Type-Two Intramolecular Diels−Alder Reactions of Pyrazolo-*o*-quinodimethanes

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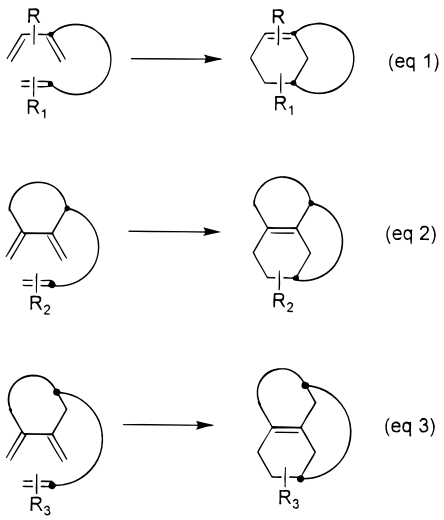
Two isomeric series of homologous *N*-(acryloyloxy)alkylated pyrazolo-3-sulfolenes **10a**−**c** and **18a**−**c** have been efficiently synthesized from a common starting material, 4,6-dihydro-1*H*-thieno[3,4-*c*]-pyrazole (**5**). Thermolysis of these fused 3-sulfolenes provides the corresponding *o*-quinodimethanes which simultaneously undergo "type-two" intramolecular Diels−Alder reactions to form two- and three-atom-bridged tricyclic pyrazoles which are otherwise difficult to prepare. It was also demostrated that, depending on the *N*-substitution position of the pyrazolo-fused 3-sulfolenes, the temperature required for the thermal extrusion of SO_2 and the regioselectivity of the T2-IMDA reactions were influenced substantially.

Introduction

"Type-two" intramolecular Diels−Alder (T2-IMDA) reactions have been well studied in the past two decades[1] and have found utility in the synthesis of natural products.[2] T2-IMDA reactions differ from the "type-one" intramolecular Diels−Alder reactions in that the dienophile is tethered to the diene at the 2-position for the former rather than at the 1-position for the latter. Because the products of T2-IMDA reactions contain an unsaturated bridgehead which is conceivably more strained than the fused bicyclic products of comparable type-one IMDA reactions, T2-IMDA reactions usually do not proceed as readily as type-one IMDA reactions.[1c] Almost all T2-IMDA reactions developed so far have been applied toward the construction of one-atom-bridged bicyclic systems (eq 1) because bicyclic systems containing bridges of two or more atoms have been considered to be much more difficult to achieve via a T2-IMDA reaction because of the increased distance between their diene and dienophile. We recently reported the first-ever construction of a two-atom-bridged tricyclic system by a T2-IMDA reaction (eq 2),[3] and we thought it would be of interest to examine whether T2-IMDA reactions could be of use in the construction of polycyclic molecules containing a bridge with three or more atoms (eq 3).[4]



It has been shown that the thermal reaction of an inseparable mixture (1:3) of the methylated pyrazolo-3-sulfolenes **1** and **2** with *N*-phenylmaleimide gave a 1:3 mixture of the [4+2] cycloadducts **3** and **4**.[5] Therefore, we anticipated that the pyrazolo-*o*-quinodimethane should be an ideal diene moiety[6] for the T2-IMDA reactions just by tethering the dienophile to either of the two nitrogen atoms in the pyrazole ring (eq 2 and 3). One advantage of this approach is that the T2-IMDA reactions of both isomers can be examined using the same starting material. In this paper, we wish to describe the details of our work on the preparation of *N*-(acryloyloxy)alkylated pyrazolo-3-sulfolenes **10a**−**c** and **18a**−**c** and their subsequent success in the T2-IMDA reactions to form two- and three-atom-bridged tricyclic pyrazoles. The regioselectivity of these T2-IMDA reactions will also be discussed.

† Deceased February 25, 1999.

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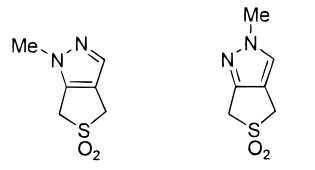
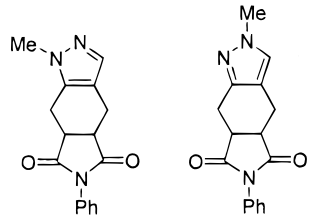


1 **2**



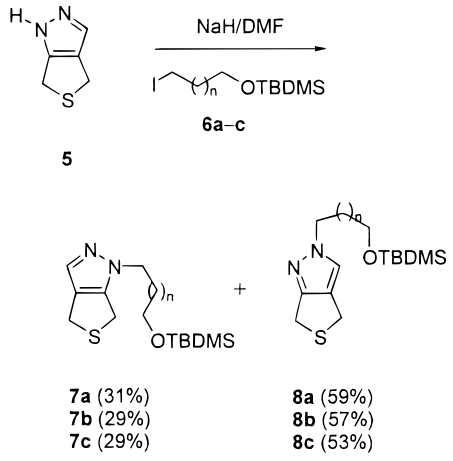
3 **4**

Results and Discussions

Two-Atom-Bridged Tricyclic Pyrazoles. When pyrazolo-fused dihydrothiophene **5**[7] was treated with NaH at 0 °C followed by the addition of the siloxypropyl iodide **6a**,[8] an isomeric mixture of the *N*-substituted products **7a** and **8a** was obtained which were separated by column chromatography (Scheme 1). The regiochemical assignments of **7a** and **8a** were supported by analyses of their respective NOESY spectra. The key NOE cross-peaks used to assign the regiochemistry of **7a** and **8a** are highlighted in Figure 1. For the major isomer **8a**, NOE correlations between H_7 and the olefinic proton (H_3) indicated their proximity. These correlations provided evidence that the alkylation took place on the *N*-2 position. Likewise, the lack of a correlation signal between H_7 and the olefinic proton (H_3) in the NOESY spectrum for **7a** was supportive of the alkylation occurring on the *N*-1 position.

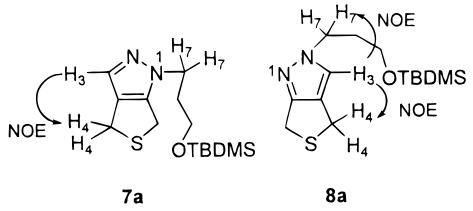
Compound **7a** was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) giving rise to the fused 3-sulfolene **9a**. Desilylation of **9a** with HOAc followed by esterification of the resulting alcohol with acryloyl chloride in the presence of Hunig's base provided the desired compound **10a** in 80% yield. When a benzene solution of compound **10a** (0.005 M) was thermolyzed at 180 °C in a sealed tube, the two-atom-bridged tricyclic compound **12a** was

Scheme 1



7a (31%) **8a** (59%)
7b (29%) **8b** (57%)
7c (29%) **8c** (53%)

a: n = 1; **b**: n = 2; **c**: n = 3



7a **8a**

Figure 1. Key NOE interactions for **7a** and **8a**.

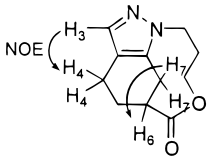


Figure 2. Key NOE interactions for **12a**.

formed as the sole product in 90% yield via a T2-IMDA reaction of *o*-quinodimethane **11a** formed *in situ* (Scheme 2). Analytical HPLC gave no indication of the presence of any other regioisomeric cycloadducts (i.e., **13a**). The regiochemical assignment of **12a** was based on the analysis of its COSY, NOESY, and HMQC spectra. The NOESY spectrum showed NOE correlations between H_3 and H_4, as well as between H_7 and the methine proton H_6, indicating their proximity (Figure 2).

We postulate that the regiospecificity of the T2-IMDA reaction of **11a** is highly influenced by the length of the tether joining the diene and dienophile moieties by restricting the dienophile's direction of attack. To test the above hypothesis, compounds **10b** and **10c** (1- and 2-carbon homologues of **10a**, respectively) were prepared and their T2-IMDA reactions studied. Alkylation of compound **5** with siloxybutyl iodide **6b**[9] gave an isomeric mixture of alkylated products **7b** and **8b** which were separated chromatographically (Scheme 1). Treatment of **7b** by the same sequence of reactions as for compound **7a** led to the isolation of thermolysis precursor **10b** in high yield. Similarly, thermolysis precursor **10c** was synthesized via the same sequence of reactions described above using siloxypentyl iodide **6c**[10] as the alkylating agent.

