An Expedient Route for the Stereoselective Construction of Bridged Polyheterocyclic Ring Systems Using the Tandem "Pincer" Diels−Alder Reaction

Mark Lautens* and Eric Fillion

Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

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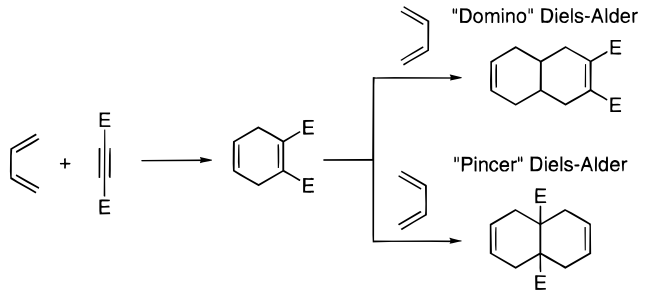
The tandem "pincer" Diels−Alder reaction, consisting of two consecutive [4 + 2] cycloadditions between two dienes and an acetylenic bis-dienophile, has been applied toward the rapid construction of bridged polyoxacyclic ring systems when furan derivatives are used as the diene components. The study has demonstrated the stereoselectivity (*exo-exo* adduct), the chemoselectivity ("pincer" *vs* "domino"), as well as the regioselectivity of the reaction. The reaction has been successfully applied to a variety of 2-substituted furans and tethered bis-furans in combination with mono-activated and diactivated dienophiles. The synthesis of unsymmetrical cycloadducts starting from the aza- and oxanorbornadiene-type intermediate has also been realized.

Introduction

The Diels−Alder reaction is among the most powerful C−C bond-forming processes and one of the most widely used and studied transformations in organic chemistry.[1] Its widespread application arises from the versatility and the predictability of the stereochemical as well as the regiochemical outcome of the reaction based on well-defined rules.[2] The development of a variety of elegant strategies using tandem Diels−Alder cycloadditions has allowed the construction of multiple carbon−carbon bonds generating an array of complex polycyclic structures in a single chemical step with control of multiple stereocenters.[3] We were interested in the applicability of the "pincer" Diels−Alder reaction of furan derivatives as the diene component directed toward the rapid construction of bridged polyoxacyclic ring systems.[4−6] The latter are valuable and important intermediates arising from their ability to be ring-opened to highly functionalized cyclohexane derivatives.

Scheme 1



The tandem "pincer" Diels−Alder reaction consists of two consecutive Diels−Alder cycloadditions between two dienes and an acetylenic dienophile, which acts as a bis-dienophile. The sequence is called a tandem "domino" Diels−Alder reaction when the second cycloaddition occurs at the newly formed double bond of the cyclohexadiene intermediate (Scheme 1).[6] The tandem "pincer" and "domino" Diels−Alder reactions have served as the cornerstone in Paquette's classic synthesis of dodecahedrane[6] and Prinzbach's synthesis of pagodane,[7] respectively. Despite these successful examples, the synthetic potential of the tandem "domino" and "pincer" Diels−Alder reactions remains underutilized in organic synthesis.

The dioxacyclic compounds obtained from the "pincer" Diels−Alder reaction between 2 equiv of furan derivative and 1 equiv of acetylenic dienophile have been known for 65 years.[8] However, they have essentially remained a chemical "curiosity", and no substantial progress has been made in optimizing their preparation. As far as their utilization in synthesis is concerned, it has been limited to very few examples.[9] In the cases reported to date, the diene counterparts were limited to furan,[10,11] 1,3-diphenylisobenzofuran,[12] and a few other symmetrical furan derivatives.[13] The dienophiles generally used were

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1997.

(1) For recent reviews on the Diels−Alder reaction, see: (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990. (b) Intermolecular Diels−Alder reactions: Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 315. (c) Heterodienophile additions to dienes: Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 401. (d) Heterodiene additions: Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 451. (e) Intramolecular Diels−Alder reactions: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 513. (f) Retrograde Diels−Alder reactions: Sweger, R. W.; Czarnik, A. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 551.

(2) For a critical survey on the mechanistic aspect of Diels−Alder reactions, see: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(3) For recent reviews on tandem Diels−Alder cycloadditions: (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (c) Ho, T.-L. *Tandem Organic Reactions*; John Wiley and Sons: New York, 1992.

(4) (a) For a recent review on aromatic heterocycles as intermediates in synthesis, see: Shipman, M. *Contemp. Org. Synth.* **1995**, *2*, 1. (b) For the synthesis of a symmetrical dioxapentacycle and its enantioselective desymmetrization, see: Marchionni, C.; Vogel, P.; Roversi, P. *Tetrahedron Lett.* **1996**, *37*, 4149.

(5) (a) For recent reviews on the ring opening of oxabicyclic systems, see: Woo, S.; Keay, B. *Synthesis* **1996**, 669. (b) Chiu, P.; Lautens, M. *Topics in Current Chemistry*; Springer-Verlag: Berlin, in press. (c) Lautens, M. *Synlett* **1993**, 177. (d) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532. (e) Lautens, M.; Klute, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 442.

(6) (a) For the first use of the terms "pincer" and "domino" Diels−Alder, see: Paquette, L. A.; Wyvratt, M. J.; Berk, H. C.; Moerck, R. E. *J. Am. Chem. Soc.* **1978**, *100*, 5845. (b) Paquette, L. A.; Balogh, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 774.

(7) Fessner, W.-D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc.* **1987**, *109*, 4626.

(8) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1931**, *490*, 243.

(9) (a) Tochtermann, W.; Malchow, A.; Timm, H. *Chem. Ber.* **1978**, *111*, 1233. (b) Lin, C.-T.; Chou, T.-C. *Synthesis* **1988**, 628.

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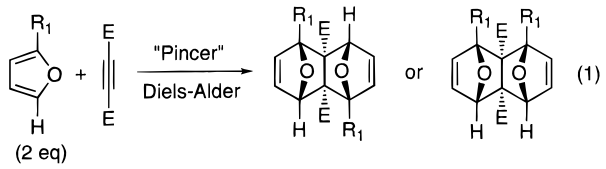
dimethyl acetylenedicarboxylate (DMAD) (**1**) and acetylenedicarboxylic acid (**2**). The conditions used for their synthesis have generally led, in modest yields, to mixtures of stereo- and regioisomers ("pincer" *vs* "domino" adducts) and to the formation of mono, bis, and tris cycloadducts. Very reactive dienophiles as well as Lewis acids[14a] or high-pressure conditions[15] did not enhance the yield or the selectivity of the reaction. Finally, dioxacycles have been isolated as side products in the Diels–Alder reaction between a furan derivative and an acetylenic dienophile,[16] especially when the reaction was carried out in the presence of highly reactive fluorinated acetylenes.[17] The problem encountered in the synthesis of this family of compounds is mainly due to the reversibility of the cycloaddition reaction.[14a]

Our overall plan relies on the "pincer" Diels–Alder reaction between 2 equiv of a substituted furan component and 1 equiv of an acetylenic dienophile (eq 1). Many

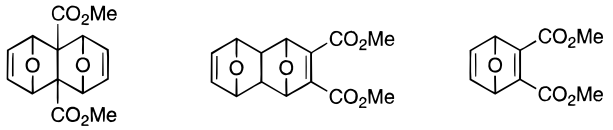


permutations can be envisioned for the rapid construction of a large variety of bridged polycycles by varying the furans and/or the dienophiles.

