b) i) DIBAL-H, toluene/THF,-78 °C, ii) allyl-TMS, $BF_3.Et_2O$, CH_2Cl_2, -78 °C.
c) **G-II** (2 mol%), CH_2Cl_2, rt, 8 h

metal complexes[32] and chiral auxiliaries.[33] Similarly the diallyl hydantoin **2d** was then treated under similar two step conditions with DIBAL-H and allyl trimethylsilane in the presence of $BF_3{\cdot}OEt_2$ to give triallyl hydantoin **18** in 60% yield (Scheme 4). A selective ring-closing metathesis of the triene **18** afforded the tetrahydroimidazo[1,5-a]pyridin-3(5*H*)-one ring system **19**.

CONCLUSION

In conclusion, we have demonstrated that selective *N* and C(5) alkylation of hydantoin followed by the RCM reaction provides an easy access to a variety of spiro and fused bicyclic hydantoin derivatives, a group of structures that represent alkaloid-like scaffolds for lead generation. The methodology establishes that the hydantoin containing triene can undergo tandem metathesis sequences to prepare either the functionalized spiro compound or bicyclic hydantoin dimer. Since hydantoin derivatives are the immediate precursors for racemic and chiral amino acid derivatives, the method establishes a RCM based approach to prepare unsaturated cyclic amino acids from commercially available hydantoin. Spirocyclic hydantoins can produce cyclic α-amino acids as exemplified in a four-step synthesis of cyclopentene amino acid. The fused hydantoins can serve as the precursors for proline homologues. The synthesis of tetrahydrobenzoimidazolone route can be used for the stereoselective synthesis of cyclic vicinal diamines.

EXPERIMENTAL SECTION

General Information. All experiments were carried out under an inert atomosphere of argon in flame-dried flasks. The solvents were used as technical grade and freshly distilled prior use. All starting materials were obtained from commercial suppliers and used as received. Products were purified by flash chromatography on silica gel (100−200 mesh). Unless otherwise stated, yields refer to analytical pure samples. All melting points are uncorrected. ^1H and ^{13}C NMR NMR spectra were recorded in $CDCl_3$ at 278 K unless otherwise stated and are reported in ppm relative to tetramethylsilane (TMS). Infrared (FTIR) spectra were recorded with the KBr disk and KBr plate techniques for solid and liquid samples, ν_{max} cm^{-1}. HRMS analyses were performed with Q-TOF YA263 high resolution instruments by positive mode electrospray ionization.

General Procedure for Preparation of Compounds 2. To a suspension of hydantoin (1.0 g, 10 mmol, 1.0 equiv) and K_2CO_3 (4.1 g, 30 mmol, 3.0 equiv) in dry DMF (5 mL/1 mmol) was added MeI or BnBr or allyl bromide or PMBCl (3 equiv). The resulting mixture was stirred at 60 °C for 12 h. The reaction was stopped by adding water, and then the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (20/80 to 35/65) to give compound **2**.

*1,3-Dimethylimidazolidine-2,4-dione (**2a**).*[21b] Using the general procedure, methyl iodide (1.8 mL, 30 mmol, 3 equiv) provided compound **2a** (2.1 g, 54%) as a colorless oil: ^1H NMR (500 MHz) 3.76 (2H, s), 2.87 (3H, s), 2.87 (3H, s); ^{13}C NMR (125 MHz) 170.0, 157.0, 51.6, 29.5, 24.7; IR 3444, 2949, 2358, 1760, 1699, 1493, 1419, 1388, 1272, 1248, 1110, 1077, 10005, 756, 599; HRMS (ESI) calcd for $C_5H_9N_2O_2$ $[M + H]^+$ 129.0664, found 129.0689.

*1,3-Dibenzylimidazolidine-2,4-dione (**2b**).*[21g] Using the general procedure, benzyl bromide (3.6 mL, 30 mmol, 3.0 equiv) provided compound **2b** (6.3 g, 75%) as a colorless solid: mp 66−67 °C; ^1H NMR (500 MHz) 7.45 (2H, d, *J* = 6.9 Hz), 7.35−7.34 (6H, m), 7.25 (2H, d, *J* = 6.9), 4.69 (2H, s), 4.54 (2H, s), 3.70 (2H, s); ^{13}C NMR (125 MHz) 169.5, 156.4, 136.0, 135.2, 129.0, 128.5, 128.5, 127.9, 127.7, 49.0, 47.0, 42.4; IR (KBr) 3465, 3063, 3032, 2926, 2363, 1769, 1710, 1496, 1453, 1383, 1358, 1237, 1204; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2$ $[M + H]^+$ 281.1290, found 281.1294.

*1,3-Bis(4-methoxybenzyl)imidazolidine-2,4-dione (**2c**).* Using the general procedure, *p*-methoxybenzyl chloride (4.0 mL, 30 mmol, 3.0 equiv) provided compound **2c** (7.7 g, 75%) as a colorless solid: mp 125−126 °C; ^1H NMR (500 MHz) 7.37 (2H, d, *J* = 8.5 Hz), 7.15 (2H, d, *J* = 8.5 Hz), 6.87−6.82 (4H, m), 4.59 (2H, s), 4.45 (2H, s), 3.77 (3H, s), 3.76 (3H, s), 3.66 (2H, s); ^{13}C NMR (125 MHz) 169.4, 159.3, 159.2, 156.4, 130.1, 129.4, 128.3, 127.3, 114.2, 113.8, 55.1, 55.0, 48.8, 45.9, 41.9; IR (KBr) 2929, 2837, 2362, 1767, 1710, 1612, 1514, 1462, 1354, 1295, 1247, 1177, 1140, 1109, 1033; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_4$ $[M + H]^+$ 241.1501, found 241.1529.

*1,3-Diallylimidazolidine-2,4-dione (**2d**).* Using the general procedure, allyl bromide (2.5 mL, 30 mmol, 3.0 equiv) provided compound **2d** (3.8 g, 70%) as a colorless oil: ^1H NMR (400 MHz) 5.79−5.75 (2H, m), 5.25−5.20 (4H, m), 4.10 (2H, d, *J* = 7.32 Hz), 3.99 (2H, d, *J* = 6.1 Hz), 3.82 (2H, s); ^{13}C NMR (100 MHz) 169.6, 156.1, 131.5, 131.1, 119.2, 118.1, 49.1, 45.2, 41.0; IR 3430, 3085, 2968, 2925, 2352, 1769, 1463, 1883,1325, 1237, 1182, 1155; HRMS (ESI) calcd for $C_9H_{13}N_2O_2$ $[M + H]^+$ 181.0977, found 181.09559.

General Procedure for Preparation of Compounds 3. The imidazolidinediones **2** (1 equiv) were dissolved in anhydrous THF (10 mL/1 mmol), and the solution was cooled to −20 °C under N_2. Then LiHMDS (3.0 equiv, solution in THF) was added at this temperature, and the mixture was stirred for 30 min followed by addition of the allyl bromide (3.0 equiv). The mixture was warmed up to room temperature and stirred for 12 h. The reaction was subsequently quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (5/95 to 20/80) to give compound **3.**

*5,5-Diallyl-1,3-dimethylimidazolidine-2,4-dione (**3a**).* Using the general procedure, 1,3-dimethylimidazolidine-2,4-dione **2a** (500 mg, 3.9 mmol, 1.0 equiv) and allyl bromide (1.0 mL, 11.7 mmol, 3.0 equiv) and LiHMDS (11.7 mL, 11.7 mmol, 3.0 equiv) provided compound **3a** (527 mg, 2.5 mmol, 65%) as a colorless oil: ^1H NMR (400 MHz) 5.48−5.39 (2H, m), 5.12−5.05 (4H, m), 2.93 (3H, s), 2.84 (3H, s), 2.55 (2H, dd, *J* = 17.9, 8.8 Hz), 2.38 (2H, dd, *J* = 18.1, 9.3 Hz); ^{13}C NMR (100 MHz) 174.4, 156.2, 129.9, 120.3, 67.9, 38.4, 24.6, 24.4; IR (KBr) 3424, 2939, 2348, 1750, 1679, 1483, 1429, 1288, 1272, 1248, 1110, 1067; HRMS (ESI) calcd for $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1290, found 209.12765.

*5,5-Diallyl-1,3-dibenzylimidazolidine-2,4-dione (**3b**).* Using the general procedure, 1,3-dibenzylimidazolidine-2,4-dione **2b** (500 mg, 1.8 mmol, 1.0 equiv) and allyl bromide (0.5 mL, 5.4 mmol, 3.0 equiv) and LiHMDS (5.4 mL, 5.4 mmol, 3.0 equiv) provided compound **3b** (402 mg, 1.1 mmol, 62%) as a colorless oil: ^1H NMR (500 MHz) 7.44−7.42 (2H, m), 7.41−7.39 (2H, m), 7.35−7.26 (6H, m), 5.22−5.14 (2H, m), 4.89−4.85 (4H, m), 4.67 (2H, s), 4.51 (2H, s), 2.49 (2H, dd, *J* = 14.3, 7.5 Hz), 2.38 (2H, dd, *J* = 14.3, 7.0 Hz); ^{13}C NMR

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(125 MHz) 173.8, 156.6, 137.1, 135.9, 129.5, 128.7, 128.4, 128.3, 128.2, 127.7, 127.5, 120.3, 68.9, 43.6, 42.2, 38.9; IR (KBr) 3467, 3065, 3033, 2926, 1769, 1708, 1496, 1446, 1392, 1359, 1242, 1200, 1142, 1077, 995; HRMS (ESI) calcd for $C_{23}H_{25}N_2O_2$ $[M + H]^+$ 361.1916, found 361.19270.