The T2-IMDA reaction of *o*-quinodimethane **11b**, prepared by the thermolysis of a benzene solution of **10b** at 180 °C in a sealed tube, led to the isolation of cycloadduct **12b** as the sole product in 94% yield (Scheme 2). No trace of the other possible regioisomer **13b** was detected by analytical HPLC. The regiochemistry of compound **12b** was confirmed by 2D NMR experiments and single-crystal X-ray analysis. Apparently, a six-atom tether between the diene and dienophile is still restrictive enough to produce, in a regiospecific manner, the T2-IMDA cycloadduct in high yield.

Thermolysis of compound **10c**, the 2-carbon homologue of compound **10a**, resulted in the isolation of two tricyclic compounds **12c** and **13c** in 88% and 4% yield, respectively. 2D-NMR experiments and several comparison studies with previously synthesized compounds allowed the determination of the regiochemistry of the major

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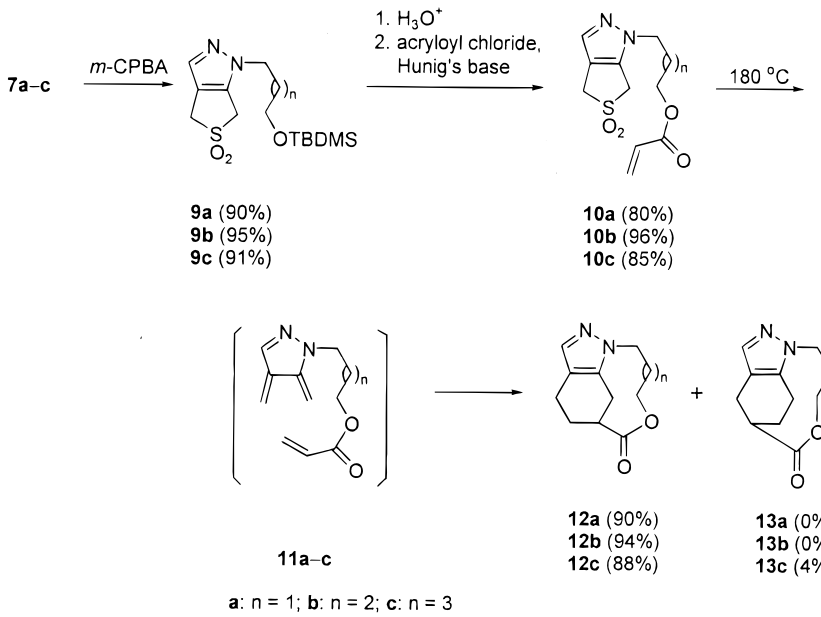
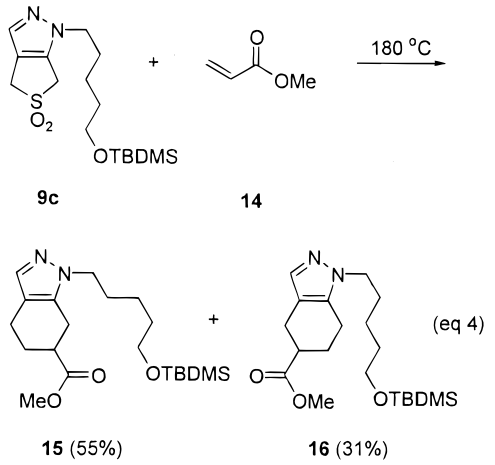
Scheme 2



cycloadduct **12c**. The ^{1}H NMR chemical shifts and coupling patterns of **12c** and **12b** are similar, thus indicating their structure similarity. The structure of compound **13c** was unequivocally established by X-ray crystallography which also served as indirect confirmation of the regiochemistry assigned to compound **12c**.

The results of these series T2-IMDA reactions indicate a preference for "*meta*" or 1,3-cycloaddition regiochemistry. This follows the general trend observed for previously described T2-IMDA cyaloadditions.[11] An intermolecular Diels–Alder reaction was also carried out in order to determine whether the high regioselectivity observed for the T2-IMDA reactions of **11a**–**c** was indeed influenced by the presence of a tether. Thus, heating compound **9c** with methyl acrylate (**14**) at 180 °C in a sealed tube readily produced the regioisomeric mixture of cycloadducts **15** and **16** in a 1.8:1 ratio which could be separated by HPLC (eq 4). The structures of **15** and **16**



were assigned by NOESY experiments with the key NOE correlations being highlighted in Figure 3. For isomer **15**, the presence of a correlation between the allylic methylene protons (H_4) and both the olefinic proton (H_3) and the *C*-5 methylene proton (H_5) indicated the cycloaddition leading to compound **15** is *meta* to the *N*-1 atom. Whereas for **16**, the presence of a correlation between the allylic methylene protons (H_4) and both the olefinic proton (H_3) and the *C*-5 methine proton (H_5) indicated the cycloaddition leading to compound **16** is "*para*" to the *N*-1 atom.

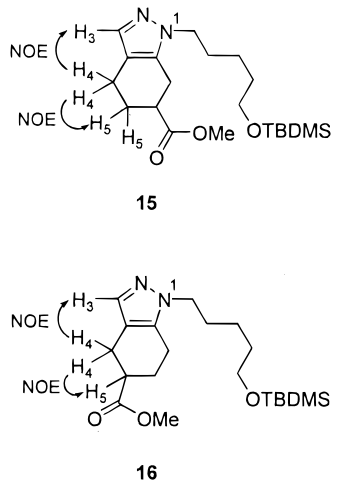


Figure 3. Key NOE interactions for **15** and **16**.

The lack of any significant regioselectivity in the intermolecular Diels–Alder reaction between compounds **9c** and **14** supports the contention that the tether is paramount for achieving a high level of regioselectivity in the T2-IMDA cycloaddition reaction. The two possible transition states for the cycloaddition reaction of **10c** are depicted below and labeled **A** and **B**. It can be seen that transition state **B** has more torsional strain when compared to transition state **A**. This is in good agreement with the product distribution obtained in which cycloadduct **12c**, the product due to transition state **A**, is the major regioisomer. The decrease in regioselectivity of the T2-IMDA reaction of compound **11c** as compared to that of compounds **11a** and **11b** is an indication that, as the length of the tether linking the diene and dienophile

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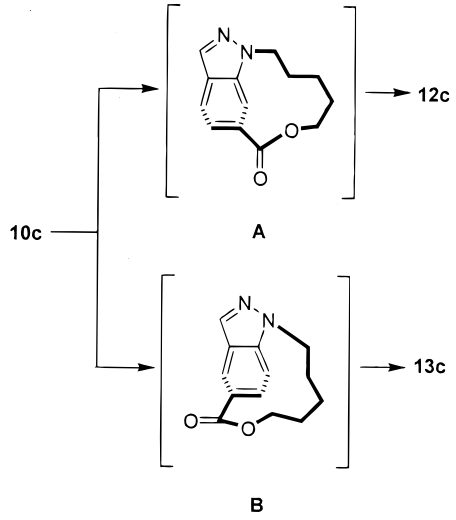
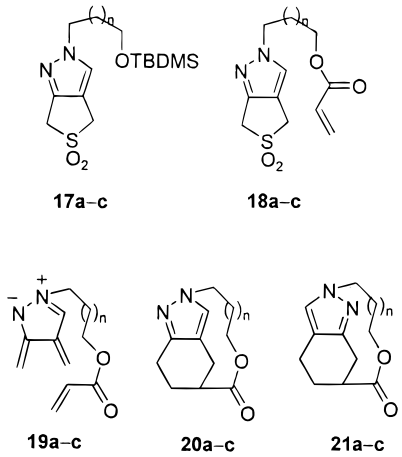
moieties is increased, the reaction will increasingly resemble that of a bimolecular process.