In this paper, we have addressed the issue of regio-, chemo-, and stereocontrol in the tandem Diels–Alder reaction and shown that the starting materials are readily available. The dioxacycles thus obtained can be utilized as precursors to a wide variety of fused polycyclic compounds as we reported in a preliminary communication.[18]

Background

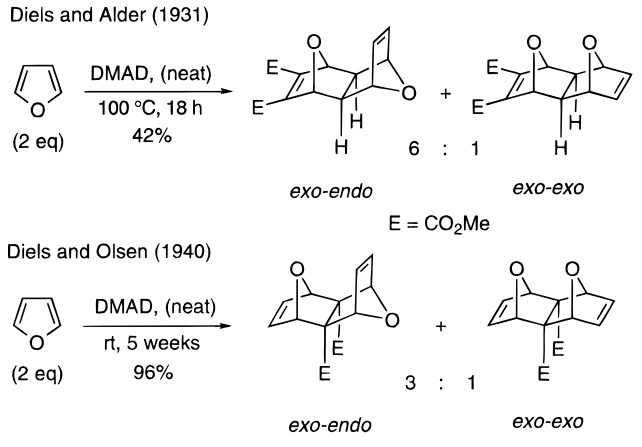
In 1931, Diels and Alder incorrectly proposed that the "pincer" adduct **3** was produced when an excess of furan was reacted with dimethyl acetylenedicarboxylate (**1**) at elevated temperature.[8] In 1940, Diels and Olsen carried out the previous experiment at room temperature and characterized a 2:1 cycloadduct that they proved to have structure **3**. In fact, the earlier experiment was shown to give the adduct **4**.[10a,f] In both experiments, the monoadduct **5** and some tris cycloadducts were also isolated.



3 **4** **5**

It was not until 1970 that Slee and LeGoff determined the configurations of the cycloadducts **3** and **4** reported by Diels, Alder, and Olsen using ^{1}H NMR spectroscopy (Scheme 2).[10f] At low temperature, the double bond substituted with carbomethoxy groups acts as a dienophile ("pincer" mode),[19] whereas at high temperature, equilibration occurred to give reaction at the less substituted but less activated double bond ("domino" mode). These observations were explained by the thermal lability of the furan Diels–Alder adducts.[20] Exclusive attack of the incoming diene on the *exo* face of the oxanorbornadiene intermediate **5** was a key feature of these reactions.

Scheme 2



(10) Furan and diactivated dienophile: (a) Diels, O.; Olsen, S. *J. Prakt. Chem.* **1940**, *156*, 285. (b) Stockman, H. *J. Org. Chem.* **1961**, *26*, 2025. (c) Weis, C. D. *J. Org. Chem.* **1963**, *28*, 74. (d) Kallos, J.; Deslongchamps, P. *Can. J. Chem.* **1966**, *44*, 1239. (e) Gandhi, R. P.; Chadha, V. K. *J. Chem. Soc., Chem. Commun.* **1968**, 552. (f) Slee, J. D.; LeGoff, E. *J. Org. Chem.* **1970**, *35*, 3897. (g) Weber, G.; Menke, K.; Hopf, H. *Chem. Ber.* **1980**, *113*, 531. (h) Maier, G.; Jung, W. A. *Tetrahedron Lett.* **1980**, *21*, 3875. (i) Maier, G.; Jung, W. A. *Chem. Ber.* **1982**, *115*, 804. (j) Gorgues, A.; Stephan, D.; Belyasmine, A.; Khanous, A.; Le Coq, A. *Tetrahedron* **1990**, *46*, 2817.

(11) Furan and monoactivated dienophile: (a) Gelin, R.; Debard, A. *Bull. Soc. Chim. Fr.* **1966**, 144. (b) McCulloch, A. W.; Smith, D. G.; McInnes, A. G. *Can. J. Chem.* **1974**, *52*, 1013. (c) McCulloch, A. W.; McInnes, A. G. *Can. J. Chem.* **1975**, *53*, 1496. (d) For an example of a regioselective Diels–Alder reaction of 2-methylfuran with an unsymmetrical diactivated acetylenic dienophile, see: Gorgues, A.; Simon, A.; Le Coq, A.; Hercouet, A.; Corre, F. *Tetrahedron* **1986**, *42*, 351. (e) Lasne, M.-C.; Ripoll, J.-L. *Bull. Soc. Chim. Fr.* **1986**, 766.

(12) (a) Berson, J. A. *J. Am. Chem. Soc.* **1953**, *75*, 1240. (b) Sasaki, T.; Kanematsu, K.; Iizuka, K. *Heterocycles* **1975**, *3*, 109.

(13) (a) Kapicak, L. A.; Battiste, M. A. *J. Chem. Soc., Chem. Commun.* **1973**, 930. (b) Hall, R. H.; Harkema, S.; den Hertog, H. J.; van Hummel, G. J.; Reinhoudt, D. N. *Rec. Trav. Chim. Pays-Bas* **1981**, *100*, 312. (c) Halverson, A.; Keehn, P. M. *J. Am. Chem. Soc.* **1982**, *104*, 6125. (d) Wollenweber, M.; Fritz, H.; Rihs, G.; Prinzbach, H. *Chem. Ber.* **1991**, *124*, 2465.

(14) (a) For a detailed study on the Diels–Alder reaction between furan and dimethyl acetylenedicarboxylate, see: McCulloch, A. W.; Smith, D. G.; McInnes, A. G. *Can. J. Chem.* **1973**, *51*, 4125. (b) An explanation of the stereoselective cycloaddition of furan with oxanorbornadienomaleimide and oxanorbornadiene anhydride intermediates based on semiempirical molecular orbital calculations has been reported; see: Warrener, R. N.; Elsey, G. M.; Maksimovic, L.; Johnston, M. R.; Kennard, C. H. L. *Tetrahedron Lett.* **1995**, *42*, 7753.

(15) Jurczak, J.; Belniak, S.; Kozluk, T.; Pikul, S.; Salanski, P. *Bull. Pol. Acad. Sci., Chem.* **1984**, *32*, 135.

(16) (a) Iten, P. X.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 1134. (b) Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762. (c) Suzuki, T.; Kubomura, K.; Fuchii, H.; Takayama H. *J. Chem. Soc., Chem. Commun.* **1990**, 1687. (d) Suzuki, T.; Kubomura, K.; Fuchii, H.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1991**, 204. (e) Suzuki, T.; Kubomura, K.; Takayama, H. *Heterocycles* **1994**, *38*, 961. (f) Takeshita, H.; Mori, A.; Kato, N.; Kurahashi, Y.; Ito, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2669.