*5,5-Diallyl-1,3-bis(4-methoxybenzyl)imidazolidine-2,4-dione (**3c**).* 1,3-Bis(4-methoxybenzyl)imidazolidine-2,4-dione **2c** (500 mg, 1.5 mmol, 1 equiv) and allyl bromide (0.4 mL, 4.5 mmol, 3.0 equiv) and LiHMDS (4.5 mL, 4.5 mmol, 3 equiv) provided compound **3c** (441 mg, 0.95 mmol, 70%) as a white crystal (EtOAc/hexane): mp 101−103 °C; ^{1}H NMR (400 MHz) 7.33−7.29 (4H, m), 6.85−6.80 (4H, m), 5.18−5.08 (2H, m), 4.89−4.83 (4H, m), 4.57 (2H, s), 4.42 (2H, s), 3.78 (3H, s), 3.77 (3H, s), 2.46 (2H, dd, J = 17.9, 9.4 Hz), 2.35 (2H, dd, J = 17.9, 9.4 Hz); ^{13}C NMR (100 MHz) 173.9, 159.2, 159.0, 156.7, 130.2, 130.0, 129.7, 129.3, 128.4, 120.5, 113.8, 113.6, 69.0, 55.2 (2C), 43.2, 41.8, 39.1; IR (KBr) 3446, 2933, 2836, 2543, 2052, 1872, 1612, 1512, 1445, 1246, 1176, 1033, 930, 847; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_4$ $[M + H]^+$ 421.2127, found 421.2141.

*1,3,5,5-Tetraallylimidazolidine-2,4-dione (**3d**).* 1,3-Diallylimidazolidine-2,4-dione **2d** (1.0 g, 5.6 mmol, 1.0 equiv) and allyl bromide (1.4 mL, 16.8 mmol, 3.0 equiv) and 16.8 mL of LiHMDS provided compound **3d** (742 mg, 51%) as a colorless oil: ^{1}H NMR (400 MHz) 5.96−5.86 (1H, m), 5.78−5.68 (1H, m), 5.55−5.44 (2H, m), 5.31−5.27 (1H, m), 5.23−5.18 (2H, m), 5.15−5.07 (5H, m), 4.05−4.03 (2H, m), 3.93 (2H, d, J = 7.83 Hz), 2.56 (2H, dd, J = 18.0, 8.8 Hz), 2.46 (2H, dd, J = 18.0, 8.8 Hz); ^{13}C NMR (125 MHz) 173.7, 155.8, 133.5, 131.1, 129.9, 120.6, 118.1, 117.7, 68.7, 42.9, 40.6, 38.9; IR (KBr) 3468, 3082, 2983, 2925, 1771, 1710, 1644, 1452, 1414, 1157, 993, 928, 760, 682, 547; HRMS (ESI) calcd for $C_{15}H_{21}N_2O_2$ $[M + H]^+$ 261.1603, found 261.1619.

Preparation of 3-Benzylimidazolidine-2,4-dione (4a).[21g] To a suspension of hydantoin (1.0 g, 10 mmol, 1.0 equiv) and K_2CO_3 (4.0 g, 30 mmol, 3.0 equiv) in dry DMF (25 mL) was added BnBr (1.4 mL, 36 mmol, 1.2 equiv). The resulting mixture was stirred at rt for 12 h. The reaction was stopped by adding water, and then the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (20/80 to 35/65) to give compound **4a** (1.24 g, 65%) as a colorless solid: mp 132−133 °C; ^{1}H NMR (500 MHz) 7.37−7.36 (2H, m), 7.32−7.26 (3H, m), 6.84 (1H, s_{br}, NH), 4.64 (2H, s), 3.91 (2H, s); ^{13}C NMR (125 MHz) 171.3, 158.6, 136.0, 128.7, 128.5, 128.0, 46.6, 42.2; IR (KBr) 3460, 3025, 2948, 2915, 2352, 1759, 1463, 1883, 1325, 1237, 1182, 1155, 1118, 994, 934, 757, 700, 582, 550; HRMS (ESI) calcd for $C_{10}H_{11}N_2O_2$ $[M + H]^+$ 191.0821, found 191.0824.

Preparation of *tert*-Butyl 2,5-dioxoimidazolidine-1-carboxylate (4b). To a suspension of hydantoin **1** (1.0 g, 10 mmol, 1.0 equiv) in CH_3CN (50 mL), Boc_2O (4.8 g, 22 mmol, 2.2 equiv) and DMAP (122 mg, 1 mmol, 0.1 equiv) were added at room temperature. The resulting solution was stirred for 12 h at room temperature, and then the solvent was evaporated under reduced pressure. The reaction was stopped by adding water, and then the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (20/80 to 35/65) to give compound **4b** (1.7 g, 89%) as a colorless solid: mp 141−143 °C; ^{1}H NMR (500 MHz) 8.93 (1H, br, s), 4.24 (2H, s), 1.52 (9H, s); ^{13}C NMR (125 MHz) 168.2, 152.3, 148.3, 84.7, 50.1, 28.0; IR (KBr) 3460, 3225, 3048, 2915, 2752, 1719, 1563, 1783, 1425, 1237, 1172, 1145, 1018, 994, 834, 787, 720, 522, 500; HRMS (ESI) calcd for $C_8H_{13}N_2O_4$ $[M + H]^+$ 201.0875, found 201.0881.

General Procedure for the Preparation of *N*(1)-Substituted Hydantoin 5. To a suspension of 3-benzylimidazolidine-2,4-dione (1.0 g, 5.3 mmol, 1.0 equiv) and K_2CO_3 (726 mg, 5.3 mmol, 1.0 equiv) in dry DMF (5 mL/1 mmol) was added allyl bromide or 3-bromo-2-methylprop-1-ene (3.7 mmol, 0.7 equiv). The resulting mixture was stirred at 50 °C for 8 h. The reaction was stopped by adding water, and then the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (10/90 to 30/70) to give compound **5**.

*1-Allyl-3-benzylimidazolidine-2,4-dione (**5a**).* Using the general procedure, allyl bromide (0.3 mL, 3.7 mmol, 0.7 equiv) provided compound **5a** (889 mg, 73%) as a colorless oil: ^{1}H NMR (400 MHz) 7.39−7.37 (2H, m), 7.28−7.25 (3H, m), 5.76−5.67 (1H, m), 5.21−5.20 (2H, m), 4.62 (2H, s), 3.95−3.94 (2H, m), 3.76 (2H, s); ^{13}C NMR (100 MHz) 169.4, 156.1, 135.9, 131.5, 128.5, 128.4, 127.7, 118.9, 49.0, 45.1, 42.3; IR 3459, 2922, 2354, 1769, 1710, 1462, 1235, 1141, 996, 935, 755, 700; HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2$ $[M + H]^+$ 231.1134, found 231.1157.

*3-Benzyl-1-(2-methylallyl)imidazolidine-2,4-dione (**5b**).* Using the general procedure, 3-bromo-2-methylprop-1-ene (0.4 mL, 3.7 mmol, 0.7 equiv) provided compound **5b** (905 mg, 70%) as a colorless oil: ^{1}H NMR (500 MHz) 7.38−7.37 (2H, m), 7.28−7.23 (3H, m), 4.92 (1H, s), 4.81 (1H, s), 4.64−4.62 (2H, m), 3.88−3.86 (2H, m), 3.73−3.71 (2H, m), 1.67 (3H, s); ^{13}C NMR (125 MHz) 169.3, 156.2, 139.2, 135.8, 128.3, 128.2, 127.5, 113.6, 48.9, 48.5, 42.2, 19.5; IR 3469, 2912, 2344, 1759, 1700, 1262, 1235, 1041, 996, 925, 705, 603; HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ $[M + H]^+$ 245.1290, found 245.1279.

General Procedure for the Preparation of 5,5-Diallyl-3-substitutedimidazolidine-2,4-dione 6. The compounds **4** (1.0 equiv) were dissolved in anhydrous THF (10 mL/1 mmol), and the solution was cooled to −40 °C under N_2. LiHMDS (3.0 equiv, solution in THF) was added at this temperature, and the mixture was stirred for 30 min followed by addition of the allyl bromide (3 equiv). The mixture was stirred at room temperature for 12 h, and the reaction was then quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (5/95 to 20/80) to give compound **6**.

*5,5-Diallyl-3-benzylimidazolidine-2,4-dione (**6a**).* Using the general procedure, compound **4a** (1.0 g, 5.3 mmol, 1 equiv) and allyl bromide (1.4 mL, 15.9 mmol, 3.0 equiv) and 15.9 mL of LiHMDS provided compound **6a** (1.1 g, 75%) as a colorless oil: ^{1}H NMR (400 MHz) 7.34−7.31 (2H, m), 7.30−7.24 (3H, m), 6.74 (1H, brs, NH), 5.59−5.49 (2H, m), 5.10−5.01 (4H, m), 4.60 (2H, s), 2.48 (2H, dd, J = 17.3, 9.4 Hz), 2.39 (2H, dd, J = 17.5, 9.1 Hz); ^{13}C NMR (100 MHz) 175.1, 157.2, 135.9, 130.1, 128.4, 128.3, 126.7, 120.7, 64.8, 42.0, 40.6; IR (KBr) 3323, 2076, 1771, 1642, 1444, 1349, 1122, 1074, 995, 924, 756, 698; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_2$ $[M + H]^+$ 271.1447, found 271.1450.