Three-Atom-Bridged Tricyclic Pyrazoles. Analogous to the above investigation, the reactivity and regioselectivity of the T2-IMDA reaction of another homologous series of *N*-substituted *o*-quinodimethane **19a**−**c** were also studied. Compound **18a**, the immediate precursor to intermediate **19a**, was synthesized starting from bicyclic compound **8a**. Oxidation of compound **8a** with *m*-CPBA gave the corresponding fused 3-sulfolene **17a**. Desilylation of **17a** followed by subsequent esterification with acryloyl chloride gave **18a** in good yield. Although it was reported that both **1** and **2** extrude SO_2 at 200 °C,[5] compound **18a** appeared to be more thermally stable than **10a**. Thus, when a benzene solution of compound **18a** (0.005 M) was thermolyzed in a sealed tube at 180 °C for 6 h, the starting material was recovered intact. This was not unexpected due to the necessity of compound **18a** to form zwitterionic *o*-quinodimethane **19a** in order to undergo a T2-IMDA reaction. The generation of zwitterionic **19a** should be less favorable than the formation of the neutral species **11a** from **10a**.[12] Gratifyingly, when compound **18a** was thermolyzed at 210 °C for 4 h, extrusion of SO_2 led to the formation of the transient intermediate **19a** which underwent a T2-IMDA reaction to form two three-atom-bridged tricyclic heterocycles **20a** and **21a** in a 1.5:1 ratio. The mixture of the T2-IMDA reaction products could be separated by HPLC and the regiochemistry of the major isomer, **20a**, was unambiguously ascertained by single-crystal X-ray analysis.

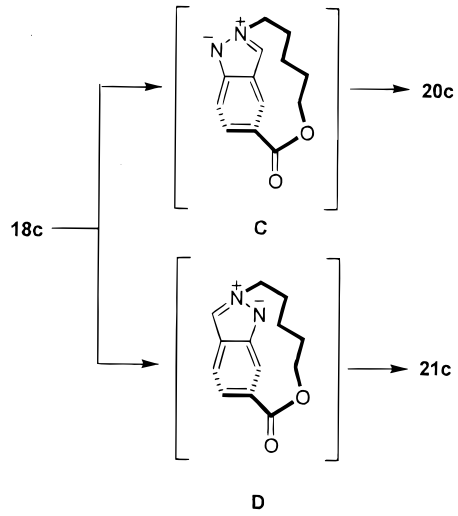
The length of the tether was then extended by one methylene unit to six atoms by the synthesis of compound **18b** from **8b** in a procedure analogous to the above sequence. Thermolysis of **18b** at 210 °C for 4 h led to the formation of the three-atom-bridged tricyclic heterocycles **20b** and **21b** in a 1:1 ratio via transient intermediate **19b**. The mixture of the T2-IMDA reaction products could also be separated by HPLC, and the regiochemistry of the more polar isomer **20b** was again unequivocally determined by single-crystal X-ray analysis.

The length of the tether was then further extended to a seven-atom spacer by the synthesis of compound **18c** from **8c**. Again, **18c** was thermolyzed at 210 °C in benzene for 4 h and the intermediate *o*-quinodimethane **19c** underwent a T2-IMDA reaction to give a mixture of tricyclic heterocycles **20c** (52%) and **21c** (43%). These two



a: n = 1; **b**: n = 2; **c**: n = 3

cycloadducts were separated by HPLC and the structure of the less polar isomer **21c** was determined by single-crystal X-ray analysis. As compared with **11a**−**c**, the relative lack of regioselectivity for the T2-IMDA reaction of **19a**−**c** can be rationalized by the smaller geometric difference between the two possible transition states **C** and **D**.



An intermolecular Diels−Alder reaction was also studied to investigate the factors affecting the regioselectivity of the T2-IMDA reactions of **19a**−**c**. Heating compound **17c** with methyl acrylate (**14**) at 210 °C in a sealed tube for 4 h readily produced a regioisomeric mixture of cycloadducts **22** and **23** in a 2:1 ratio. These two cycloadducts were separated by HPLC and the regiochemical assignments were established based on their COSY, NOESY, and HMQC spectral analyses. The NOESY spectrum of the minor isomer **23** showed NOE correlations between H_3 and H_4, as well as H_7 and the methine proton H_6, indicating their proximity (Figure 4). These correlations confirm that the cycloaddition was *meta* to the *N*-1 atom. The regioselectivity is different from the result of the T2-IMDA reaction of **19c** which gave the *para* cycloadduct **20c** and *meta* cycloadduct **21c** in a 1.2:1 ratio.

(12) (a) Chao, I.; Lu, H. F.; Chou, T. S. *J. Org. Chem*. **1997**, *62*, 7882. (b) Chou, T. S.; Ko, C. W. *Molecules* **1996**, *1*, 93. (c)White, L. A.; Storr, R. C. *Tetrahedron* **1996**, *52*, 3117.

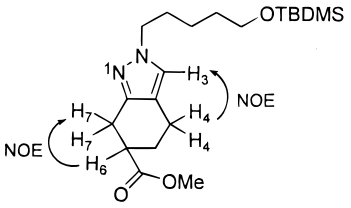
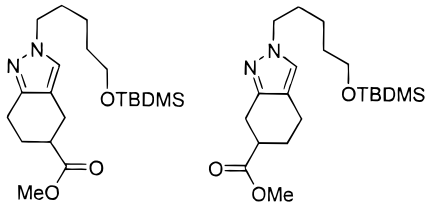


Figure 4. Key NOE interactions for **23**.



To gain insight into the reasons for the decreased *para* ratio in **20a**/**21a**, **20b**/**21b**, and **20c**/**21c**, conformational searches were carried out for both *para* and *meta* isomers of these compounds to identify low energy conformers. A Monte Carlo multiple minimum (MCMM) search was performed on each structure[13] with AMBER* all-atom force field[14] in a vacuum using MacroModel V6.5.[15] The lowest energy conformers obtained corresponded well with the available X-ray crystal structures. The strain energies of the lowest energy conformers calculated by MM3(94)[16] are listed in Table 1. As expected, tricyclic systems with lactone bridges (**20a**−**c** and **21a**−**c**) have larger strain energies than the bicyclic analogues (**22** and **23**). Furthermore, the tricyclic systems with the shorter lactone bridges have the larger strain energies. Interestingly, for the bicyclic systems, it is the *para* isomer which has less strain energy, whereas for the tricyclic systems the *para* isomers all have larger strain energies as compared to their corresponding *meta* isomers. Detailed comparison of force field results showed no indication of any dominant energy components (such as stretching, bending, nonbonded interaction, etc.) that could be responsible for the larger strain energy in the *para* tricyclic systems. It seems to be a combined effect from all the energy contributions. Examination of the distance between the two bridgeheads of the lactone bridge ($D_{N...C}$, where N refers to the bridgehead N-atom in the pyrazole moiety and C refers to the bridgehead C-atom to which the lactone bridge is connected) shows the *meta* products to have shorter end-to-end distances than the *para* products (Table 1) because of short N−N and C−N bonds in the pyrazole ring. In other words, the lactone bridge needs to stretch out more in the *para* products than in the *meta* products. This would explain why all the *para* products bear more strain energy than the corresponding *meta* products in the tricyclic systems. With this understanding, we reasoned that the lactone bridge should also impose more strain on the *para* transition states of the tricyclic Diels−Alder adducts than the *meta* transition states. Because the electronic effect exerted by substituents in the bicyclic and tricyclic systems are similar, the above results imply that the reduced *para* ratio in the tricyclic systems is due to larger strain imposed on the *para* transition states by the lactone bridges.

Table 1. MM3 Sigma Strain Energy (E_{Strain}) and End-to-end Distance of the Lactone Bridge ($D_{N...C}$) of the Lowest Energy Structure for Each Compound Obtained from MCMM Search (energy unit, kcal/mol; distance, Å.)

	22[a]	**23**[a]	**20a**	**21a**	**20b**	**21b**	**20c**	**21c**
E_{strain}	−2.17	−0.43	31.58	30.49	21.15	19.96	12.22	11.41
$D_{N...C}$	4.500[b]	4.456[b]	3.882	3.880	4.132	4.082	4.270	4.227

[a] The substituent on the pyrazole N-atom is replaced by an H-atom during the calculations for **22** and **23**. [b] For **22** and **23**, N refers to the N-2 atom in the pyrazole moiety and C refers to the C-atom which is connected to the methoxycarbonyl substituent.

In summary, we have demonstrated herein a facile synthesis of compounds **12a**−**c**, **13c**, **20a**−**c**, and **21a**−**c**. The efficient synthesis of the precursors **10a**−**c** and **18a**−**c** makes T2-IMDA reactions useful for the construction of bridged tricyclic pyrazoles which are otherwise difficult to prepare. In this way, the T2-IMDA reaction should become useful in the synthesis of polycyclic macrocycles. We have also demonstrated that, depending on the *N*-substitution position of the pyrazolo-fused 3-sulfolenes, the temperature required for the thermal extrusion of SO_2 and the regioselectivity of the T2-IMDA reactions were influenced substantially.