(17) (a) Russell, R. A.; Longmore, R. W.; Weerasuria, K. D. V.; Warrener, R. N. *Aust. J. Chem.* **1991**, *44*, 1341. (b) Nezis, A.; Fayn, J.; Cambon, A. *J. Fluorine Chem.* **1991**, *53*, 285. (c) Barlow, M. G.; Tajammal, S.; Tipping, A. E. *J. Fluorine Chem.* **1993**, *62*, 95. (d) Barlow, M. G.; Pritchard, R. G.; Tajammal, S.; Tipping, A. E. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1993**, *C49*, 2151. (e) Barlow, M. G.; Suliman, N. N. E.; Tipping, A. E. *J. Fluorine Chem.* **1995**, *70*, 59. (f) Barlow, M. G.; Suliman, N. N. E.; Tipping, A. E. *J. Fluorine Chem.* **1995**, *70*, 95. (g) Barlow, M. G.; Suliman, N. N. E.; Tipping, A. E. *J. Fluorine Chem.* **1995**, *70*, 109.

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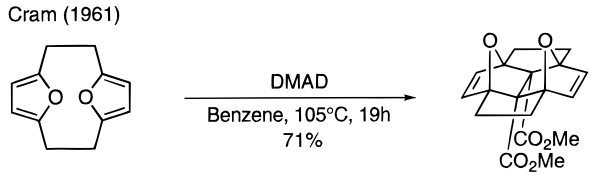
(19) Slee and LeGoff reported a 15:1 ratio of *exo-endo vs exo-exo*, which was shown to be erroneous by McInnis and co-workers (ref 14a). We observed a 3:1 ratio in accordance with the results of McInnis.

(20) (a) For an example of "pincer" Diels–Alder using a tethered bis-pyrrole see: Visnick, M.; Battiste, M. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1621. (b) The *exo* addition of furan on the oxanorbornadiene intermediate, yielding predominantly the *exo-endo* adduct, was explained by Slee and LeGoff in terms of the bulk of the methyl esters (ref 10f).

Scheme 3



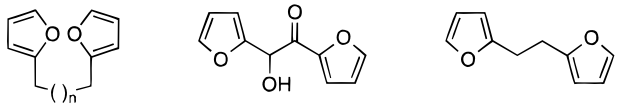
In 1961, Cram and co-workers reported[21] the first and only example of a "pincer" Diels–Alder reaction using a tethered bis-furan to give a hexacyclic adduct of *exo-exo*[22] stereochemistry (Scheme 3). Deslongchamps and Kallos in 1966 established that the "pincer" cycloadduct possessing the *exo-exo* stereochemistry is formed exclusively when acetylenedicarboxylic acid (**2**) is used as the dienophile instead of DMAD (**1**) at room temperature.[10d,23] McInnes and co-workers rationalized Deslongchamps and Kallos' observation on the basis of a selective crystallization of the *exo-exo* product and confirmed the reversible nature of the Diels–Alder reactions.[14a] The *exo-endo* adduct is the major product after a few hours, whereas the *exo-exo* adduct becomes predominant in solution over time and starts to crystallize, thus driving the equilibrium toward its further formation. This study also revealed that the molar ratio of diene and dienophile, the temperature, and the reaction time are the important factors in controlling the final ratio of products.[14b]

Since the mid-1960's interest in the dioxacycles has been minimal. It is only recently that these compounds have been "rediscovered" and used as templates for the construction of belt and cavity molecules[24] as well as cage molecules[25] and ladder polymers.[26]

In some cases, the "intermediate" aza- and oxanorbornadiene-type systems can be isolated in good yields by careful control of the reaction conditions.[27,28] The isolation of "mixed" dioxatetracyclic compounds starting from an isolated oxanorbornadiene system and reaction with a second and different diene have been reported by Weis[10c] and Slee and LeGoff.[10f]

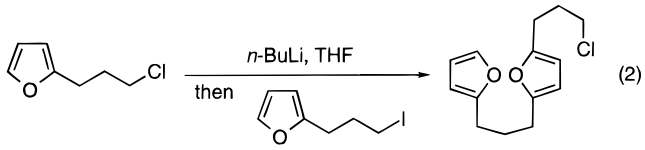
Results and Discussion

Preparation of the Dienes. Bis-furans **6** and **7** were prepared by trapping 2 equiv of 2-lithiofuran with 1 equiv of 1,3-diiodopropane and 1,4-diiodobutane, respectively. The preparation of 1,2-bis(2-furyl)ethane (**9**) was performed according to Wenkert's procedure[29] starting from furoin (**8**).



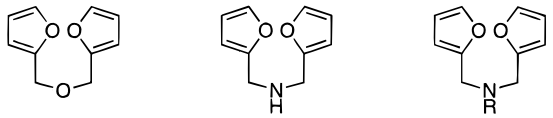
6, n=1, 37%
7, n=2, quant.
8
9

3-(2-Furyl)-1-chloropropane (**10**)[30] was deprotonated with *n*-BuLi and coupled with 3-(2-furyl)-1-iodopropane (**11**),[30] providing the tethered bis-furan **12** in 48% yield (eq 2).



10 **11** **12** (2)

The heteroatom-substituted tethered bis-furans **13**–**15** were synthesized in one step from furfuryl bromide (prepared from furfuryl alcohol and PBr_3 in Et_2O[31]). The latter was subsequently condensed with furfuryl alcohol to give the ether **13** in 85% yield and in the same manner with furfuryl amine, yielding the secondary amine **14** in 36% yield.[32] The treatment of 2 equiv of furfuryl bromide with 1 equiv of *p*-anisidine gave the *p*-methoxyphenyl (PMP)-protected bis-furan **15** in 34% yield. The secondary amine **14** was converted to its tertiary benzyl **16** and *p*-methoxybenzyl (PMB) **17** derivatives under standard conditions.



13 **14**
15 R=PMP
16 R=Bn
17 R=PMB

The synthesis of tetrahydrobenzofuran (**19**) commenced with the preparation of benzofuranone **18** as described by Hammond.[33] The latter was reductively deoxygenated with a 1:1 mixture of $LiAlH_4$ and $AlCl_3$ to give 4,5,6,7-tetrahydro-4-benzofuran (**19**) in 50% yield (eq 3).[34]

Preparation of the Acetylenic Unsymmetrical Bis-Dienophiles. 3-(Benzenesulfonyl)prop-2-ynoic acid methyl ester (**21**) was synthesized using Schultz's pro-

(21) (a) Cram, D. J.; Knox, G. R. *J. Am. Chem. Soc.* **1961**, *83*, 2204. (b) Cram, D. J.; Montgomery, C. S.; Knox, G. R. *J. Am. Chem. Soc.* **1966**, *88*, 515.

(22) Some authors refer to this stereochemistry as *endo-endo* (refs 10a,b,e, 11b, and 14a).

(23) Stockman was the first to perform this experiment (ref 10b) but incorrectly assigned the stereochemistry as *exo-endo*.