*tert-Butyl 4,4-diallyl-2,5-dioxoimidazolidine-1-carboxylate (**6b**).* Using the general procedure, compound **4b** (1.0 g, 5.0 mmol, 1 equiv) and allyl bromide (1.3 mL, 15.0 mmol, 3.0 equiv) and 15.0 mL of LiHMDS provided compound **6a** (1.13 g, 81%) as a white crystal (EtOAc/hexane): mp 103−105 °C; ^{1}H NMR (400 MHz) 8.72 (1H, s_{br}), 5.62−5.52 (2H, m), 5.17 (2H, s_{br}), 5.14 (2H, d, J = 2.7 Hz), 2.92 (2H, dd, J = 17.3, 10.2 Hz), 2.61(2H, dd, J = 17.3, 8.5 Hz), 1.56 (9H, s); ^{13}C NMR (125 MHz) 173.1, 152.1, 148.3, 129.4, 121.2, 84.3, 71.0, 39.0, 28.0; IR (KBr) 3424, 3228, 3152, 2929, 2726, 2358, 1650, 1629, 1413, 1422, 1218, 1200, 1148, 1110, 1047; HRMS (ESI) calcd for $C_{14}H_{20}N_2O_4Na$ $[M + Na]^+$ 303.1321, found 303.1326.

General Procedure for the Preparation of Trisubstituted Imidazolidine-2,4-dione 7b−e. Alkenyl bromide (0.7 equiv) was added to a solution of 1-allyl-3-benzylimidazolidine-2,4-dione **5** (1 equiv) and LiHMDS (1.2 equiv) in anhydrous THF (10 mL/1 mmol) at −20 °C. The mixture was stirred at room temperature for 12 h, and the reaction was then quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (5/95 to 20/80) to give compound **7**.

*1,5-Diallyl-3-benzylimidazolidine-2,4-dione (**7b**).* Using the general procedure, compound **5a** (500 mg, 2.2 mmol, 1.0 equiv) and allyl

bromide (0.1 mL, 1.5 mmol, 0.7 equiv) and LiHMDS (2.64 mL, 2.64 mmol, 1.2 equiv) provided compound **7b** (463 mg, 78%) as a colorless oil: ^{1}H NMR (400 MHz) 7.38−7.36 (2H, m), 7.30−7.26 (3H, m), 5.76−5.71 (1H, m), 5.52−5.44 (1H, m), 5.26−5.22 (2H, m), 5.09 (2H, dd, J = 17.1, 9.8 Hz), 4.69−4.59 (2H, m), 4.43−4.38 (1H, m), 4.01 (1H, t, J = 5.5 Hz), 3.64−3.59 (1H, m), 2.62−2.57 (2H, m); ^{13}C NMR (100 MHz) 172.0, 159.9, 135.9, 131.8, 130.0, 128.4, 127.7, 120.3, 119.0, 58.4, 43.4, 42.4, 32.8; IR (KBr) 3452, 3070, 3023, 2921, 2353, 1757, 1720, 1435, 1328, 1254, 1123, 1075; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_2$ $[M + H]^+$ 271.1447, found 271.1462.

*3-Benzyl-1,5-bis(2-methylallyl)imidazolidine-2,4-dione (**7c**).* Using the general procedure, compound **5b** (500 mg, 2.0 mmol, 1.0 equiv) and 3-bromo-2-methylprop-1-ene (0.2 mL, 1.4 mmol, 0.7 equiv) and LiHMDS (2.4 mL, 2.4 mmol, 1.2 equiv) provided compound **7c** (327.8 mg, 55%) as a colorless oil: ^{1}H NMR (500 MHz) 7.32−7.30 (2H, m), 7.25−7.19 (3H, m), 4.86 (1H, d, J = 1.3 Hz), 4.73−4.71 (2H, m), 4.69 (1H, s_{br}), 4.64−4.54 (2H, m), 4.33 (1H, d, J = 15.8 Hz), 3.94 (1H, t, J = 5.3 Hz), 3.49 (1H, d, J = 15.5 Hz), 2.47 (2H, dd, J = 9.5, 5.3 Hz), 1.58 (3H, s), 1.53 (3H, s); ^{13}C NMR (125 MHz) 172.4, 156.4, 139.7, 139.6, 136.0, 128.5, 127.8, 115.2, 113.8, 57.2, 46.8, 42.6, 37.5, 22.5, 19.9; IR (KBr) 3437, 2926, 1710, 1448, 1417, 1390, 1353,1142, 753, 700, 627; HRMS (ESI) calcd for $C_{18}H_{23}N_2O_2$ $[M + H]^+$ 299.1760, found 299.1748.

*1-Allyl-3-benzyl-5-(but-3-enyl)imidazolidine-2,4-dione (**7d**).* Using the general procedure, compound **5a** (500 mg, 2.2 mmol, 1.0 equiv) and 4-bromobut-1-ene (0.2 mL, 1.5 mmol, 0.7 equiv) and LiHMDS (2.64 mL, 2.64 mmol, 1.2 equiv) provided compound **7d** (300 mg, 48%) as a colorless oil: ^{1}H NMR (400 MHz) 7.40−7.38 (2H, m), 7.32−7.24 (3H, m), 5.79−5.63 (2H, m), 5.24−5.20 (2H, m), 4.92 (2H, t, J = 15.5 Hz), 4.68−4.59 (2H, q, J = 18.1 Hz), 4.39−4.33 (1H, m), 3.99−3.97 (1H, m), 3.62−3.56 (1H, m), 2.85−1.97 (2H, m), 1.93−1.76 (2H, m); ^{13}C NMR (100 MHz) 172.5, 156.0, 136.3, 136.0, 131.8, 128.5, 127.8, 119.0, 115.8, 58.2, 43.4, 42.4, 27.4, 27.3; IR (KBr) 3458, 3072, 2973, 2915, 1761, 1720, 1634, 1442, 1424, 1147, 993, 928, 760; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1603, found 285.1610.

*1-Allyl-3-benzyl-5-(pent-4-enyl)imidazolidine-2,4-dione (**7e**).* Using the general procedure, compound **5a** (700 mg, 3.0 mmol, 1.0 equiv) and 5-bromopent-1-ene (0.24 mL, 2.1 mmol, 0.7 equiv) and LiHMDS (3.6 mL, 3.6 mmol, 1.2 equiv) provided compound **7e** (411 mg, 46%) as a colorless oil: ^{1}H NMR (400 MHz) 7.38−7.32 (2H, m), 7.31−7.22 (3H, m), 5.76−5.61 (2H, m), 5.22−5.18 (2H, m), 4.94−4.90 (2H, m), 4.63 (2H, q, J = 17.9 Hz), 4.37−4.31 (1H, m), 3.96−3.94 (1H, dd, J = 7.0, 4.3 Hz), 3.58−3.52 (1H, m), 2.01−1.94 (2H, m), 1.90−1.83 (1H, m), 1.76−1.68 (1H, m), 1.32−1.23 (1H, m), 1.20−1.12 (1H, m); ^{13}C NMR (100 MHz) 172.6, 156.1, 137.4, 137.0, 131.8, 128.5, 128.4, 127.7, 119.0, 115.2, 58.6, 43.4, 42.4, 33.0, 27.6, 21.9; IR (KBr) 3464, 3067, 3033, 2928, 2862, 1769, 1710, 1641, 1496, 1448, 1417, 1390, 1353, 1235, 1144, 1073; HRMS (ESI) calcd for $C_{18}H_{23}N_2O_2$ $[M + H]^+$ 299.1760, found 299.1757.

General Procedure for the Preparation of 5-Allyl-1,3-disubstitutedimidazolidine-2,4-dione 7a, 15. Allyl bromide (0.7 equiv) was added to a solution of 1,3-dibenzylimidazolidine-2,4-dione **2** (1.0 g, 1.0 equiv) and LHMDS (1.2 equiv) in anhydrous THF (10 mL/1 mmol) at −20 °C. The mixture was stirred at room temperature for 12 h, and the reaction was then quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (5/95 to 20/80) to give compound **7a**, **15**.

*1,3,5-Triallylimidazolidine-2,4-dione (**7a**).* Using the general procedure, 1,3-diallylimidazolidine-2,4-dione **2d** (1.0 g, 5.6 mmol, 1.0 equiv) and allyl bromide (0.33 mL, 3.9 mmol, 0.7 equiv) and LiHMDS (6.72 mL, 6.72 mmol, 1.2 equiv) provided compound **7a** (801 mg, 65%) as a colorless oil: ^{1}H NMR (400 MHz) 5.77−5.66 (2H, m), 5.59−5.49 (1H, m), 5.22−5.08 (6H, m), 4.38−4.33(1H, m), 4.09−3.97 (3H, dt, J = 11.3, 6.9 Hz), 3.61−3.55 (1H, m), 2.63−2.51 (2H, m); ^{13}C NMR (100 MHz) 171.8, 155.7, 131.7, 131.0, 130.1, 120.3, 118.9, 117.6, 58.3, 43.3, 40.7, 32.7; IR (KBr) 3252, 3060, 3010, 2904, 2223, 1742, 1620, 1425, 1318, 1226, 1104, 1025; HRMS (ESI) calcd for $C_{12}H_{17}N_2O_2$ $[M + H]^+$ 221.1290, found 221.1268.