Experimental Section

General Procedure for the Alkylation of Pyrazolo-3-sulfolene 5. To a solution of **5** (0.16 g, 1.28 mmol) in dried DMF (5 mL) at 0 °C was added NaH (0.07 g, 1.78 mmol), and the mixture was stirred at 0 °C for 1 h. To this suspension was added iodide **6** (1.93 mmol) and the resulting mixture was gradually warmed to room temperature. The mixture was then stirred at room temperature for 17 h and H_2O (1 mL) was added to quench the reaction. After the solvent was removed under reduced pressure, the regioisomers (**7a**/**8a**, **7b**/**8b**, or **7c**/**8c**) were separated by HPLC (LiChrosorb column, hexane/EtOAc, 4:1). Compounds **8a**, **8b**, and **8c** were the less polar isomers obtained first from the HPLC column, whereas compounds **7a**, **7b**, and **7c** were the more polar isomers.

1-{3-(*tert*-Butyldimethylsilyl)oxy}propyl-4,6-dihydro-1*H*-thieno[3,4-*c*]pyrazole (7a) was obtained from the reaction of compound **5** and 3-(*tert*-butyldimethylsiloxy)-1-iodopropane (**6a**) in 31% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16 (s,1H), 4.06 (t, J = 6.9 Hz, 2H), 3.91 (bs, 2H), 3.89 (bs, 2H), 3.58 (t, J = 5.8 Hz, 2H), 2.07−1.97 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 146.8, 132.4, 124.8, 59.4, 46.9, 32.9, 27.9, 26.9, 25.9, 18.2, −5.4. IR (neat): 2955, 1471, 1420, 1258, 1101 cm^{-1}. MS (*m*/*z*): 298 (M^+), 241 (100%), 184, 139. HRMS calcd for $C_{14}H_{26}N_2OSSi$: 298.1535. Found: 298.1531.

2-{3-(*tert*-Butyldimethylsilyl)oxy}propyl-2,6-dihydro-4*H*-thieno[3,4-*c*]pyrazole (8a) was obtained from the reaction of compound **5** and 3-(*tert*-butyldimethylsiloxy)-1-iodopropane (**6a**) in 59% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.08 (s, 1H), 4.16 (t, J = 6.7 Hz, 2H), 3.97 (bs, 2H), 3.88 (bs, 2H), 3.58 (t, J = 5.6 Hz, 2H), 2.07−1.98 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 157.7, 123.8, 122.1, 59.4, 49.3, 33.1, 29.0, 27.6, 25.8, 18.1, −5.5. IR

(13) X-ray crystal structures of **20b** and **21c** were used as starting geometry for the MCMM search, whereas all the others were built using the structure-building module implemented in MacroModel. The structures were fully optimized using the PR conjugated gradient method followed by the full matrix Newton−Raphson method prior to the MCMM search. The search was performed by random variation of selected torsions at each Monte Carlo step. A total of 1500 structures was sampled for each compound, and unique conformations within 3 kcal/mol of the global minimum were used for optimization with MM3-(94).

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(15) *MacroModel, Interactive Molecular Modeling System*, version 6.5, Department of Chemistry, Columbia University: New York, 1998.

(16) Allinger, N. L. *MM3(94)*; University of Georgia: Athens, GA, 1994.

(neat): 2929, 1566, 1471, 1255, 1107 cm^{-1}. MS (*m*/*z*): 298 (M^+), 241 (100%), 184, 139. HRMS calcd for $C_{14}H_{26}N_2OSSi$: 298.1535. Found: 298.1544.

1-{4-(*tert*-Butyldimethylsilyl)oxy}butyl-4,6-dihydro-1*H*-thieno[3,4-*c*]pyrazole (7b) was obtained from the reaction of compound **5** and 4-(*tert*-butyldimethylsiloxy)-1-iodobutane (**6b**) in 29% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.14 (s, 1H), 3.98 (t, J = 7.1 Hz, 2H), 3.88 (bs, 4H), 3.61 (t, J = 6.2 Hz, 2H), 1.93−1.83 (m, 2H), 1.55−1.45 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 146.1, 132.0, 125.0, 62.3, 50.4, 29.6, 27.7, 26.9, 26.6, 25.8, 18.2, −5.5. IR (neat): 2971, 1681, 1434, 1263 cm^{-1}. MS (*m*/*z*): 312 (M^+), 255, 198 (100%). HRMS calcd for $C_{15}H_{28}N_2OSSi$: 312.1692. Found: 312.1699.

2-{4-(*tert*-Butyldimethylsilyl)oxy}butyl-2,6-dihydro-4*H*-thieno[3,4-*c*]pyrazole (8b) was obtained from the reaction of compound **5** and 4-(*tert*-butyldimethylsiloxy)-1-iodobutane (**6b**) in 57% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.05 (s, 1H), 4.06 (t, J = 7.0 Hz, 2H), 3.96 (s, 2H), 3.88 (s, 2H), 3.61 (t, J = 6.3 Hz, 2H), 1.94−1.84 (m, 2H), 1.54−1.45 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 157.5, 123.2, 122.2, 62.4, 52.5, 29.6, 29.0, 27.6, 27.1, 25.8, 18.2, −5.5. IR (neat): 2953, 1684, 1464, 1256 cm^{-1}. MS (*m*/*z*): 312 (M^+), 298, 271, 255 (100%). HRMS calcd for $C_{15}H_{28}N_2OSSi$: 312.1692. Found: 312.1686.

1-{5-(*tert*-Butyldimethylsilyl)oxy}pentyl-4,6-dihydro-1*H*-thieno[3,4-*c*]pyrazole (7c) was obtained from the reaction of compound **5** and 5-(*tert*-butyldimethylsiloxy)-1-iodopentane (**6c**) in 29% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.12 (s, 1H), 3.92 (t, J = 7.2 Hz, 2H), 3.86 (bs, 2H), 3.85 (bs, 2H), 3.56 (t, J = 6.2 Hz, 2H), 1.85−1.75 (m, 2H), 1.55−1.46 (m, 2H), 1.36−1.31 (m, 2H), 0.85 (s, 9H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 146.2, 132.2, 125.1, 62.8, 50.6, 32.3, 30.0, 27.9, 27.0, 25.9, 23.0, 18.3, 6.0. IR (neat): 2933, 2859, 1463, 1415, 1253, 1098 cm^{-1}. MS (*m*/*z*): 326 (M^+), 311, 269 (100%). HRMS calcd for $C_{16}H_{30}N_2OSSi$: 326.1848. Found: 326.1846

2-{5-(*tert*-Butyldimethylsilyl)oxy}pentyl-2,6-dihydro-4*H*-thieno[3,4-*c*]pyrazole (8c) was obtained from the reaction of compound **5** and 5-(*tert*-butyldimethylsiloxy)-1-iodopentane (**6c**) in 53% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.02 (s, 1H), 4.01 (t, J = 7.0 Hz, 2H), 3.94 (bs, 2H), 3.86 (bs, 2H), 3.56 (t, J = 6.4 Hz, 2H), 1.87−1.77 (m, 2H), 1.56−1.46 (m, 2H), 1.36−1.28 (m, 2H) 0.85 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 157.7, 123.3, 122.3, 62.8, 52.8, 32.2, 30.4, 29.1, 27.7, 25.9, 22.9, 18.3, −5.3. IR (neat): 2930, 2857, 1565, 1471, 1387, 1259, 1098 cm^{-1}. MS (*m*/*z*): 326 (M^+), 311, 269 (100%). HRMS calcd for $C_{16}H_{30}N_2OSSi$: 326.1848. Found: 326.1845.

General Procedure for the Oxidation of Substituted-4,6-dihydro-1*H*-thieno[3,4-*c*]pyrazole 7a−c, and Substituted-2,6-dihydro-4*H*-thieno[3,4-*c*]pyrazole 8a−c. To a solution of substituted-dihydrothieno[3,4-*c*]pyrazole (**7** or **8**, 0.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added 55% *m*-CPBA (75 mg, 0.24 mmol), and the mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous $Na_2S_2O_3$ (30 mL x 3) and saturated aqueous $NaHCO_3$ (30 mL x 3). The organic layer was dried ($MgSO_4$), and the solvent was then removed under reduced pressure. The residue was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:2) to give the oxidative product.