(24) (a) Warrener, R. N.; Butler, D. N.; Liao, W. Y.; Pitt, I. G.; Russell, R. A. *Tetrahedron Lett.* **1991**, *32*, 1889. (b) Warrener, R. N.; Maksimovic, L. *Tetrahedron Lett.* **1994**, *35*, 2389. (c) Warrener, R. N.; Maksimovic, L.; Butler, D. N. *J. Chem. Soc., Chem. Commun.* **1994**, 1831. (d) Warrener, R. N.; Wang, S.; Maksimovic, L.; Tepperman, P. M.; Butler, D. N. *Tetrahedron Lett.* **1995**, *36*, 6141. (e) Warrener, R. N.; Maksimovic, L.; Pitt, I. G.; Mahadevan, I.; Russell, R. A.; Tiekink, E. R. T. *Tetrahedron Lett.* **1996**, *36*, 3773.

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(28) (a) McCulloch, A. W.; Stanovnik, B.; Smith, D. G.; McInnes, A. G. *Can J. Chem.* **1969**, *47*, 4319. (b) Anderson, W. K.; Dewey, R. H. *J. Med. Chem.* **1977**, *20*, 306. (c) Xing, Y. D.; Huang, N. Z. *J. Org. Chem.* **1982**, *47*, 140. (d) For the asymmetric synthesis of oxanorbornadiene intermediates see: Sha, C.-K.; Shen, C.-Y.; Lee, R.-S.; Lee, S.-R.; Wang, S.-L. *Tetrahedron Lett.* **1995**, *36*, 1283.

(29) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203.

(30) Rogers, C.; Keay, B. A. *Can. J. Chem.* **1992**, *70*, 2929.

(31) Zanetti, J. E. *J. Am. Chem. Soc.* **1927**, *49*, 1065.

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(33) Zambias, R. A.; Caldwell, C. G.; Kopka, I. E.; Hammond, M. L. *J. Org. Chem.* **1988**, *53*, 4135.

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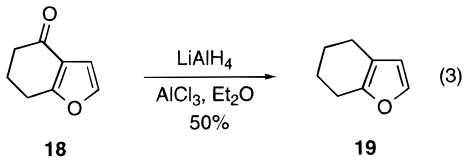
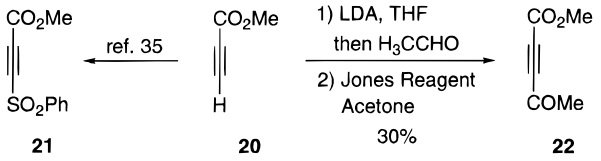


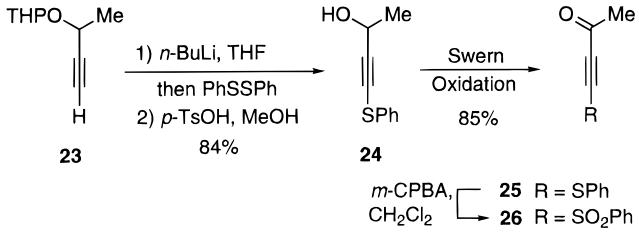
tocol[35] starting from methyl propiolate (**20**) (Scheme 4). After a quick purification, the unstable dienophile was immediately used in the cycloaddition reaction. 4-Oxopent-2-ynoic acid methyl ester (**22**) was prepared via a modification of Jones and co-workers' procedure.[36] Methyl propiolate (**20**) was deprotonated with LDA and treated with acetaldehyde. The resulting propargylic alcohol was oxidized using Jones reagent to yield the ketoester **22** in 30% overall yield (Scheme 4).

The synthesis of 4-(benzenesulfonyl)but-3-yn-2-one (**26**) started with the tetrahydropyranyl ether of 3-butyn-2-ol (**23**).[37] Deprotonation of the latter mixture of diastereomers using *n*-BuLi and trapping of the resulting organolithium species with diphenyl disulfide gave a mixture of (phenylthio)alkynes that were deprotected to provide the free alcohol **24** in 84% yield for the two operations. Sequential oxidation of the alcohol[38] and of the sulfide gave the keto sulfone **26**. The latter was not purified due to its instability (rapid polymerization) and was used directly in the cycloaddition reaction (Scheme 5).

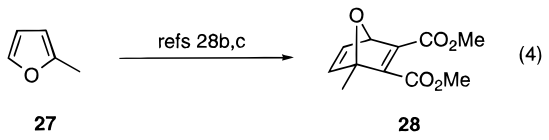
Scheme 4



Scheme 5

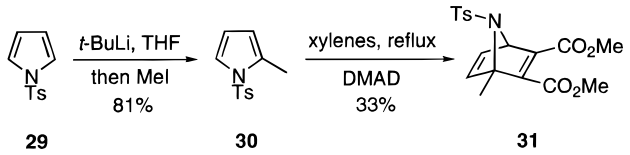


Synthesis of the Aza- and Oxanorbornadiene-Type Adducts. The oxanorbornadiene intermediate **28** was prepared in one step from 2-methylfuran (**27**) and DMAD (**1**) (eq 4).[28b,c]

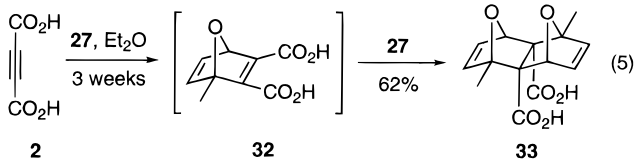


Three steps were necessary to access the azanorbornadiene intermediate **31**. Pyrrole was tosylated,[39] deprotonated[40] with *t*-BuLi, and then alkylated with MeI to give **30**. The latter was submitted to the Diels–Alder reaction under Prinzbach's conditions[27a] in the presence of DMAD to give the azanorbornadiene derivative **31** in 33% yield (Scheme 6).

Scheme 6



Study of the Tandem "Pincer" Diels–Alder Cycloaddition. The feasibility of the regio- and stereocontrolled "pincer" Diels–Alder reaction was first explored using 2-methylfuran (**27**) as the diene counterpart. A solution of acetylenedicarboxylic acid (**2**) and 2 equiv of 2-methylfuran (**27**) in ether was allowed to stand for 3 weeks at room temperature, during which time the "pincer" cycloadduct **33** slowly crystallized out of the solution (eq 5).[10d] The only product isolated of the 16



possible isomers was identified as the C_2-symmetrical *exo-exo* adduct **33** bearing the two bridgehead methyl groups in an "*anti*" relationship as readily confirmed by ^{13}C NMR spectroscopy. To the best of our knowledge, this is the first example of a regioselective "pincer" Diels–Alder reaction controlled solely by steric factors. Steric repulsion between the methyl group on the oxanorbornadiene intermediate **32** and the methyl group on the incoming 2-methylfuran (**27**) in the transition state of the second cycloaddition must be responsible for the production of the "*anti*" product. A ^1H NMR study of the ethereal solution showed that the oxanorbornadiene intermediate **32** is the predominant component in the reaction mixture. The cycloadduct **33** is found in low concentration in solution possibly due to its insolubility in ether and its rapid crystallization as soon as it is formed. The "*anti*" dimethyl *exo-endo* cycloadduct was also detected, but no trace of the "*syn*" dimethyl cycloadducts was observed. The stereoselectivity (*exo vs endo*) as well as the chemoselectivity ("pincer" *vs* "domino") of 2-methylfuran (**27**) toward the ambident dienophile **32** are in agreement with Deslongchamps and Kallos' observation on the reactivity of furan with acetylenedicarboxylic acid.[10d] The stereoselectivity may be driven by crystal packing forces that cause selective crystallization of the symmetrical *exo-exo* product, whereas the chemoselectivity of 2-methylfuran (**27**) toward the tetrasubstituted olefin of the ambident dienophile **32** is due to kinetic control in the tandem Diels–Alder reaction.[20a] In a single step, two new rings, four C–C bonds, and six stereocenters have been formed.