*5-Allyl-1,3-dibenzylimidazolidine-2,4-dione (**15**).* 1,3-Dibenzylimidazolidine-2,4-dione **2b** (1.0 g, 3.6 mmol, 1.0 equiv) and allyl bromide (0.2 mL, 2.5 mmol, 0.7 equiv) and LiHMDS (4.32 mL, 4.32 mmol, 1.2 equiv) provided compound **15** (806 mg, 70%) as a colorless oil: ^{1}H NMR (500 MHz) 7.38−7.36 (2H, m), 7.34−7.26 (6H, m), 7.24−7.22 (2H, m), 5.46−5.39 (1H, m), 5.09−5.00 (3H, m), 4.71−4.62 (2H, m), 4.06 (1H, d, J = 15.1 Hz), 3.82−3.81(1H, m), 2.57−2.52 (2H, m); ^{13}C NMR (125 MHz) 171.9, 156.4, 135.9, 135.4, 129.9, 128.8, 128.4, 128.0, 127.7, 127.4, 126.8, 120.3, 58.1, 44.6, 42.5, 32.7; IR 3455, 3043, 3012, 2976, 2343, 1883,1315, 1237, 1182, 1145; HRMS (ESI) calcd for $C_{20}H_{21}N_2O_2$ $[M + H]^+$ 321.1603, found 321.1631.

General Procedure for the Preparation of 5,5-Dialkenyl-1,3-disubstituted imidazolidine-2,4-dione 8. Allyl bromide or 3-bromo-2-methylprop-1-ene or bromobutene (1.5 equiv) was added to a solution of **7a** (1.0 equiv) and LHMDS (1.5 equiv) in dry THF at −20 °C. The mixture was stirred at room temperature for 12 h, and the reaction was then quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (5/95 to 20/80) to give compounds **8**.

*1,5,5-Triallyl-3-benzylimidazolidine-2,4-dione (**8a**).* Using the general procedure, 1,5-diallyl-3-benzylimidazolidine-2,4-dione **7b** (500 mg, 1.9 mmol, 1.0 equiv) and allyl bromide (0.25 mL, 2.9 mmol, 1.5 equiv) and LiHMDS (2.85 mL, 2.85 mmol, 1.5 equiv) provided compound **8a** (401 mg, 68%) as a colorless oil: ^{1}H NMR (400 MHz) 7.29−7.26 (2H, m), 7.22−7.13 (3H, m), 5.89−5.79 (1H, m), 5.38−5.26 (2H, m), 5.23−5.18 (1H, m), 5.14−5.09 (1H, m), 4.97−4.90 (2H, m), 4.89 (2H, d, J = 12.7 Hz), 4.53 (2H, s), 3.85 (2H, d, J = 8.1 Hz), 2.46 (2H, dd, J = 17.7, 9.2 Hz), 2.37 (2H, dd, J = 18.0, 8.9 Hz); ^{13}C NMR (100 MHz) 173.8, 156.0, 135.9, 133.6, 129.8, 128.5, 128.2, 127.6, 120.5, 118.1, 68.7, 42.9, 42.2, 39.0; IR 3462, 3080, 3033, 2921, 2353, 1767, 1710, 1445, 1338, 1254, 1133, 1075, 994, 926, 755, 700; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_2$ $[M + H]^+$ 311.1760, found 311.1776.

*1,5-Diallyl-3-benzyl-5-(2-methylallyl)imidazolidine-2,4-dione (**8b**).* Using the general procedure, 1,5-diallyl-3-benzylimidazolidine-2,4-dione **7b** (500 mg, 1.9 mmol, 1.0 equiv) and 3-bromo-2-methylprop-1-ene (0.29 mL, 2.9 mmol, 1.5 equiv) and LiHMDS (2.85 mL, 2.85 mmol, 1.5 equiv) provided compound **8b** (523 mg, 85%) as a colorless oil: ^{1}H NMR (400 MHz) 7.35−7.33 (2H, m), 7.25−7.18 (3H, m), 5.95−5.85 (1H, m), 5.44−5.34 (1H, m), 5.25 (1H, d, J = 21.4 Hz), 5.15 (1H, d, J = 12.2 Hz), 5.01−4.95 (1H, m), 4.49 (1H, d, J = 12.9 Hz), 4.66 (1H, s), 4.58 (3H, d, J = 11.05), 4.12−4.04 (1H, m), 3.73−3.66 (1H, m), 2.53−2.38 (4H, m), 1.39 (3H, s); ^{13}C NMR (100 MHz) 173.9, 155.9, 138.7, 135.7, 133.6, 129.7, 128.7, 128.2, 127.6, 120.7, 118.1, 116.1, 68.5, 43.3, 42.3, 41.8, 40.4, 23.2; IR (KBr) 3437, 2926, 1710, 1645, 1453, 1359, 1441, 1242, 1132, 1018, 746, 699; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_2$ $[M + H]^+$ 325.1916, found 325.1921.

General Procedure for the Preparation of Spirocylic Hydantoin Derivatives 9 by RCM. To a stirring solution of **3**, **6**, **8** (0.2 mmol, 1 equiv) in CH_2Cl_2 (4 mL) was added **G-II** (2 mol %), and the mixture was stirred for 8 h at room temperature. The reaction mixture was then concentrated and purified on silica gel (EtOAc−hexane, 10/90 to 20/80) to give compound **9.**

*1,3-Dimethyl-1,3-diazaspiro[4.4]non-7-ene-2,4-dione (**9a**).* Using the general procedure, compound **3a** (50 mg, 0.24 mmol, 1.0 equiv) provided compound **9a** (41 mg, 95%) as a colorless oil: ^{1}H NMR (400 MHz) 5.73(2H, s), 3.02(3H, s), 2.95 (2H, d, J = 16.5 Hz), 2.80 (3H, s), 2.49 (2H, d, J = 16.5 Hz); ^{13}C NMR (125 MHz) 176.8, 155.3, 127.8, 68.8, 41.7, 29.7, 24.9; IR (KBr) 3424, 2929, 2348, 1660, 1599, 1433, 1429, 1318, 1262, 1238, 1210, 1047; HRMS (ESI) calcd for $C_9H_{13}N_2O_2$ $[M + H]^+$ 181.0977, found 181.0980.

*1,3-Dibenzyl-1,3-diazaspiro[4.4]non-7-ene-2,4-dione (**9b**).* Using the general procedure, compound **3b** (50 mg, 0.14 mmol, 1.0 equiv) provided compound **9b** (45 mg, 97%) as a white crystal (EtOAc/

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hexane): mp 78−80 °C; ^{1}H NMR (500 MHz) 7.41−7.39 (2H, m), 7.33−7.30 (2H, m), 7.28−7.23 (6H, m), 5.62 (2H, s), 4.71 (2H, s), 4.39 (2H, s), 2.85 (2H, d, J = 16.4 Hz), 2.31 (2H, d, J = 16.4 Hz) ; ^{13}C NMR (125 MHz) 176.4, 155.5, 137.7, 136.2, 128.6, 128.4, 128.4, 128.1, 127.9, 127.8, 127.6, 69.5, 43.6, 42.6, 42.4; IR (KBr) 3425, 3043, 3022, 2916, 2333, 1709, 1700, 1466, 1423, 1363, 1358, 1277, 1204, 1139, 1021, 1019; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_2$ [M + H]$^+$ 333.1603, found 333.1627.

*1,3-Bis(4-methoxybenzyl)-1,3-diazaspiro[4.4]non-7-ene-2,4-dione (**9c**).* Using the general procedure, compound **3c** (60 mg, 0.14 mmol, 1.0 equiv) provided compound **9c** (49 mg, 89%) as a colorless solid: mp 86−87 °C; ^{1}H NMR (400 MHz) 7.41 (2H, d, J = 10.7 Hz), 7.25 (2H, d, J = 10.7 Hz), 6.90 (2H, d, J = 10.8 Hz), 6.84 (2H, d, J = 10.7 Hz), 5.69 (2H, s), 4.69 (2H, s), 4.38 (2H, s), 3.82 (3H, s), 3.81 (3H, s), 2.91−2.86 (2H, m), 2.38−2.34 (2H, m) ; ^{13}C NMR (100 MHz) 176.4, 159.0, 158.9, 155.3, 129.9, 129.8, 129.3, 128.4, 127.9, 113.8, 113.6, 69.2, 55.1, 42.9, 42.3, 42.0; IR (KBr) 3078, 2934, 2837, 1765, 1710, 1613, 1513, 1343, 1294, 1247, 1177, 1033, 996; HRMS (ESI) calcd for $C_{23}H_{25}N_2O_4$ [M + H]$^+$ 393.1814, found 393.1819.