1-{3-(*tert*-Butyldimethylsilyl)oxy}propyl-4,6-dihydro-1*H*-thieno[3,4-*c*]pyrazole 5,5-dioxide (9a) was obtained from the reaction of compound **7a** and *m*-CPBA in 90% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43 (s, 1H), 4.22 (s, 4H), 4.13 (t, J = 6.7 Hz, 2H), 3.48 (t, J = 5.5 Hz, 2H), 2.01−1.93 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 135.0, 133.1, 110.4, 58.9, 55.0, 52.4, 47.4, 32.6, 25.8, 18.2, −5.4. IR ($CDCl_3$): 2956, 1329, 1185, 1125 cm^{-1}. MS (*m*/*z*): 331 (M^++1), 273, 209 (100%). HRMS calcd for $C_{14}H_{26}N_2O_3SSi$: 330.1433. Found: 330.1454.

2-{3-(*tert*-Butyldimethylsilyl)oxy}propyl-2,6-dihydro-4*H*-thieno[3,4-*c*]pyrazole 5,5-dioxide (17a) was obtained from the reaction of compound **8a** and *m*-CPBA in 90% yield as a white solid; mp 53−54 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (s,1H), 4.24−4.19 (m, 6H), 3.54 (t, J = 5.7 Hz, 2H), 2.04−1.96 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 143.9, 126.2, 110.3, 59.2, 53.8, 53.1, 49.5, 33.0, 25.8, 18.2, −5.4. IR (KBr): 2931, 1485, 1319, 1129, 1095 cm^{-1}. MS (*m*/*z*): 331 (M^++1), 273, 209 (100%). Anal. Calcd for $C_{14}H_{26}N_2O_3SSi$: C, 50.88; H, 7.93; N, 8.48. Found: C, 50.51; H, 7.75; N, 8.58.

1-{4-(*tert*-Butyldimethylsilyl)oxy}butyl-4,6-dihydro-1*H*-thieno[3,4-*c*]pyrazole 5,5-dioxide (9b) was obtained from the reaction of compound **7b** and *m*-CPBA in 95% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45 (s, 1H), 4.26 (s, 2H), 4.22 (s, 2H), 4.09 (t, J = 7.2 Hz, 2H), 3.62 (t, J = 6.0 Hz, 2H), 1.95−1.86 (m, 2H), 1.53−1.44 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 134.6, 132.3, 110.7, 62.2, 54.9, 52.4, 51.1, 29.5, 26.6, 25.8, 18.2, −5.4. IR (neat): 3025, 1330, 1210, 1185 cm^{-1}. MS (*m*/*z*): 287 ($M^+ - C_4H_9$), 230, 166, 135, 107 (100%). HRMS calcd for $C_{15}H_{28}N_2O_3SSi-(C_4H_9)$: 287.0886. Found: 287.0883.

2-{4-(*tert*-Butyldimethylsilyl)oxy}butyl-2,6-dihydro-4*H*-thieno[3,4-*c*]pyrazole 5,5-dioxide (17b) was obtained from the reaction of compound **8b** and *m*-CPBA in 96% yield as a colorless oil.^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 (s, 1H), 4.25 (s, 2H), 4.22 (s, 2H), 4.17 (t, J = 7.0 Hz, 2H), 3.63 (t, J = 6.0 Hz, 2H), 1.96−1.89 (m, 2H), 1.55−1.46 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 143.7, 125.9, 110.5, 61.8, 53.7, 52.9, 52.5, 29.2, 27.0, 25.8, 25.6, −3.7. IR (neat): 2959, 1325, 1207, 1122 cm^{-1}. MS (*m*/*z*): 344 (M^+), 329, 287, 223 (100%). HRMS calcd for $C_{15}H_{28}N_2O_3SSi-(C_4H_9)$: 287.0886. Found: 287.0889.

1-{5-(*tert*-Butyldimethylsilyl)oxy}pentyl-4,6-dihydro-1*H*-thieno[3,4-*c*]pyrazole 5,5-dioxide (9c) was obtained from the reaction of compound **7c** and *m*-CPBA in 91% yield as a colorless oil.^1H NMR ($CDCl_3$, 300 MHz): δ 7.43 (s, 1H), 4.24 (bs, 2H), 4.20 (bs, 2H), 4.03 (t, J = 7.1 Hz, 2H), 3.56 (t, J = 6.2 Hz, 2H), 1.88−1.78 (m, 2H), 1.57−1.46 (m, 2H), 1.34−1.28 (m, 2H) 0.85 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 134.7, 132.3, 110.7, 62.6, 55.0, 52.4, 51.3, 32.1, 29.8, 25.9, 22.9, 18.3, 6.0. IR (neat): 2932, 1466, 1318, 1121 cm^{-1}. MS (*m*/*z*): 358 (M^+), 343, 301 (100%), 237. HRMS calcd for $C_{16}H_{30}N_2O_3SSi$: 358.1746. Found: 358.1701.

2-{5-(*tert*-Butyldimethylsilyl)oxy}pentyl-2,6-dihydro-4*H*-thieno[3,4-*c*]pyrazole 5,5-dioxide (17c) was obtained from the reaction of compound **8c** and *m*-CPBA in 93% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31 (s, 1H), 4.23 (bs, 2H), 4.20 (bs, 2H), 4.12 (t, J = 7.0 Hz, 2H), 3.57 (t, J = 6.2 Hz, 2H), 1.90−1.81 (m, 2H), 1.57−1.47 (m, 2H), 1.38−1.33 (m, 2H), 0.85 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 143.8, 125.7, 110.5, 62.7, 53.8, 53.1, 53.0, 32.1, 30.2, 25.9, 22.9, 18.3, 6.0. IR (neat): 2933, 1466, 1322, 1252, 1184, 1099 cm^{-1}. MS (*m*/*z*): 358 (M^+), 343, 301, 237 (100%). HRMS calcd for $C_{16}H_{30}N_2O_3SSi$: 358.1746. Found: 358.1754.

General Procedure for the Preparation of 10a, 10b, 10c, 18a, 18b, and 18c. A mixture of silyl ether (**9** or **17**, 0.13 mmol) in HOAc/H_2O/THF (3:1:1, 10 mL) was stirred at room temperature for 36 h. The solvent was removed under reduced pressure, and the residue was diluted with MeOH (1 mL). The mixture was then concentrated in vacuo. After the residue in CH_2Cl_2 (30 mL) and *N*,*N*-diisopropylethylamine (0.34 mmol) was stirred at 0 °C for 30 min, acryloyl chloride (0.15 mmol) was added. The resulting mixture was gradually warmed to room temperature, and the stirring was continued for 17 h, after which time CH_2Cl_2 (100 mL) was added. The mixture was washed with 1N HCl (10 mL) and then saturated aqueous $NaHCO_3$ (20 mL x 2). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:4) to give the target acrylic acid ester.

3-(4,6-Dihydro-5,5-dioxo-1*H*-thieno[3,4-*c*]pyrazol-1-yl)-propyl 2-propenoate (10a) was obtained from the acidic desilylation of compound **9a** and subsequent esterification with acryloyl chloride in 80% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (s, 1H), 6.42 (d, J = 17.6 Hz, 1H), 6.11 (dd, J = 10.4, 17.6 Hz, 1H), 5.87 (d, J = 10.4 Hz, 1H), 4.28 (s, 2H), 4.23 (s, 2H), 4.19−4.14 (m, 4H), 2.31−2.22 (m,

2H). IR (neat): 2995, 1724, 1330, 1106 cm^{-1}. MS (*m*/*z*): 270 (M^+), 206, 151 (100%). HRMS calcd for $C_{11}H_{14}N_2O_4S$: 270.0674. Found: 270.0681.

3-(5,5-Dioxo-4*H*-thieno[3,4-*c*]pyrazol-2(6*H*)-yl)propyl 2-propenoate (18a) was obtained from the acidic desilylation of compound **17a** and subsequent esterification with acryloyl chloride in 81% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (s, 1H), 6.36 (d, J = 17.1 Hz, 1H), 6.05 (dd, J = 10.4, 17.1 Hz, 1H), 5.81 (d, J = 10.4 Hz, 1H), 4.20 (s, 2H), 4.17 (s, 2H), 4.22−4.10 (m, 4H), 2.24−2.15 (m, 2H). IR (neat): 3028, 1723, 1409, 1325, 1195, 1125 cm^{-1}. MS (*m*/*z*): 270 (M^+), 206, 167, 149 (100%). HRMS calcd for $C_{11}H_{14}N_2O_4S$: 270.0674. Found: 270.0646.