In order to verify the hypothesis of the steric interaction between the methyl groups in the regioselective formation of **33**, the experiment described above was repeated using the unsymmetrical diactivated dienophile **21** (eq 6). The highly activated dienophile **21** has been shown to react in a highly regioselective manner with an unsymmetrical diene where the methoxycarbonyl

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(36) Jones, E. R. H.; Shen, T. Y.; Whiting, M. C. *J. Chem. Soc.* **1950**, 236.
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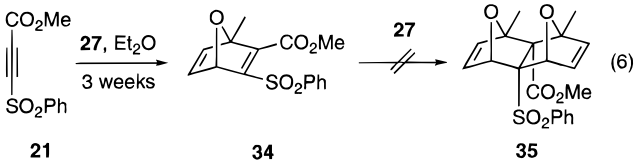
(38) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(39) Papadopoulos, E. P.; Haidar, N. F. *Tetrahedron Lett.* **1968**, *9*, 1721.
(40) Hasan, I.; Marinelli, E. R.; Chang Lin, L.-C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.



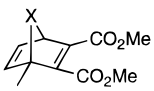
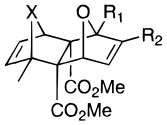
21 **34** **35**

group was the directing group.[35] After a few minutes at room temperature, the dienophile **21** and 2-methylfuran (**27**) reacted to give the oxanorbornadiene intermediate **34**. However, even after standing for 3 weeks with an excess of 2-methylfuran (**27**), no trace of the dioxatetracyclic adducts **35** bearing the two methyl groups in a "*syn*" relationship was detected by ^{1}H NMR analysis of the crude mixture. The only product present in the reaction mixture was the oxanorbornadiene intermediate **34**, which illustrates the significance of the steric interaction in the inhibition of the formation of the "*syn*" dimethyl cycloadduct in the reaction between acetylenedicarboxylic acid (**2**) and 2-methylfuran (**27**).

The generalization of this observation was achieved by the synthesis of unsymmetrical dioxatetracycles and "mixed" azaoxatetracycle starting from the aza- and oxanorbornadiene intermediates **28** and **31** (Table 1). Under the mild conditions previously used, the heteronorbornadiene dienophiles were unreactive. This difficulty was overcome by utilizing the lithium perchlorate-mediated Diels−Alder reaction developed by Grieco[41] and successfully employed in the recent synthesis of a *N*-siloxyazanorbornadiene derivative.[42] In a typical experiment, the heteronorbornadiene dienophile and the diene were dissolved in a 5 M $LiClO_4$ solution in ether and stirred for 6 weeks at room temperature. The dienophile **28** reacted with **10** and **19** to give the dioxacyclic compounds **36** and **37**, respectively, in modest yield, entries 1 and 2, Table 1. The azaoxatetracycle **38** was prepared by treatment of the dienophile **31** with 2-methylfuran (**27**) in 26% yield, entry 3, Table 1.[43] Analysis of the crude reaction mixtures by ^{1}H NMR indicated that the *exo-exo* adducts bearing the bridgehead substituents in an "*anti*" relationship were the only products. The structural assignments of the cycloadducts were made by examination of the ^{1}H NMR spectra and NOE results. In the case of **38**, the stereochemistry has been confirmed by X-ray crystallography of a diol derivative formed by reduction with $LiAlH(OMe)_3$.[44] In all the examples, the remaining products were predominantly the unreacted diene and dienophile.

In order to access the isomeric substrates with "*syn*" substituents, the tethered bis-furan **6** was reacted with acetylenedicarboxylic acid (**2**) and DMAD (**1**) to give the cycloadducts **39** and **40** in good yields, entries 1 and 2, Table 2. The symmetrical structure of the adducts was readily ascertained by ^{1}H NMR spectroscopy. Reaction of acetylenedicarboxylic acid (**2**) with **6** under the previously described conditions was significantly faster than the one of 2-methylfuran (**27**) and provided the *exo-exo* dioxapentacyclic adduct **39** after 1 week at room temperature. None of the other seven possible isomers was observed. A ^{1}H NMR analysis of the reaction mixture showed the absence of the oxanorbornadiene intermediate. This suggests that the intramolecular cycloaddition is much faster than the reaction with a second mole of furan and that the second step (intramolecular cycloaddition) is significantly faster than the first one (intermolecular Diels−Alder). Also, no trace of the *exo-endo* cycloadduct was detected in the reaction mixture. The formation of three new rings and six stereocenters was performed in a single step.

Table 1. Unsymmetrical "Pincer" [4 + 2] Cycloadducts

Entry	Dienophile		Diene	Product [a]		Yield [b]
		X=O				
		X=NTs				
1	**28**	X=O	**10**	**36** R_1=$(CH_2)_3Cl$	R_2=H	34%
2	**28**	X=O	**19**	**37** R_1=R_2=-$(CH_2)_4$-		50%
3	**31**	X=NTs	**27**	**38** R_1=CH_3	R_2=H	26%

[a] [4 + 2] cycloaddition, details in the Experimental Section. [b] Isolated yield of analytically pure product.

The scope of the reaction has been fully defined by using a variety of bis-furans and reacting them with acetylenedicarboxylic acid (**2**) or DMAD (**1**) to give the *exo-exo* cycloadducts in yields ranging from 63% to 79% (entries 3−8, Table 2). 2,5-Substitution of the bis-diene moiety **12** did not interfere with the course of the cycloaddition, and the cycloadduct **41** was obtained in good yield (entry 3, Table 2). Interestingly, the protecting group on the amine had no effect on the reactivity of the bis-diene (entries 5−7, Table 2) except in the case of **15** (entry 5, Table 2) where the reaction had to be performed neat in order to proceed.