*1,3-Diallyl-1,3-diazaspiro[4.4]non-7-ene-2,4-dione (**9d**).* Using the general procedure, compound **3d** (50 mg, 0.28 mmol, 1.0 equiv) provided compound **9d** (62 mg, 95%) as a colorless oil: ^{1}H NMR (400 MHz) 5.84−5.73 (3H, m), 5.61−6.50 (1H, m), 5.23−5.08 (4H, m), 4.45−4.39 (1H, m), 4.15−4.05 (2H, m), 3.62−3.56 (1H, m), 2.55 (2H, d, J = 9.4 Hz), 2.32 (2H, d, J = 3.8 Hz); ^{13}C NMR (125 MHz) 175.3, 154.3, 131.2, 130.4, 123.1, 121.9, 120.5, 117.7, 60.7, 40.5, 37.6, 31.0; IR (KBr) 3430, 3085, 2968, 2925, 2352, 1769, 1710, 1365, 1246, 1136; HRMS (ESI) calcd for $C_{13}H_{17}N_2O_2$ [M + H]$^+$ 233.1290, found 233.1285.

*3-Benzyl-1,3-diazaspiro[4.4]non-7-ene-2,4-dione (**9e**).* Using the general procedure, compound **6a** (50 mg, 0.19 mmol, 1.0 equiv) provided compound **9e** (45.5 mg, 99%) as a white crystal (EtOAc/hexane): mp 146−148 °C; ^{1}H NMR (400 MHz) 7.36−7.33 (2H, m), 7.32−7.24 (3H, m), 6.52 (1H, s_{br}), 5.68 (2H, s), 4.64 (2H, s), 2.98 (2H, d, J = 15.9 Hz), 2.51 (2H, d, J = 15.9 Hz); ^{13}C NMR (100 MHz) 176.8, 156.4, 136.0, 128.6, 128.2, 127.7, 127.6, 66.6, 42.5, 42.1; IR (KBr) 3225, 3103, 2945, 2843, 1777, 1710, 1495, 1451, 1411, 1345, 1291, 1219, 1155, 1119, 1027, 964; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_2$ [M + H]$^+$ 243.1134, found 243.1130.

*1-Allyl-3-benzyl-1,3-diazaspiro[4.4]non-7-ene-2,4-dione (**9f**).* Using the general procedure, compound **8a** (50 mg, 0.16 mmol, 1.0 equiv) provided compound **9f** (43.7 mg, 97%) as a colorless oil: ^{1}H NMR (400 MHz) 7.31−7.28 (2H, m), 7.25−7.16 (3H, m), 5.72−5.70 (2H, m), 5.42−5.31 (1H, m), 5.02−5.00 (1H, m), 4.92−4.89 (1H, m), 4.58 (2H, s), 4.37−4.32 (1H, m), 3.54−3.48 (1H, m), 2.47 (2H, d, J = 9.1 Hz), 2.23 (2H, d, J = 4.3 Hz); ^{13}C NMR (125 MHz) 175.4, 154.4, 136.1, 130.3, 128.5, 128.4, 127.7, 123.1, 121.9, 120.4, 60.7, 42.1, 37.6, 37.6, 30.9; IR (KBr) 3437, 2925, 2364, 1767, 1710, 1587, 1443, 1355, 1125, 1070; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2$ [M + H]$^+$ 283.1447, found 283.1429.

*1-Allyl-3-benzyl-7-methyl-1,3-diazaspiro[4.4]non-7-ene-2,4-dione (**9g**).* Using the general procedure, compound **8b** (50 mg, 0.15 mmol, 1.0 equiv) provided compound **9g** (42.6 mg, 96%) as a colorless oil: ^{1}H NMR (400 MHz) 7.38−7.34 (2H, m), 7.30−7.23 (3H, m), 5.76 (2H, s), 4.67−4.68 (1H, m), 4.64 (3H, s), 4.42−4.37 (1H, m), 3.65−3.59 (1H, m), 2.53 (2H, s), 2.28−2.26 (2H, m), 1.42 (3H, s); ^{13}C NMR (100 MHz) 175.6, 154.7, 139.2, 135.9, 128.6, 128.4, 127.7, 123.1, 121.8, 116.1, 60.7, 42.2, 41.2, 37.9, 32.1, 23.0; IR (KBr) 3437, 2926, 1708, 1441, 1132, 1018, 746, 699; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ [M + H]$^+$ 297.1603, found 297.1609.

*tert-Butyl 2,4-dioxo-1,3-diazaspiro[4.4]non-7-ene-3-carboxylate (**9h**).* Using the general procedure, compound **6b** (50 mg, 0.18 mmol, 1.0 equiv) provided compound **9h** (44.5 mg, 98%) as a colorless solid: mp 178−179 °C; ^{1}H NMR (400 MHz) 8.56 (1H, s_{br}), 5.71 (2H, s), 2.94 (4H, s), 1.50 (9H, s); ^{13}C NMR (100 MHz) 175.9, 151.7, 147.9, 127.9, 84.6, 69.1, 43.5, 28.0; IR (KBr) 3237, 3026, 2922, 1708, 1622, 1441, 1232, 1132, 1018, 742, 629; HRMS (ESI) calcd for $C_{12}H_{17}N_2O_4$ [M + H]$^+$ 253.1188, found 253.1190.

Preparation of 1-Aminocyclopent-3-enecarboxylic acid (10). To a solution of *tert*-butyl 2,4-dioxo-1,3-diazaspiro[4.4]non-7-ene-3-carboxylate **9h** (100 mg, 0.39 mmol) in THF (5 mL), an aqueous solution of 4% $Ba(OH)_2$ (5 mL) was added. The reaction mixture was stirred at 180 °C for 72 h. After cooling, the mixture was evaporated to dryness, and the residue was washed with Et_2O (50 mL) and H_2O (50 mL). The organic layer was discarded, and the aqueous phase was washed with an additional portion of Et_2O (20 mL). The aqueous phase was then concentrated to dryness to give the compound **10** (46 mg, 93%) as a colorless solid: mp 219−220 °C; ^{1}H NMR (500 MHz) 5.78 (2H, s), 3.17 (2H, d_{br}, J = 17.0 Hz), 2.75 (2H, d_{br}, J = 16.4 Hz); ^{13}C NMR (125 MHz) 174.7, 127.3, 63.5, 43.3; IR (KBr) 3214, 3012, 2713, 2605, 1721, 1640, 1564, 1245; HRMS (ESI) calcd for $C_6H_9NO_2Na$[M + Na]$^+$ 150.0531, found 150.0535.

Preparation of Dimer 11. *(a). From the Triene **8a**.* To a solution of **8a** (50 mg, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added **HG-II** (5 mg, 0.008 mmol, 5 mol %), and the mixture was refluxed for 6 d at 45 °C. The reaction mixture was then concentrated and purified on silica gel (EtOAc−hexane, 20/80 to 40/60) to give compound **9f** (7 mg, 16%) and compound **11** (30 mg, 70%). Compound **11** was obtained as a colorless crystal (EtOAc−hexane): mp 187−188 °C; ^{1}H NMR (500 MHz) 7.28−7.19 (10H, m), 5.69−5.60 (4H, m), 4.97−4.92 (2H, m), 4.58−4.52 (4H, m), 4.28−4.23 (2H, m), 3.38−3.35 (1H, dt, J = 7.3, 4.5 Hz), 3.26−3.20 (1H, m), 2.20−2.08 (8H, m); ^{13}C NMR (125 MHz) 175.2, 175.2, 154.3, 154.2, 136.4, 136.4, 128.6, 128.6, 128.5, 128.4, 128.0, 127.8, 127.8, 127.7, 123.2, 123.1, 121.8, 121.6, 60.5, 60.4, 42.1, 42.1, 37.6, 37.5, 36.6, 36.4, 30.8, 30.7; IR (KBr) 3448, 3082, 2953, 2935, 1771, 1720, 1664, 1422, 1409, 1147, 973, 908; HRMS (ESI) calcd for $C_{32}H_{33}N_4O_4$ [M + H]$^+$ 537.2502, found 537.2528.

*(b). From the Spiro Compound **9f**.* To a stirring solution of **9f** (50 mg, 0.18 mmol, 1 equiv) in CH_2Cl_2 (4 mL) was added **HG-II** (6 mg, 0.009 mmol, 5 mol %) and the mixture was refluxed for 6 d at 45 °C. The reaction mixture was then concentrated and purified on silica gel (EtOAc−hexane, 20/80 to 40/60) to give compound **11** (35 mg, 73%).

Preparation of Cross-Metathesis Product 12. To a solution of 1-allyl-3-benzyl-1,3-diazaspiro[4.4]non-7-ene-2,4-dione **9f** (30 mg, 0.12 mmol, 1 equiv) and methyl acrylate (52 mg, 0.60 mmol, 5 equiv) in CH_2Cl_2 (0.05 M) was added **HG-II** (2.5 mg, 0.004 mmol, 3 mol %), and the mixture was stirred at 45 °C for 12 h. The reaction mixture was concentrated and purified on silica gel (ethyl acetate−hexane, 5/95 to 20/80) to yield **12** (25 mg, 62%) as a colorless oil: ^{1}H NMR (400 MHz) 7.33−7.24 (5H, m), 6.62−6.54 (1H, m), 5.86−5.82 (1H, m), 5.79 (2H, s), 4.66 (2H, d, J = 4.7 Hz), 4.49−4.44 (1H, m), 3.66 (3H, s), 3.62−3.56 (1H, m), 2.70 (2H, dd, J_1 =9.8, 1.3 Hz), 2.33 (2H, dd, J = 6.1, 3.1 Hz); ^{13}C NMR (125 MHz) 174.7, 165.6, 154.4, 140.0, 135.9, 128.6, 128.2, 127.7, 125.9, 123.3, 121.6, 60.4, 51.5, 42.3, 37.7, 35.9, 31.2; IR 3237, 2924, 2374, 1727, 1710, 1687, 1423, 1345, 1225, 1060; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_4$ [M + H]$^+$ 341.1501, found 341.1505.