4-(4,6-Dihydro-5,5-dioxo-1*H*-thieno[3,4-*c*]pyrazol-1-yl)-butyl 2-propenoate (10b) was obtained from the acidic desilylation of compound **9b** and subsequent esterification with acryloyl chloride in 96% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.48 (s, 1H), 6.40 (dd, J = 1.5, 17.6 Hz, 1H), 6.11 (dd, J = 10.5, 17.6 Hz, 1H), 5.85 (dd, J = 1.5, 10.5 Hz, 1H), 4.28 (s, 2H), 4.25 (s, 2H), 4.18 (t, J = 6.5 Hz, 2H), 4.11 (t, J = 6.9 Hz, 2H), 2.00−1.90 (m, 2H), 1.74−1.64 (m, 2H). IR (neat): 3029, 1721, 1330, 1187 cm^{-1}. MS (*m*/*z*): 285 (M^++1), 221, 133, 55 (100%). HRMS calcd for $C_{12}H_{16}N_2O_4S$: 284.0831. Found: 284.0824.

4-(5,5-Dioxo-4*H*-thieno[3,4-*c*]pyrazol-2(6*H*)-yl)butyl2-propenoate (18b) was obtained from the acidic desilylation of compound **17b** and subsequent esterification with acryloyl chloride in 96% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35 (s, 1H), 6.40 (dd, J = 1.3, 17.2 Hz, 1H), 6.11 (dd, J = 10.5, 17.2 Hz, 1H), 5.84 (dd, J = 1.3, 10.5 Hz, 1H), 4.26 (s, 2H), 4.23 (s, 2H), 4.21−4.17 (m, 4H), 2.02−1.92 (m, 2H), 1.74−1.64 (m, 2H). IR (neat): 3027, 1721, 1410, 1325, 1223, 1126 cm^{-1}. MS (*m*/*z*): 285 (M^++1), 221, 133, 55 (100%). HRMS calcd for $C_{12}H_{16}N_2O_4S$: 284.0831. Found: 284.0840.

5-(4,6-Dihydro-5,5-dioxo-1*H*-thieno[3,4-*c*]pyrazol-1-yl)-pentyl 2-propenoate (10c) was obtained from the acidic desilylation of compound **9c** and subsequent esterification with acryloyl chloride in 85% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.44 (s, 1H), 6.37 (dd, J = 1.8, 19.0 Hz, 1H), 6.08 (dd, J = 11.7, 19.0 Hz, 1H), 5.80 (dd, J = 1.3, 11.7 Hz, 1H), 4.25 (s, 2H), 4.21 (s, 2H), 4.12 (t, J = 6.3 Hz, 2H), 4.04 (t, J = 7.0 Hz, 2H), 1.91−1.81 (m, 2H), 1.70−1.63 (m, 2H), 1.41−1.35 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 166.2, 134.8, 132.4, 130.8, 128.4, 110.9, 63.9, 55.0, 52.4, 51.0, 29.5, 28.1, 23.0. IR (neat): 2941, 1718, 1409, 1318, 1187, 1126 cm^{-1}. MS (*m*/*z*): 298 (M^+), 234, 179, 108 (100%). HRMS calcd for $C_{13}H_{18}N_2O_4S$: 298.0987. Found: 298.0984.

5-(5,5-Dioxo-4*H*-thieno[3,4-*c*]pyrazol-2(6*H*)-yl)pentyl 2-propenoate (18c) was obtained from the acidic desilylation of compound **17c** and subsequent esterification with acryloyl chloride in 85% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31 (s, 1H), 6.36 (dd, J = 1.4, 18.7 Hz, 1H), 6.08 (dd, J = 11.8, 18.7 Hz, 1H), 5.80 (dd, J = 1.4, 11.8 Hz, 1H), 4.22 (s, 2H), 4.20 (s, 2H), 4.15−4.10 (m, 4H), 1.93−1.84 (m, 2H), 1.73−1.64 (m, 2H), 1.41−1.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 166.2, 143.9, 130.7, 128.4, 125.7, 110.6, 64.0, 53.8, 53.1, 52.7, 30.0, 28.1, 23.0. IR (neat): 2942, 1718, 1410, 1316, 1196, 1126 cm^{-1}. MS (*m*/*z*): 298 (M^+), 233, 133, 108, 55 (100%). HRMS calcd for $C_{13}H_{18}N_2O_4S$: 298.0987. Found: 298.0972.

General Procedure for the Intramolecular Diels−Alder Reaction of 10a, 10b, and 10c. A solution of **10** (0.025 mmol) in benzene (5 mL) was heated in a sealed tube at 180 °C for 4 h after which time the solvent was removed under reduced pressure. The crude product was purified by HPLC (LiChrosorb column, hexane/EtOAc, 4:1) to give the cycloadduct. Regioisomers (**12c**/**13c**) were separated by HPLC. Compound **12c** was the less polar isomer obtained first from the HPLC column, whereas compound **13c** was the more polar isomer.

3,4-Diaza-8-oxatricyclo[8.2.2.0^{4,12}]tetradeca-1(12),2-dien-9-one (12a)was obtained from the intramolecular Diels−Alder reaction of compound **10a** in 90% yield as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (s, 1H), 4.37−4.29 (m, 2H), 3.93−3.86 (m, 1H), 3.44−3.38 (m, 2H), 3.13−3.11 (m, 1H), 2.77−2.71 (m, 1H), 2.50−2.22 (m, 3H), 2.15−1.92 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 175.9, 143.4, 138.6, 117.1, 63.0, 44.0, 41.6, 28.1, 27.2, 23.5, 17.2. IR (neat): 2964, 1735, 1248, 1165 cm^{-1}. MS (*m*/*z*): 206 (M^+, 100%), 192, 161, 151. HRMS calcd for $C_{11}H_{14}N_2O_2$: 206.1055. Found: 206.1050.

3,4-Diaza-9-oxatricyclo[9.2.2.0^{4,13}]pentadeca-1(13),2-dien-10-one (12b) was obtained from the intramolecular Diels−Alder reaction of compound **10b** in 94% yield as a white solid; mp 90−91 °C. ^1H NMR($CDCl_3$, 300 MHz): δ 7.28 (s, 1H), 4.38 (bs, 1H), 4.24−4.19 (m, 2H), 3.59 (t, J = 10.5 Hz, 1H), 3.42−3.37 (m, 1H), 3.09 (bs, 1H), 2.75−2.70 (m, 1H), 2.56−2.53 (m, 1H), 2.45−2.33 (m, 3H), 2.01−1.75 (m, 2H), 1.45−1.40 (m, 1H), 0.70−0.52 (m, 1H). IR (KBr): 2944, 1728, 1176 cm^{-1}. MS (*m*/*z*): 220 (M^+, 100%), 175, 133. HRMS calcd for $C_{12}H_{16}N_2O_2$: 220.1212. Found: 220.1217.

3,4-Diaza-10-oxatricyclo[10.2.2.0^{4,14}]hexadeca-1(14),2-dien-11-one (12c) was obtained from the intramolecular Diels−Alder reaction of compound **10c** in 88% yield as a white solid; mp 45−47 °C. ^1H NMR($CDCl_3$, 300 MHz): δ 7.16 (s, 1H), 4.38−4.35 (m, 1H), 4.19−4.09 (m, 2H), 3.54−3.38 (m, 2H), 3.11−3.05 (m, 1H), 2.82−2.71 (m, 1H), 2.61−2.51 (m, 2H), 2.47−2.37 (m, 1H), 2.08−2.02 (m, 1H), 1.84−1.80 (m, 2H), 1.62−1.50 (m, 1H), 1.41−1.29 (m, 1H), 1.07 (bs, 1H), 0.37 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 173.2, 137.6, 137.0, 115.3, 65.4, 50.2, 39.2, 28.4, 27.7, 25.6, 23.7, 23.3, 16.8. IR (KBr): 2933, 1730, 1456, 1171 cm^{-1}. MS (*m*/*z*): 234 (M^+), 190, 161, 133 (100%). HRMS calcd for $C_{13}H_{18}N_2O_2$: 234.1368. Found: 234.1367

3,4-Diaza-10-oxatricyclo[10.3.1.0^{4,15}]hexadeca-1(15),2-dien-11-one (13c) was obtained from the intramolecular Diels−Alder reaction of compound **10c** in 4% yield as a white solid; mp 152−153 °C. ^1H NMR($CDCl_3$, 300 MHz): δ 7.23 (s, 1H), 4.70−4.65 (m, 1H), 4.24−4.18 (m, 1H), 3.92−3.83 (m, 1H), 3.33−3.24 (m, 2H), 3.07−2.94 (m, 2H), 2.65−2.57 (m, 2H), 2.42−2.32 (m, 1H), 1.91−1.72 (m, 3H), 1.46−1.21 (m, 3H), −0.28 (t, J = 10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 174.9, 139.7, 137.6, 114.5, 64.1, 49.4, 39.8, 29.2, 28.5, 27.8, 24.2, 22.7, 19.0. IR (KBr): 2927, 1719, 1278, 1126 cm^{-1}. MS (*m*/*z*): 234 (M^+, 100%), 189, 133. HRMS calcd for $C_{13}H_{18}N_2O_2$: 234.1368. Found: 234.1362.