The unsymmetrical diactivated dienophiles **21** and **26** gave the *exo-exo* cycloadducts **48** and **49** as single regioisomers (entries 9 and 10, Table 2).[11d] The only exception was with the keto ester **22**, which gave a 4:1 mixture of regioisomers (**50** and **51**) in favor of the product where the methyl ketone was the dominant directing group (entry 11, Table 2). The lower yield can be attributed to the fact that the major isomer did not crystallize out of the solution to drive the reaction to completion. The keto sulfone **26** gave a lower yield of the cycloadduct probably due to its fast polymerization (entry 10, Table 2). In the case of the very reactive dienophiles **21** and **26**, the reactions were complete after a few minutes but it took several hours before the product began to crystallize out of the solution. The structure of **48** was proven by X-ray crystallography.[44] The ^{1}H NMR spectrum showed that the chemical shift of the bridgehead proton moved upfield due to the presence of the nearby phenyl group. A similar observation was noted for **49**. Finally, the structure of the major isomer **50** was determined by X-ray crystallography.[44]

The reaction with the monoactivated dienophiles had to be performed in an ethereal solution of $LiClO_4$ (entries 12 and 13, Table 2). The reactions were highly regioselective, and the structures of the cycloadducts **52** and **54** were determined by NOE experiments. It is noteworthy that the methoxycarbonyl group is a stronger directing group than the phenylsulfonyl substituent (entry 9 *vs* 12, Table 2) even if the latter is reported to be a better activating group of the triple bond (entry 12 *vs* 13, Table 2).[35,45]

(41) (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. (b) Forman, M. A.; Dailey, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 2761.

(42) Heard, N. E.; Turner J. *J. Org. Chem.* **1995**, *60*, 4302.

(43) For the synthesis of an azaoxabicyclic system from the reaction of furo[2,3-*c*]pyrroles with 2 equiv of DMAD, see: Sha, C.-K.; Lee, R.-S.; Wang, Y. *Tetrahedron* **1995**, *51*, 193.

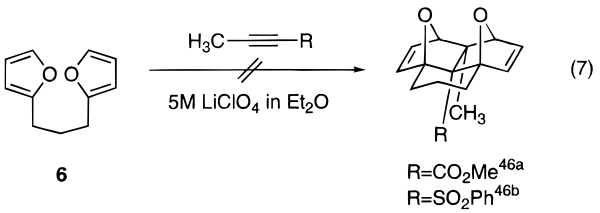
(44) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 2. "Pincer" [4 + 2] Cycloaddition

Entry	Dienophile	Bis-Diene			Product [a]		Yield [b]
(i) ***symmetrical diactivated dienophile***							
1	**2**	**6**	X=CH_2	R=H	**39**	E=CO_2H	74%
2	**1**	**6**	X=CH_2	R=H	**40**	E=CO_2Me	71%
3	**2**	**12**	X=CH_2	R=$(CH_2)_3Cl$	**41**	E=CO_2H	79%
4	**1**	**13**	X=O	R=H	**42**	E=CO_2Me	76%
5	**1**	**15**	X=NPMP	R=H	**43**	E=CO_2Me	63%
6	**1**	**16**	X=NBn	R=H	**44**	E=CO_2Me	72%
7	**1**	**17**	X=NPMB	R=H	**45**	E=CO_2Me	65%
8	**1**	**46**[c]	X=S	R=H	**47**	E=CO_2Me	71%
(ii) ***unsymmetrical diactivated dienophile***							
9	**21**	**6**			**48**	E=CO_2Me, E'=SO_2Ph	69%
10	**26**	**6**			**49**	E=COMe, E'=SO_2Ph	30%[d]
11	**22**	**6**			**50**	E=COMe, E'=CO_2Me	60%[e]
					51	E=CO_2Me, E'=COMe	
(iii) ***monoactivated dienophile***							
12	**20**	**6**			**52**	E=CO_2Me	57%
13	**53**[f]	**6**			**54**	E=SO_2Tol	83%

[a] [4 + 2] cycloaddition, details in the Experimental Section. [b] Isolated yield of analytically pure product. [c] Furfuryl sulfide is commercially available. [d] The overall yield includes the oxidation of the sulfide **25** to the sulfone and the cycloaddition. [e] Obtained as a 4:1 mixture of regioisomers **50** and **51**. [f] Ethynyl *p*-tolylsulfone is commercially available.

We have also shown that the presence of a weakly electron-donating methyl group present on the monoactivated dienophile deactivates the alkyne and inhibits the formation of the cycloadduct even in the presence of $LiClO_4$ (eq 7).

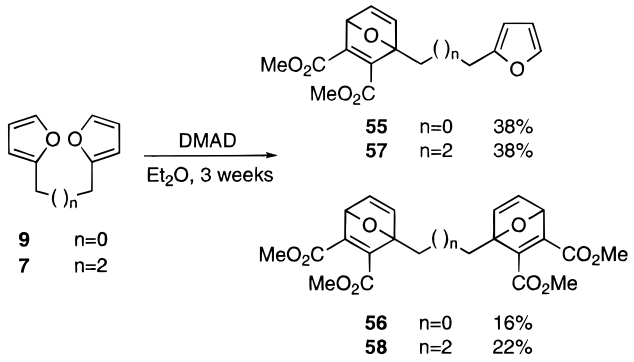


6 (7)

R=CO_2Me[46a]
R=SO_2Ph[46b]

Finally, we attempted the synthesis of dioxapentacyclic systems by changing the length of the tether separating the furans. When **7** and **9** were treated with DMAD (**1**) under the same conditions as used previously for the three-carbon tether bis-furan **6**, mixtures of two cycloadducts were obtained (Scheme 7). The major adducts

Scheme 7



9 n=0
7 n=2

55 n=0 38%
57 n=2 38%

56 n=0 16%
58 n=2 22%

(**55** and **57**) came from the reaction of 1 equiv of DMAD with the bis-furans without subsequent intramolecular cycloaddition and the minor ones (**56** and **58**) from the reaction of 2 equiv of DMAD (**1**) with the bis-furans.[47] In this case, a mixture of stereoisomers is expected even if their presence was not detected by ^1H NMR. In both cases, 19% of the unreacted starting material was isolated.

Conclusion

In conclusion, we have described a regio- and stereocontrolled approach for the simple and expedient synthesis of bridged polyheterocyclic ring systems. The flexibility of the "pincer" Diels−Alder reaction in terms of dienes and dienophiles has been demonstrated. We are currently delineating the scope of the ring opening reaction of these compounds[18] and utilizing the reaction in synthesis.

Experimental Section

The following includes general experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the compounds prepared.

General Procedure for the Alkyl-Tethered Bis-Furan Preparation: 1,3-Bis(2-furyl)propane (6). A solution of *n*-butyllithium (200 mL, 2.5 M solution in hexanes, 500 mmol) was added dropwise to a solution of furan (37 mL, 509 mmol) in THF (300 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and an additional 1 h at rt. The reaction was then cooled to 0 °C prior to the dropwise addition of 1,3-diiodopropane (25 g, 84.5 mmol). After the addition was complete, stirring was continued at rt for an additional 15 h. The reaction was quenched by the addition of water (10 mL), and the solvent was removed *in vacuo*. The residue was filtered over silica gel and the product eluted with hexanes (1000 mL). The filtrate was concentrated, and a bulb-to-bulb distillation (0.20 mmHg, 50−60 °C) of the residual oil yielded **6** (5.5 g, 37%) as a colorless oil: $R_f = 0.33$ on silica gel (100% hexanes); IR (neat) 3114, 2945, 1595, 1511, 1462 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (2H, s), 6.31−6.30 (2H, m), 6.04−6.03 (2H, m), 2.70 (4H, t, J = 7.5 Hz), 2.02 (2H, quintet, J = 7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.5, 140.8, 110.0, 105.0, 27.3, 26.5. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.70; H, 6.56.