Preparation of Olefin 13. To a solution of dimer **11** (20 mg, 0.037 mmol, 1.0 equiv) and methyl acrylate (32 mg, 0.370 mmol, 10.0 equiv) in CH_2Cl_2 (4 mL) was added **HG-II** (1.3 mg, 0.002 mmol, 5 mol %), and the mixture was stirred at 45 °C for 72 h. The reaction mixture was concentrated and purified on silica gel (ethyl acetate−hexane, 5/95 to 20/80) to yield **13** (10 mg, 79%) as a colorless oil: ^{1}H NMR (500 MHz) 7.34−7.27 (5H, m), 6.59 (1H, td, J = 7.7, 15.4 Hz), 5.84 (1H, td, J = 101, 15.5 Hz), 5.80−5.79 (2H, m), 4.66 (2H, d, J = 5.4 Hz), 4.47 (1H, dd, J = 1.7, 17.9 Hz), 3.67 (3H, s), 3.63−3.57 (1H, m), 2.70 (2H, dd, J = 1.2, 7.7 Hz), 2.35−2.33 (2H, m); ^{13}C NMR (125 MHz) 174.8, 165.7, 154.4, 140.1, 136.0, 128.7, 128.2, 127.7, 126.0, 123.4, 121.7, 60.4, 51.6, 42.3, 37.8, 36.0, 31.2; IR 3460, 3285, 3032, 2905, 2752, 2369, 1863, 1780, 1625, 1437, 1280, 1150, 1042; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_4$ [M + H]$^+$ 341.1501, found 341.1505.

Preparation of Bicyclohydantoin Derivatives 14 by RCM. To a stirring solution of **7** (0.2 mmol, 1 equiv) in toluene (3.0 mL) was added **G-II** (3.4 mg, 0.004 mmol, 2 mol %), and the mixture was stirred for 8 h at 80 °C. The reaction mixture was then concentrated and purified on silica gel (EtOAc−hexane, 10/90 to 20/80) to give compound **14.**

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*2-Allyl-8,8a-dihydroimidazo[1,5-a]pyridine-1,3(2H,5H)-dione (**14a**).* Using the general procedure, compound **7a** (40 mg, 0.18 mmol, 1.0 equiv) provided compound **14a** (29.4 mg, 85%) as a colorless oil: ^{1}H NMR (400 MHz) 5.86−5.76 (3H, m), 5.24−5.16 (2H, m), 4.37−4.32 (1H, m), 4.12−4.09 (2H, dt, J = 2.8, 1.7 Hz), 3.94 (1H, dd, J = 13.5, 6.7 Hz), 3.74−3.67 (1H, m), 2.65−2.58 (1H, m), 2.22−2.14 (1H, m); ^{13}C NMR (100 MHz) 172.9, 154.6, 131.2, 123.7, 122.5, 117.9, 53.3, 40.5, 39.1, 25.9; IR (KBr) 3428, 3064, 2923, 2905, 1721, 1710, 1624, 1432, 1224, 1047, 963, 928; HRMS (ESI) calcd for $C_{10}H_{13}N_2O_2$ $[M + H]^+$ 193.0977, found 193.0981.

*2-Benzyl-8,8a-dihydroimidazo[1,5-a]pyridine-1,3(2H,5H)-dione (**14b**).* Using the general procedure, compound **7b** (50 mg, 0.19 mmol, 1.0 equiv) provided compound **14b** (38.6 mg, 84%) as a colorless oil: ^{1}H NMR (400 MHz) 7.42−7.39 (2H, m), 7.34−7.26 (3H, m), 5.89−5.83 (1H, m), 5.80−5.75 (1H, m), 4.67 (2H, s), 7.38−4.33 (1H, m), 3.94 (1H, dd, J = 13.5, 6.6 Hz), 3.74−3.67 (1H, m), 2.65−2.56 (1H, m), 2.21−2.12 (1H, m); ^{13}C NMR (100 MHz) 172.9, 154.7, 136.2, 128.6, 128.6, 127.8, 123.8, 122.5, 53.4, 42.2, 39.2, 26.0; IR (KBr) 3458, 3072, 2953, 2925, 1761, 1710, 1634, 1442, 1424, 1147, 983, 918; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_2$ $[M + H]^+$ 243.1134, found 243.1138.

*2-Benzyl-6,7-dimethyl-8,8a-dihydroimidazo[1,5-a]pyridine-1,3-(2H,5H)-dione (**14c**).* Using the general procedure, compound **7c** (50 mg, 0.17 mmol, 1.0 equiv) provided compound **14c** (23.4 mg, 51%) as a colorless oil: ^{1}H NMR (500 MHz) 77.41−7.39 (2H, m), 7.33−7.25 (3H, m), 4.66 (2H, d, J = 2.6 Hz), 4.17 (1H, d, J = 17.7 Hz), 3.93 (1H, dd, J = 11.1, 5.5 Hz), 3.53 (1H, d, J = 16.7 Hz), 2.40 (1H, dd, J = 16.5, 5.3 Hz), 2.17−2.10 (1H, m), 1.70 (3H, s), 1.66 (3H, s); ^{13}C NMR (125 MHz) 173.2, 154.6, 136.3, 128.6, 128.5, 127.8, 122.7, 122.4, 54.2, 43.2, 42.2, 31.7, 18.9, 15.9; IR (KBr) 3448, 3062, 2943, 2915, 1751, 1730, 1534, 1432, 1414, 1147, 973, 928; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_2$ $[M + H]^+$ 271.1447, found 271.1442.

*(Z)-2-Benzyl-5,6,9,9a-tetrahydro-1H-imidazo[1,5-a]azepine-1,3(2H)-dione (**14d**).* Using the general procedure, compound **7d** (50 mg, 0.18 mmol, 1.0 equiv) provided compound **14d** (20.7 mg, 45%) as colorless oil: ^{1}H NMR (500 MHz) 7.34−7.32 (2H, m), 7.27−7.19 (3H, m), 5.91−5.87 (1H, m), 5.84−5.82 (1H m), 4.59 (2H, s), 4.02−3.98 (1H, m), 3.80 (1H, dd, J = 11.4, 2.5 Hz), 2.98−2.93 (1H, m), 2.70−2.64 (1H, m), 2.29−2.17 (3H, m); ^{13}C NMR (125 MHz) 172.0, 155.4, 136.2, 132.2, 128.6, 128.6, 127.9, 127.7, 59.4, 42.4, 41.0, 31.0, 27.8; IR (KBr) 3243, 2905, 2844, 2328, 1780, 1415, 1328, 1181, 1005, 928, 749, 701; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_2$ $[M + H]^+$ 257.1290, found 257.1286.

*(Z)-2-Benzyl-5,6,10,10a-tetrahydroimidazo[1,5-a]azocine-1,3-(2H,9H)-dione (**14e**).* Using the general procedure, compound **7e** (50 mg, 0.17 mmol, 1.0 equiv) provided compound **14e** (21.6 mg, 47%) as colorless oil: ^{1}H NMR (400 MHz) 7.34−7.31 (2H, m), 7.26−7.16 (3H, m), 5.80−5.73 (1H, m), 5.60−5.52 (1H, m), 4.59 (2H, s), 4.20−4.14 (1H, m), 3.90−3.85 (2H, m), 2.26−2.18 (1H, m), 2.13−2.06 (2H, m), 1.74−1.61 (2H, m), 1.45−1.35 (1H, m); ^{13}C NMR (100 MHz) 173.0, 155.3, 136.2, 132.5, 128.6, 127.8, 124.8, 61.1, 42.6, 38.5, 28.5, 24.7, 24.6; IR (KBr) 3443, 2945, 2644, 2428, 1750, 1415, 1228, 1171, 1105, 958, 749, 701; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_2$ $[M + H]^+$ 271.1447, found 271.1443.

General Procedure for the Preparation of 4,5-Diallyl-1,3-dibenzylimidazolidin-2-one 16 and 1,3,4-triallylimidazolidin-2-one 18. A 1 M solution of DIBAL-H in toluene (10.0 mL, 10.0 mmol) was added dropwise over 30 min to a stirred solution of **15** and **2d** (1.0 g, 3.1 mmol) in THF (50 mL) at −78 °C. The reaction mixture was stirred for 4 h, and MeOH (0.60 mL, 13 mmol) was added dropwise over 15 min. The reaction was poured into saturated NH_4Cl (50 mL) with vigorous stirring for 1 h, and then the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated NaCl, dried with Na_2SO_4, and concentrated under reduced pressure. The residual solvent was removed under high vacuum for 1 h. The crude mixture was dissolved in CH_2Cl_2 (30 mL) under argon and cooled to −78 °C. Allyltrimethylsilane (2.0 mL, 13 mmol) was added in one portion with stirring, and then BF_3−OEt_2 (1.6 mL, 13 mmol) was added dropwise over 10 min. Stirring was continued for 8 h, the ice bath was then removed, and the reaction was stirred for an additional 15 min. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by column chromatography on silica gel with EtOAc−hexane (5/95 to 20/80) to give compounds **16** and **19**, respectively.