General Procedure for the Intramolecular Diels−Alder Reaction of 18a, 18b, and 18c. A solution of **18** (0.025 mmol) in benzene (5 mL) was heated in a sealed tube at 210 °C for 4 h after which time the solvent was removed under reduced pressure. The regioisomers (**20a**/**21a**, **20b**/**21b**, or **20c**/**21c**) were separated individually by HPLC (LiChrosorb column, hexane/EtOAc, 4:1) to give the pure cycloadduct. Compounds **21a**, **21b**, and **21c** were the less polar isomers obtained first from the HPLC column, whereas compounds **20a**, **20b**, and **20c** were the more polar isomers.

2,3-Diaza-7-oxatricyclo[7.2.2.1^{3,11}]tetradeca-1,11-dien-8-one (20a) was obtained from the intramolecular Diels−Alder reaction of compound **18a** in 50% yield as a white solid; mp 130−131 °C. ^1H NMR($CDCl_3$, 300 MHz): δ 7.26 (s, 1H), 4.33 (dd, J = 5.0, 14.2 Hz, 1H), 3.91 (t, J = 12.0 Hz, 1H), 3.78−3.66 (m, 2H), 3.04−2.97 (m, 3H), 2.72−2.61 (m, 2H), 2.29−2.21 (m, 1H), 1.99−1.64 (m, 3H). IR (KBr): 3022, 1706, 1518, 1216 cm^{-1}. MS (*m*/*z*): 206 (M^+, 100%), 133. HRMS calcd for $C_{11}H_{14}N_2O_2$: 206.1055. Found: 206.1051.

2,3-Diaza-7-oxatricyclo[7.3.1.1^{3,12}]tetradeca-1,12-dien-8-one (21a) was obtained from the intramolecular Diels−Alder reaction of compound **18a** in 34% yield as a white solid; mp 118−119 °C. ^1H NMR($CDCl_3$, 300 MHz): δ 7.33 (s, 1H), 4.18−4.06 (m, 3H), 3.73−3.67 (m, 1H), 3.15 (d, J = 9.7 Hz, 2H), 2.88−2.77 (m, 2H), 2.48 (td, J = 8.8, 14.2 Hz, 1H), 1.95 (td, J = 8.3, 14.2 Hz, 1H), 1.83−1.78 (m, 2H), 1.69−1.66 (m, 1H). IR (KBr): 3020, 1700, 1518, 1216 cm^{-1}. MS (*m*/*z*): 206 (M^+, 100%), 133. HRMS calcd for $C_{11}H_{14}N_2O_2$: 206.1055. Found: 206.1047.

2,3-Diaza-8-oxatricyclo[8.2.2.1^{3,12}]pentadeca-1,12-dien-9-one (20b) was obtained from the intramolecular Diels−Alder reaction of compound **18b** in 42% yield as a white solid; mp 95−96 °C. ^1H NMR($CDCl_3$, 300 MHz): δ 7.20 (s, 1H), 4.39−4.33 (m, 1H), 4.26−4.21 (m, 1H), 3.80−3.70 (m, 1H), 3.40 (t, J = 11.0 Hz, 1H), 3.03−2.92 (m, 3H), 2.70−2.57 (m, 2H), 2.04−1.94 (m, 2H), 1.82−1.76 (m, 2H), 1.71−1.65 (m, 1H), 1.32−

1.26 (m, 1H). IR (KBr): 2956, 1706, 1206 cm^{-1}. MS (*m*/*z*): 220 (M^+), 177, 133 (100%). HRMS calcd for $C_{12}H_{16}N_2O_2$: 220.1212. Found: 220.1219.

2,3-Diaza-8-oxatricyclo[8.3.1.1^{3,13}]pentadeca-1,13-dien-9-one (21b) was obtained from the intramolecular Diels−Alder reaction of compound **18b** in 45% yield as a colorless oil. ^{1}H NMR($CDCl_3$, 300 MHz): δ 7.16 (s, 1H), 4.26−4.22 (m, 1H), 4.14−4.08 (m, 1H), 3.77−3.61 (m, 2H), 3.24−3.19 (m, 1H), 3.18−2.99 (m, 1H), 2.74−2.65 (m, 2H), 2.55−2.45 (m, 1H), 2.31−2.15 (m, 1H), 2.05−1.94 (m, 2H), 1.78−1.64 (m, 2H), 1.00−0.92 (m, 1H). IR (neat): 2944, 1713, 1142 cm^{-1}. MS (*m*/*z*): 220 (M^+), 193, 177 (100%), 133. HRMS calcd for $C_{12}H_{16}N_2O_2$: 220.1212., Found: 220.1216.

2,3-Diaza-9-oxatricyclo[9.2.2.1^{3,13}]hexadeca-1,13-dien-10-one (20c) was obtained from the intramolecular Diels−Alder reaction of compound **18c** in 52% yield as a colorless oil. ^{1}H NMR($CDCl_3$, 300 MHz): δ 7.18 (s, 1H), 4.38−4.32 (m, 1H), 4.22−4.20 (m, 1H), 3.77−3.73 (m, 1H), 3.45−3.38 (m, 1H), 3.05−2.95 (m, 2H), 2.82−2.74 (m, 2H), 2.71−2.52 (m, 2H), 1.98−1.93 (m, 1H), 1.73−1.55 (m, 2H), 1.38−1.28 (m, 1H), 1.17−1.03 (m, 1H), 0.84−0.72 (m, 1H), 0.56−0.84 (m, 1H). ^{13}C NMR($CDCl_3$, 75.4 MHz): δ 174.1, 150.6, 132.9, 117.5, 64.1, 51.8, 40.4, 31.7, 30.1, 25.8, 24.7, 20.8, 19.4. IR (neat): 2940, 1715, 1451, 1173 cm^{-1}. MS (*m*/*z*): 234 (M^+), 233 (100%), 190, 133. HRMS calcd for $C_{13}H_{18}N_2O_2$: 234.136. Found: 234.1363.

2,3-Diaza-9-oxatricyclo[9.3.1.1^{3,14}]hexadeca-1,14-dien-10-one (21c) was obtained from the intramolecular Diels−Alder reaction of compound **18c** in 43% yield as a white solid; mp 67−68 °C. ^{1}H NMR($CDCl_3$, 300 MHz:) δ 7.08 (s, 1H), 4.35−4.46 (m, 1H), 4.06−4.02 (m, 2H), 3.31−3.23 (m, 2H), 3.03−3.00 (m, 1H), 2.66−2.51 (m, 4H), 1.92−1.84 (m, 2H), 1.57−1.55 (m, 1H), 1.37−1.23 (m, 2H), 1.08−0.89 (m, 1H), 0.25−0.16 (m, 1H). ^{13}C NMR($CDCl_3$, 75.4 MHz): δ 173.6, 150.2, 128.9, 116.2, 63.9, 51.5, 40.2, 31.4, 31.3, 27.5, 25.6, 20.9, 16.3. IR (KBr): 2932, 1717, 1450, 1166 cm^{-1}. MS (*m*/*z*): 234 (M^+), 233, 190, 133 (100%), 119. HRMS calcd for $C_{13}H_{18}N_2O_2$: 234.1368. Found: 234.1372.