1,4-Bis(2-furyl)butane (7). The reaction was carried out as in the general procedure using *n*-butyllithium (134 mL, 2.5 M solution in hexanes, 335 mmol), furan (24.2 mL, 333 mmol), and 1,4-diiodobutane (7.4 mL, 56 mmol). Bulb-to-bulb distillation (0.20 mmHg, 60−70 °C) provided **7** (10.7 g, 100%) as a colorless oil: $R_f = 0.25$ on silica gel (100% hexanes); IR (neat) 3150, 3140, 2930, 2860, 1596, 1507, 1462, 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, m), 6.26 (2H, dd, J = 3.2, 2.1

(45) A similar observation has been noted by Danishefsky in his work with β-(phenylsulfinyl)-α,β-unsaturated carbonyl dienophiles. Danishefsky, S.; Harayama, T. J.; Singh, R. K. *J. Am. Chem. Soc.* **1979**, *101*, 7008.

(46) (a) Commercially available. (b) Truce, W. E.; Onken, D. W. *J. Org. Chem.* **1975**, *40*, 3200.

(47) For the synthesis of 2,2′-bifuryl-DMAD adducts, see: Grigg, R.; Roffey, P.; Sargent, M. V. *J. Chem. Soc. C* **1967**, 2327.

Hz), 5.96 (2H, dd, J = 3.1, 0.9 Hz), 2.64 (4H, t, J = 6.8 Hz), 1.68 (4H, quintet, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.9, 140.6, 110.0, 104.7, 27.6, 27.4; HRMS calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.0999.

5-(3-Chloropropyl)-1,3-bis(2-furyl)propane (12). A solution of *n*-butyllithium (7.26 mL, 2.5 M solution in hexanes, 18.15 mmol) was added dropwise to a solution of 3-(2-furyl)-1-chloropropane[30] (**10**) (2.50 g, 17.29 mmol) in THF (30 mL) at 0 °C. After the mixture was stirred for 2 h at 0 °C, a solution of 3-(2-furyl)-1-iodopropane[30] (**11**) (4.08 g, 17.28 mmol) in THF (20 mL) was added dropwise, and the resulting mixture was stirred for an additional 15 h at rt. The reaction was quenched by the addition of water (10 mL), and the solvent was removed *in vacuo*. The aqueous layer was extracted (3×) with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residual oil by flash chromatography (100% hexanes) yielded **12** as a colorless oil (2.11 g, 48%): R_f = 0.09 on silica gel (100% hexanes); IR (neat) 3114, 2952, 1433, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (1H, s), 6.32−6.29 (1H, m), 6.03 (1H, d, J = 2.3 Hz), 5.95−5.90 (2H, m), 3.58 (2H, t, J = 7.7 Hz), 2.81−2.61 (6H, m), 2.17−1.91 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.5, 154.0, 152.4, 140.7, 109.9, 105.9, 105.4, 104.9, 44.1, 31.0, 27.4, 27.3, 26.5, 25.2. Anal. Calcd for $C_{14}H_{17}O_2Cl_1$: C, 66.53; H, 6.78. Found: C, 66.71; H, 6.47.

General Procedure for the Heteroatom-Substituted Tethered Bis-Furan Preparation: Di-α-furfuryl ether (13).[31] A solution of phosphorus tribromide (5.0 g, 18.5 mmol) in Et_2O (5 mL) was added over 20 min to a solution of freshly distilled furfuryl alcohol (5.0 g, 51.0 mmol) in Et_2O (25 mL) at 0 °C. The mixture was allowed to stand for 30 min at rt and then decanted into an Erlenmeyer flask. The solution was cooled to 0 °C and treated *cautiously* with a 40% KOH solution (15 mL). The ether layer was decanted into a round-bottom flask and treated with excess solid KOH (10 g). Furfuryl alcohol (4.0 g, 40.8 mmol) was added to the furfuryl bromide solution, and the solvent was boiled off. The remaining residue was dissolved in water and extracted with Et_2O (3×). The combined organic layers were washed with brine (2×), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (hexanes−EtOAc 9:1) gave **13** (6.2 g, 85%) as a colorless oil: R_f = 0.50 on silica gel (hexanes−EtOAc 9:1); IR (neat) 3149, 3121, 2910, 2861, 1504, 1068 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41−7.40 (2H, m), 6.34−6.32 (4H, m), 4.47 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.2, 142.5, 110.0, 109.3, 63.1.

Bis(furan-2-ylmethyl)amine (14).[32] The reaction was carried out as in the general procedure using phosphorus tribromide (5.0 g, 18.5 mmol), furfuryl alcohol (5.0 g, 51.0 mmol), and furfurylamine (4.0 g, 41.2 mmol). Purification by flash chromatography (hexanes−EtOAc 1:1) gave **14** (2.63 g, 36%) as a colorless oil: R_f = 0.43 on silica gel (hexanes−EtOAc 1:1); IR (neat) 3339, 3276, 3114, 2924, 2833, 1602 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (2H, dd, J = 1.8, 0.9 Hz), 6.24 (2H, dd, J = 3.2, 1.8 Hz), 6.12 (2H, dd, 3.3, 0.7 Hz), 3.70 (4H, s), 1.72 (1H, bs); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.2, 141.5, 109.8, 106.8, 44.7.

Bis(furan-2-ylmethyl)(4-methoxyphenyl)amine (15). The reaction was carried out as in the general procedure using phosphorus tribromide (12.0 g, 44.1 mmol), furfuryl alcohol (12.0 g, 121.8 mmol), and *p*-anisidine (5.0 g, 40.6 mmol). Purification by flash chromatography (hexanes−EtOAc 9:1) gave **15** (3.9 g, 34%) as a colorless oil: R_f = 0.47 on silica gel (hexanes−EtOAc 9:1); IR (neat) 3117, 3047, 2993, 2935, 2906, 2833, 1513, 1454, 1244, 1183, 1149, 1042, 1009 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, dd, J = 1.9, 0.9 Hz), 6.88−6.85 (2H, m), 6.81−6.78 (2H, m), 6.28 (2H, dd, J = 3.2, 1.7 Hz), 6.13 (2H, bs), 4.37 (4H, s), 3.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 152.2, 143.0, 141.8, 116.3, 114.4, 110.2, 107.6, 55.5, 48.3; HRMS calcd for $C_{17}H_{17}NO_3$ $[M]^+$ 283.1208, found 282.1210.