*4,5-Diallyl-1,3-dibenzylimidazolidin-2-one (**16**).* Using the general procedure, compound **15** (1.0 g, 3.1 mmol, 1.0 equiv) provided compound **16** (837 mg, 78%) as colorless oil: ^{1}H NMR (500 MHz) 7.38−7.33 (5H, m), 7.31−7.27 (5H, m), 5.53−5.45 (2H, m), 4.99 (2H, d, J = 10.2 Hz), 4.96 (1H, s), 4.94−4.90 (3H, m), 4.02 (2H, d, J = 15.3 Hz), 3.20−3.18 (2H, m), 2.16 (4H, d, J = 6.0 Hz); ^{13}C NMR (125 MHz) 159.4, 137.0, 132.1, 128.3, 127.9, 127.1, 118.7, 55.1, 45.1, 35.9; IR (KBr) 3416, 3064, 3030, 2921, 2358, 1710, 1453, 1359, 1242, 1142, 1078, 1028, 996; HRMS (ESI) calcd for $C_{23}H_{27}N_2O$ $[M + H]^+$ 347.2123, found 347.2139.

*1,3,4-Triallylimidazolidin-2-one (**18**).* Using the general procedure, compound **2d** (1.0 g, 5.6 mmol, 1.0 equiv) provided compound **18** (692 mg, 60%) as colorless oil: ^{1}H NMR (500 MHz) 5.77−5.64 (3H, m), 5.21−5.09 (6H, m), 4.15−4.10 (1H, dt, J = 15.7, 4.9 Hz), 3.84−3.79 (1H, dt, J = 15.4, 6.0 Hz), 3.76−3.74 (1H, dt, J = 15.4, 6.2 Hz), 3.62−3.55 (2H, m), 3.30 (1H, t, J = 8.8 Hz), 2.94 (1H,dd, J = 8.9, 7.1 Hz), 2.45−2.40 (1H, m), 2.21−2.15 (1H, m); ^{13}C NMR (125 MHz) 160.2, 133.7, 133.5, 132.6, 118.5, 117.5, 117.4, 52.0, 47.4, 46.8, 44.5, 36.5; IR (KBr) 3443, 2922, 2351, 1647, 1539, 1270, 1116, 1053, 772, 665; HRMS (ESI) calcd for $C_{12}H_{19}N_2O$ $[M + H]^+$ 207.1497, found 207.1493.

Preparation of 1,3-Dibenzyl-3a,4,7,7a-tetrahydro-1*H*-benzo-[d]imidazol-2(3*H*)-one (17). To a solution of **16** (0.14 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added **G-II** (2.5 mg, 0.003 mmol, 2 mol %), and the mixture was stirred for 8 h at room temperature. The reaction mixture was then concentrated and purified on silica gel (EtOAc−hexane, 10/90 to 20/80) to give compound **17** (44 mg, 99%) as a colorless crystal (EtOAc/hexane): mp 137−139 °C; ^{1}H NMR (500 MHz) 7.36 (4H, d, J = 4.5 Hz), 7.32−7.30 (1H, m), 5.56 (1H, d, J = 3.3 Hz), 4.61 (1H, d, J = 15.0 Hz), 4.38 (1H, d, J = 15.0 Hz), 2.96−2.93 (1H, m), 2.25−2.20 (1H, m), 1.95−1.90 (1H, m) ; ^{13}C NMR (125 MHz) 163.1, 137.3, 128.4, 128.3, 127.2, 125.0, 57.1, 47.1, 29.7; IR (KBr) 3422, 2911, 2334, 1720, 1355, 1236, 1126, 1116, 1053, 772, 665; HRMS (ESI) calcd for $C_{21}H_{23}N_2O$ $[M + H]^+$ 319.1810, found 319.1817.

Preparation of 2-Allyl-1,2,8,8a-tetrahydroimidazo[1,5-a]-pyridin-3(5*H*)-one (19). To a solution of **18** (50 mg, 0.24 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added **G-II** (4 mg, 0.005 mmol, 2 mol %), and the mixture was stirred for 8 h at room temperature. The reaction mixture was then concentrated and purified on silica gel (EtOAc−hexane, 10/90 to 20/80) to give compound **19** (26 mg, 60%) as a colorless oil: ^{1}H NMR (400 MHz) 5.79−5.71 (3H, m), 5.22−5.15 (2H,m), 4.18−4.12 (1H, m), 3.82 (2H, d, J = 7.57 Hz), 3.60−3.54 (2H, m), 3.46 (1H, t, J = 10.3 Hz), 2.97 (1H, dd, J = 10.7, 6.7 Hz), 2.17−2.13 (2H, m) ; ^{13}C NMR (125 MHz) 164.8, 133.6, 124.8, 123.5, 117.5, 49.5, 48.4, 46.8, 40.8, 29.7; IR 3433, 2912, 2341, 1657, 1549, 1260, 1126, 1043, 772, 665; HRMS (ESI) calcd for $C_{10}H_{15}N_2O$ $[M + H]^+$ 179.1184, found 179.1158.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data and NMR spectra of all synthetic compounds, and X-ray crystallographic data (CIF) of **9e**, **11**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Reviews: (a) Ware, E. *Chem. Rev.* **1950**, *46*, 403. (b) Meusel, M.; Gutschow, M. *Org. Prep. Proced. Int.* **2004**, *36*, 391.

(2) (a) Moloney, G. P.; Martin, G. R.; Mathews, N.; Milne, A.; Hobbs, H.; Dosworth, S.; Sang, P. Y.; Knight, C.; Williams, M.; Maxwell, M.; Glen, R. C. *J. Med. Chem.* **1999**, *42*, 2504. (b) Last-Barney, K .; Davidson, W.; Cardozo, M.; Frye, L. L.; Grygon, C. A.; Hopkins, J. L.; Jeanfavre, D. D.; Pav, S.; Qian, C.; Stevenson, J. M.; Tong, L.; Zindell, R.; Kelly, T. A. *J. Am. Chem. Soc.* **2001**, *123*, 5643. (c) Somsák, L.; Kovács, L.; Tóth, M.; Ösz, E.; Szilágyi, L.; Györgydeák, Z.; Dinya, Z.; Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 2843. (d) Thenmozhiyal, J. C.; Wong, P. T. H.; Chui, W. K. *J. Med. Chem.* **2004**, *47*, 1527. (e) Muccioli, G. G.; Fazio, N.; Scriba, G. K. E.; Poppitz, W.; Cannata, F.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. *J. Med. Chem.* **2006**, *49*, 417. (f) Kaschani, F.; Clerc, J.; Krahn, D.; Bier, D.; Hong, T. N.; Ottmann, C.; Niessen, S.; Colby, T.; van der Hoorn, R. A. L.; Kaiser, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 5230.

(3) (a) Coker, J. N.; Kohlhase, W. L.; Martens, T. F.; Rogers, O.; Allan, G. G. *J. Org. Chem.* **1962**, *27*, 3201. (b) Sarges, R.; Howard, H. R., Jr.; Kelbaugh, P. R. *J. Org. Chem.* **1982**, *47*, 4081. (c) Bovy, P.; Lenaers, A.; Callaert, M.; Herickx, N.; Gillet, C.; Roba, J.; Dethy, J.-M; Callaert-Deveen, B.; Janssens, M. *Eur. J. Med. Chem.* **1988**, *23*, 165. (d) Sarges, R.; Goldstein, S. W.; Welch, W. M.; Swindell, A. C.; Siegel, T. W.; Beyer, T. A. *J. Med. Chem.* **1990**, *33*, 1859. (e) Park, K.-H.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 3520. (f) Gomez-Monterrey, I.; Santelli, G.; Campiglia, P.; Califano, D.; Falasconi, F.; Pisano, C.; Vesci, L.; Lama, T.; Grieco, P.; Novellino, E. *J. Med. Chem.* **2005**, *48*, 1152. (g) Sacchetti, A.; Silvani, A.; Gatti, F. G.; Lesma, G.; Pilati, T.; Trucchi, B. *Org. Biomol. Chem.* **2011**, *9*, 5515.

(4) (a) Sano, H.; Sugai, S. *Tetrahedron* **1995**, *51*, 4635. (b) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369.

(5) (a) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindo, M.; Honma, T.; Tohjigamori, M.; Haneishi, T. J. *Antibiotics* **1991**, *44*, 293. (b) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133.

(6) (a) Sankhavasi, W.; Kohmoto, S.; Yamamoto, M.; Nishio, T.; Iida, I.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 935. (b) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293. (c) Fraile, J. M.; Lafuente, G.; Mayoral, J. A.; Pallarés, A. *Tetrahedron* **2011**, *67*, 8639. (d) Wehner, V.; Blum, H.; Kurz, M.; Stilz, H. U. *Synthesis* **2002**, 2023−2036.