Methyl 1-{5-(*tert*-butyldimethylsilyl)oxy}pentyl-4,5,6,7-tetrahydro-1*H*-indazole-6-carboxylate (15) and Methyl 1-{5-(*tert*-butyldimethylsilyl)oxy}pentyl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate (16). A solution of **9c** (0.035 mmol) and methyl acrylate (0.17 mmol) in benzene (5 mL) was heated in a sealed tube at 180 °C for 4 h after which time the solvent was removed under reduced pressure. The regioisomers were separated by HPLC (LiChrosorb column, hexane/ EtOAc 3:1) to give the less polar isomer **15** (55%) and the more polar isomer **16** (31%). Compound **15**: colorless oil. ^{1}H NMR($CDCl_3$, 300 MHz): δ 7.21 (s, 1H), 3.94 (t, J = 7.3 Hz, 2H), 3.71 (s, 3H), 3.56 (t, J = 6.3 Hz, 2H), 2.85−2.49 (m, 5H), 2.21−2.14 (m, 1H), 1.80−1.70 (m, 3H), 1.53−1.46 (m, 2H), 1.35−1.27 (m, 2H), 0.84 (s, 9H), 0.03 (s, 6H). ^{13}C NMR($CDCl_3$, 75.4 MHz): δ 175.2, 136.2, 135.9, 114.8, 62.8, 51.9, 48.8, 40.0, 32.4, 30.1, 26.3, 25.9, 23.9, 23.0, 19.9, 18.3, −5.3. IR (neat): 2938, 1737, 1445, 1253, 1099 cm^{-1}. MS (*m*/*z*): 380 (M^+), 323 (100%), 263, 193, 133. HRMS calcd for $C_{20}H_{36}N_2O_3Si$: 380.2495. Found: 380.2501. Compound **16**: colorless oil. ^{1}H NMR($CDCl_3$, 300Mz): δ 7.22 (s, 1H), 3.94 (t, J = 7.8 Hz, 2H), 3.68 (s, 3H), 3.55 (t, J = 6.2 Hz, 2H), 2.79−2.61 (m, 5H), 2.58−2.54 (m, 1H), 1.82−1.72 (m, 3H), 1.52−1.45 (m, 2H), 1.33−1.26 (m, 2H), 0.84 (s, 9H), 0.09 (s, 6H). ^{13}C NMR($CDCl_3$, 75.4 MHz): δ 175.5, 136.6, 136.3, 113.9, 62.8, 51.8, 48.8, 40.0, 32.3, 30.0, 25.9, 25.5, 23.6, 23.0, 20.5, 18.3, −5.3. IR (neat): 2930, 1731, 1249, 1098 cm^{-1}. MS (*m*/*z*): 380 (M^+), 323 (100%), 263, 193. HRMS calcd for $C_{20}H_{36}N_2O_3Si$: 380.2495. Found: 380.2502.

Methyl 2-{5-(*tert*-butyldimethylsilyl)oxy}pentyl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate (22) and Methyl 2-{5-(*tert*-butyldimethylsilyl)oxy}pentyl-4,5,6,7-tetrahydro-1*H*-indazole-6-carboxylate (23). A solution of **17c** (0.035 mmol) and methyl acrylate (0.17 mmol) in benzene (5 mL) was heated in a sealed tube at 210 °C for 4 h after which time the solvent was removed under reduced pressure. The regioisomers were separated by HPLC (LiChrosorb column, hexane/ EtOAc 2:1) to give the less polar isomer **23** (29%) and the more polar isomer **22** (58%). Compound **22**: colorless oil. ^{1}H NMR($CDCl_3$, 300 MHz): δ 7.08 (s, 1H), 4.01 (t, J = 7.3 Hz, 2H), 3.77 (s, 3H), 3.58 (t, J = 6.5 Hz, 2H), 2.87−2.63 (m, 5H), 2.23−2.20 (m, 1H), 1.91−1.78 (m, 3H), 1.58−1.48 (m, 2H), 1.39−1.30 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H). IR (neat): 2953, 1731, 1217 cm^{-1}. MS (*m*/*z*): 380 (M^+), 323 (100%), 264, 193. HRMS calcd for $C_{20}H_{36}N_2O_3Si$: 380.2495. Found: 380.2506. Compound **23**: colorless oil. ^{1}H NMR($CDCl_3$, 300 MHz): δ 7.05 (s, 1H), 4.01 (t, J = 7.1 Hz, 2H), 3.70 (s, 3H), 3.57 (t, J = 6.4 Hz, 2H), 2.98 (dd, J = 5.5, 16.0 Hz, 1H), 2.88−2.61 (m, 3H), 2.56−2.50 (m, 1H), 2.19−2.10 (m, 1H), 1.87−1.71 (m, 3H), 1.54−1.47 (m, 2H), 1.37−1.23 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H). IR (neat): 2953, 1731, 1222 cm^{-1}. MS (*m*/*z*): 380 (M^+), 323 (100%), 263, 189. HRMS calcd for $C_{20}H_{36}N_2O_3Si$: 380.2495. Found: 380.2484.

X-ray Structure Analysis of Compound 12b. Crystal data: $C_{12}H_{16}N_2O_2$, M = 220.27, monoclinic system, space group $P2_1/n$; a = 9.270(2), b = 10.082(7), c = 12.320(4) Å, β = 105.88(3)°; V = 1107.5(9) Å^3, Z = 4, F(000) = 472, D_{calc} = 1.321 mg m^{-3}, μ = 0.91 cm^{-1}. Of the 1939 reflections collected ($2\theta_{max}$ = 50°), 1389 unique reflections were considered observed ($I > 2\sigma(I)$) after Lorentz polarization and empirical absorption corrections. The reliability factors converged to R_1 = 0.037.[17]

X-ray Structure Analysis of Compound 13c. Crystal data: $C_{13}H_{18}N_2O_2$, M = 234.29, monoclinic system, space group $P2_1/n$; a = 11.786(6), b = 7.099(3), c = 14.155(13) Å, β = 90.69(6)°; V = 1184.2(13) Å^3, Z = 4, F(000) = 504, D_{calc} = 1.314 mg m^{-3}, μ = 0.89 cm^{-1}. Of the 2090 reflections collected ($2\theta_{max}$ = 50°), 1558 unique reflections were considered observed ($I > 2\sigma(I)$) after Lorentz polarization and empirical absorption corrections. The reliability factors converged to R_1 = 0.047.[17]

X-ray Structure Analysis of Compound 20a. Crystal data: $C_{11}H_{14}N_2O_2$, M = 206.24, monoclinic system, space group $P2_1/n$; a = 6.4560(14), b = 10.109(2), c = 15.028(7) Å, β = 94.12(3)°; V = 978.3(5) Å^3, Z = 4, F(000) = 440, D_{calc} = 1.400 mg m^{-3}, μ = 0.98 cm^{-1}. Of the 1720 reflections collected ($2\theta_{max}$ = 50°), 1720 unique reflections were considered observed ($I > 2\sigma(I)$) after Lorentz polarization and empirical absorption corrections. The reliability factors converged to R_1 = 0.046.[17]

X-ray Structure Analysis of Compound 20b. Crystal data: $C_{12}H_{16}N_2O_2$, M = 220.27, monoclinic system, space group $P2_1/n$; a = 10.403(6), b = 9.202(2), c = 11.985(4) Å, β = 108.53(3)°; V = 1087.9(7) Å^3, Z = 4, F(000) = 472, D_{calc} = 1.345 mg m^{-3}, μ = 0.93 cm^{-1}. Of the 1898 reflections collected ($2\theta_{max}$ = 50°), 1348 unique reflections were considered observed ($I > 2\sigma(I)$) after Lorentz polarization and empirical absorption corrections. The reliability factors converged to R_1 = 0.042.[17]

X-ray Structure Analysis of Compound 21c. Crystal data: $C_{13}H_{18}N_2O_2$, M = 234.29, orthorhombic system, space group *Pbca*; a = 9.827(3), b = 10.397(3), c = 24.257(10) Å; V = 2479(2) Å^3, Z = 8, F(000) = 1008, D_{calc} = 1.256 mg m^{-3}, μ = 0.86 cm^{-1}. Of the 2003 reflections collected ($2\theta_{max}$ = 50°), 1325 unique reflections were considered observed ($I > 2\sigma(I)$) after Lorentz polarization and empirical absorption corrections. The reliability factors converged to R_1 = 0.047.[17]

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Supporting Information Available: ^{1}H NMR spectra of all new compounds; ^{13}C NMR spectra of **7a**−**c**, **8a**−**c**, **9a**−**c**, **10c**, **12a**, **12c**, **13c**, **15**, **16**, **17a**−**c**, **18c**, **20c**, and **21c**; ^{1}H−^{1}H COSY spectra of **12a**, **22**, and **23**; NOESY spectra of **7a**−**c**, **8a**−**c**, **12a**, **15**, **16**, **22**, and **23**; ^{1}H−^{13}C HMQC spectra of **12a**, **22**, and **23**; and the ORTEP drawing of **12b**, **13c**, **20a**, **20b**, and **21c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.