(7) (a) Ben-Ishai, D.; Goldstein, E. *Tetrahedron* **1971**, *27*, 3119. (b) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. *Org. Lett.* **2004**, *6*, 735. (c) Alsina, J.; Scott, W. L.; O'Donne, M. J. *Tetrahedron Lett.* **2005**, *46*, 3131. (d) Pesquet, A.; Daïch, A.; Hijfte, L. V. *J. Org. Chem.* **2006**, *71*, 5303. (e) Lu, Y.; Geib, S. J.; Damodaran, K.; Sui, B.; Zhang, Z.; Curran, D. P.; Zhang, W. *Chem. Commun.* **2010**, *46*, 7578. (f) Albers, H. M. H. G.; Hendrickx, L. J. D.; van Tol, R. J. P.; Hausmann, J.; Perrakis, A.; Ovaa, H. *J. Med. Chem.* **2011**, *54*, 4619.

(8) (a) Daugan, A.; Grondin, P.; Ruault, C.; Le monnier de Gouville, A. C.; Coste, H.; Linget, J. M.; Kirilovsky, J.; Hyafil, F.; Labaudinière, R. *J. Med. Chem.* **2003**, *46*, 4533. (b) Hotha, S.; Yarrow, J. C.; Yang, J. G.; Garrett, S.; Renduchintala, K. V.; Mayer, T. U.; Kapoor, T. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2379.

(9) (a) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535. (b) Zancanella, M. A.; Romo, D. *Org. Lett.* **2008**, *10*, 3685. (c) Cernak, T. A.; Gleason, J. L. *J. Org. Chem.* **2008**, *73*, 102.

(10) (a) Graus, S.; Casabona, D.; Uriel, S.; Cativiela, C.; Serrano, J. L. *CrystEngComm* **2010**, *12*, 3132. (b) Chattopadhyay, B.; Mukherjee, A. K.; Narendra, N.; Hemantha, H. P.; Sureshbabu, V. V.; Helliwell, M.; Mukherjee, M. *Cryst. Growth Des.* **2010**, *10*, 4476. (c) Park, Y. S.; Seo, S.; Kim, E.-H.; Paek, K. *Org. Lett.* **2011**, *13*, 5904.

(11) Jamieson, A. G.; Russell, D.; Hamilton, A. D. *Chem. Commun.* **2012**, *48*, 3709.

(12) For recent examples on synthesis of substituted hydantoins: (a) Beller, M.; Eckert, M.; Moradi, W.; Neumann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1454. (b) Chowdari, N. S.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 867. (c) Gao, M.; Yang, Y.; Wu, Y.-D.; Deng, C.; Shu, W.-M; Zhang, D.-X.; Cao, L.-P.; She, N.-F.; Wu, A.-X. *Org. Lett.* **2010**, *12*, 4026. (d) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Nicolini, S.; Perrulli, F. R.; Santeusanio, S. *Org. Lett.* **2011**, *13*, 353. (e) Miura, T.; Mikano, Y.; Murakami, M. *Org. Lett.* **2011**, *13*, 3560.

(13) (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003. For leading reviews, see: (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (m) Chauvin, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3740. (e) Schrock, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 3748. (f) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760. (g) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (h) Holub, N.; Blechert, S. *Chem.—Asian J.* **2007**, *2*, 1064. (i) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708. (j) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783. (k) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746. (l) Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68*, 397.

(14) For specific examples on RCM: (a) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. (b) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056. (c) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Org. Lett.* **2005**, *7*, 3183. (d) Scholte, A. A.; An, M. H.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 4759. (e) Berlin, J. M.; Campbell, K; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339. (f) Schmidt, B.; Biernat, A. *Org. Lett.* **2008**, *10*, 105. (g) Dowling, M. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 15090. (h) Wang, Y.; Jimenez, M.; Hansen, A. S.; Raiber, E.-A.; Schreiber, S. L.; Young, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 9196.

(15) For examples of ROM−RCM: (a) Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139. (b) Stapper, C.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 6456. (c) Morgan, J. P.; Morrill, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67. (d) Sello, J. K.; Andreana, P. R.; Lee, D.; Schreiber, S. L. *Org. Lett.* **2003**, *4*, 4125. (e) Holtsclaw, J.; Koreeda, M. *Org. Lett.* **2004**, *6*, 3719. (f) Malik, C. K.; Ghosh, S. *Org. Lett.* **2007**, *9*, 2537. (g) Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 13873. (h) Zhu, Z.-B.; Shi, M. *Org. Lett.* **2010**, *12*, 4462. (i) Bose, S.; Ghosh, M.; Ghosh, S. *J. Org. Chem.* **2012**, *77*, 6345.

(16) For examples of CM: (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. For leading references: (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (c) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (d) Donohoe, T. J.; Bower, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3373. (e) Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094. (f) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697.

(17) (a) Dyatkin, A. B. *Tetrahedron Lett.* **1997**, *38*, 2065. (b) Bujisman, R. C.; Vuuren, E. V.; Sterrenburg, J. G. *Org. Lett.* **2001**, 3785. (c) Dieltiens, N.; Claeys, D. D.; Zhdankin, V. V.; Nemykin, V. N.; Allaert, B.; Verpoort, F.; Stevens, C. V. *Eur. J. Org. Chem.* **2006**, 2649.

(18) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (b) Connor, C. J. O'; Beckmannw, H. S. G.; Spring, D. R. *Chem. Soc. Rev.* **2012**, DOI: 10.1039/c2cs35023h.

(19) (a) Dash, J.; Arseniyadis, S.; Cossy, J. *Adv. Synth. Catal.* **2007**, *349*, 152. (b) Hoffman, T. J.; Dash, J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2009**, *11*, 2756. (c) Dash, J.; Melillo, B.; Arseniyadis, S.; Cossy, J. *Tetrahedron Lett.* **2011**, *52*, 2246.

(20) Dhara, K.; Paladhi, S.; Midya, G. C.; Dash, J. *Org. Biomol. Chem.* **2011**, *9*, 3801.

(21) (a) Cortes, S.; Liao, Z. K.; Watson, D.; Kohn, H. *J. Med. Chem.* **1985**, *28*, 601. (b) Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 773. (c) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369. (d) Ulgheri., F.; Giunta., D.; Spanu., P. *Tetrahedron* **2008**, *64*, 11768. (e) Volgraf, M.; Lumb, J. P.; Brastianos, H. C.; Carr, G.; Chung, M. K. W.; Muenzel, M.; Mauk, A. G.; Andersen, R. J.; Trauner, D. *Nat. Chem. Biol.* **2008**, *4*, 535. (f) Havel, V.; Svec, J.; Wimmerova, M.; Dusek, M.; Pojarova, M.; Sindelar, V. *Org. Lett.* **2011**, *13*, 4000. (g) Fraile, J. M.; Lafuente, G.; Mayoral, J. A.; Pallares, A. *Tetrahedron* **2011**, *67*, 8639. (h) Das, S.; Addis, D.; Knoepke, L. R.; Bentrup, U.; Junge, K.; Brueckner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9180.

(22) The crystal structure of **9e** (CCDC 881290), **11** (CCDC 881289), and **17** (CCDC 881291) have been deposited at the Cambridge Crystallographic Data Centre.

(23) (a) Haines, D. R; Fuller, R. W.; Ahmad, S.; Vistica, D. T.; Marquez, V. E. *J. Med. Chem.* **1987**, *30*, 542. (b) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*; VCH: Weinheim, 1995. For some examples: (c) Burton, S. G.; Dorrington, R. A. *Tetrahedron: Asymmetry* **2004**, *15*, 2737.

(24) (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (b) Sutherland, J. C.; Hess, G. P. *Nat. Prod. Rep.* **2000**, *17*, 621. (c) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131. (d) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785.

(25) (a) Pellicciari, R.; Costantino, G. *Curr. Opin. Chem. Biol.* **1999**, *3*, 433. (b) Monn, J. A.; Schoepp, D. D. *Annu. Rep. Med. Chem.* **2000**, *35*, 1. (c) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597.

(26) (a) Casabona, D.; Cativiela, C. *Synthesis* **2006**, 2440. (b) For a RCM approach to hydroxy carboxylic acid, see: Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944.

(27) For few specific examples, see: (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (b) Abell, A. D.; Gardiner, J. *Org. Lett.* **2002**, *4*, 3663. (c) Fustero, S.; Bartolomé, A.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Soler, J. F.; Arellano, C. R. de; Fuentes, A. S. *Org. Lett.* **2003**, *5*, 2523. (d) Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem.* **2005**, *70*, 3838. (e) Teichert, J. F.; Zhang, S.; Zijl, A. W.; van; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658.

(28) (a) Tietze, L. F.; Beifus, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (c) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.

(29) Nagasawaj, H. T.; Elberltnpg, A.; Fraser, S.; Mizuno, N. S. *J. Med. Chem.* **1971**, *6*, 501.

(30) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867.

(31) Akester, J.; Cui, J.; Fraenkel, G. *J. Org. Chem.* **1997**, *62*, 431.

(32) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Kremzow, D.; Seidel, G.; Lehmann, C. W.; Fürstner, A. *Chem.—Eur. J.* **2005**, *11*, 1833.

(33) (a) Davies, S. G.; Mortlock, A. A. *Tetrahedron Lett.* **1992**, *33*, 1117. (b) Davies, S. G.; Edwards, A. J.; Evans, G. B.; Mortlock, A. A. *Tetrahedron* **1994**, *50*, 6621.