Benzylbis(furan-2-ylmethyl)amine (16). A solution of *n*-butyllithium (1.06 mL, 2.5 M solution in hexanes, 2.65 mmol) was added dropwise to a solution of **14** (426 mg, 2.41 mmol) in THF (5 mL) at −78 °C. The mixture was stirred for 10 min at −78 °C and 10 min at 0 °C. The mixture was cooled to −78 °C for the dropwise addition of benzyl bromide (358 mL, 3.01 mmol). The mixture was stirred for 2 h at rt. The reaction was quenched by the addition of water (10 mL), and the solvent was removed *in vacuo*. The residue was dissolved in water and extracted (3×) with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography purification yielded **16** as a colorless oil (463 mg, 72%): R_f = 0.49 on silica gel (hexanes−EtOAc 9:1); IR (neat) 3112, 3053, 3030, 2928, 2830, 1598, 1497, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.22 (7H, m), 6.33 (2H, dd, J = 2.9, 1.8 Hz), 6.23 (2H, d, J = 2.9 Hz), 3.66 (4H, s), 3.62 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 141.9, 138.9, 128.9, 128.2, 126.9, 110.0, 108.7, 57.1, 49.3. Anal. Calcd for $C_{17}H_{17}N_1O_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.75; H, 6.51; N, 5.16.

Bis(furan-2-ylmethyl)(4-methoxybenzyl)amine (17). A solution of **14** (3.0 g, 16.9 mmol) in THF (20 mL) was added to a suspension of NaH (745 mg, 18.6 mmol, 80% in oil) and KH (194 mg, 1.7 mmol, 35% in oil) (washed three times with pentane) in THF (30 mL) and DMF (5 mL). The mixture was stirred for 3 h at rt. A solution of *p*-methoxybenzyl bromide (3.7 g, 18.6 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred for an additional 15 h at rt. The reaction was quenched by the addition of water, and the solvent was removed *in vacuo*. The residue was dissolved in water and extracted (3×) with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes−EtOAc 9:1) gave **17** (4.43 g, 88%) as a colorless oil: R_f = 0.44 on silica gel (hexanes−EtOAc 9:1); IR (neat) 3062, 3032, 2999, 2951, 2928, 2830, 1611, 1509, 1454, 1245 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, dd, J = 1.8, 0.7 Hz), 7.30−7.26 (2H, m), 6.87−6.83 (2H, m), 6.32 (2H, dd, J = 3.0, 1.9 Hz), 6.21 (2H, m), 3.78 (3H, s), 3.63 (4H, s), 3.54 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 152.4, 141.9, 130.8, 130.0, 113.6, 110.0, 108.7, 56.4, 55.2, 49.1; HRMS calcd for $C_{18}H_{19}NO_3$ $[M]^+$ 297.1365, found 297.1358.

4,5,6,7-Tetrahydro-4-benzofuran (19).[34b,c] A solution of $LiAlH_4$ (100 mL, 1.0 M in Et_2O, 100 mmol) was placed in a three-necked flask equipped with a dropping funnel, a reflux condenser, and a large vent. A solution of $AlCl_3$ (13.3 g, 100 mmol) in Et_2O (100 mL) was added dropwise. The formation of a white precipitate was observed. A solution of 4,5,6,7-tetrahydro-4-benzofuranone[33] **18** (13.6 g, 100 mmol) in Et_2O (200 mL) was added at a rate such as to produce a gentle reflux. After the addition was complete, the reaction mixture was stirred for an additional 2 h at rt. The reaction was quenched by the addition of water (20 mL) followed by 6N H_2SO_4 (50 mL) and extracted with Et_2O (3×). The combined organic layers were washed with water (1×) followed by brine (1×), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Vacuum distillation (∼10 mmHg, 95 °C) using a water pump produced **19** (5.93 g, 50%) as a colorless oil: R_f = 0.81 on silica gel (hexanes−EtOAc 10:1); IR (neat) 3114, 2931, 2854, 1631, 1560, 1511, 1448, 1300, 1223, 1103, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, J = 1.8 Hz), 6.22 (1H, d, J = 1.8 Hz), 2.61 (2H, t, J = 5.7 Hz), 2.49−2.42 (2H, m), 1.91−1.68 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 140.6, 117.1, 110.9, 23.6 (2C), 22.6 (2C).

4-Oxopent-2-ynoic Acid Methyl Ester (22).[36] A solution of *n*-butyllithium (25.0 mL, 2.5 M solution in hexanes, 62.5 mmol) was added dropwise to a solution of diisopropylamine (8.6 mL, 59.5 mmol) in THF (300 mL) at 0 °C. The mixture was stirred for 15 min at −78 °C and 15 min at 0 °C. The reaction was cooled to −78 °C prior to the dropwise addition of a solution of methyl propiolate (**20**) (5.0 g, 59.5 mmol) in THF (25 mL). The mixture was stirred for 1 h at −78 °C, and a solution of acetaldehyde (4.0 mL, 75.56 mmol) in THF (25 mL) was added. The mixture was stirred for an additionnal 2 h at −78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. THF was removed *in vacuo*, and the residue was extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated.

The crude alcohol was dissolved in acetone (150 mL) and carefully treated with a solution of Jones' reagent at 0 °C until the solution remained a dark brown color. The mixture was

stirred for an additional 15 min at 0 °C prior to the addition of $NaHCO_3$ (5.0 g) and $MgSO_4$. The mixture was filtered over silica gel and the solid washed several times with Et_2O. The filtrate was concentrated and the residue purified by flash chromatography (hexanes−EtOAc 5:1) to give **22** (2.22 g, 30%) as a colorless oil: $R_f = 0.51$ on silica gel (hexanes−EtOAc 4:1); IR (neat) 3009, 2966, 2847, 2362, 2341, 1729, 1694, 1265 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.83 (3H, s), 2.41 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.1, 152.3, 80.8, 77.1, 53.1, 32.0.

4-(Phenylsulfenyl)but-3-yn-2-ol (24). A solution of *n*-butyllithium (9.53 mL, 2.5 M solution in hexanes, 23.83 mmol) was added dropwise to a solution of 2-[(1-methylprop-2-ynyl)-oxy]tetrahydropyran[37] (**23**) (3.50 g, 22.70 mmol) in THF (75 mL) at −78 °C. After the mixture was stirred for 1 h at −78 °C, a solution of phenyl disulfide (5.20 g, 23.82 mmol) in THF (25 mL) was added dropwise. After the addition was complete, the mixture was warmed to rt, and stirring was continued for an additional 2 h. The reaction was quenched by the addition of water and diluted with Et_2O. The organic layer was washed with a 5 M NaOH solution (4×) and brine (1×), dried ($MgSO_4$), filtered, and concentrated.

The residual oil was dissolved in MeOH (300 mL), treated with *p*-TsOH (432 mg, 2.27 mmol), and stirred at rt for 5 h. The reaction was quenched by adding 300 mL of a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (2×), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes−EtOAc 4:1) yielded the alcohol **24** (3.40 g, 84%) as a colorless oil: $R_f = 0.34$ on silica gel (hexanes−EtOAc 4:1); IR (neat) 3543, 3339, 3058, 2981, 2875, 2184, 1581, 1370, 1124, 1075, 688 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45−7.18 (5H, m), 4.75 (1H, q, $J = 6.7$ Hz), 2.66 (1H, bs), 1.54 (3H, d, $J = 6.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 132.3, 129.1, 126.5, 126.1, 100.6, 70.9, 59.1, 24.1; HRMS calcd for $C_{10}H_{10}O_1S_1$ $[M]^+$ 178.0452, found 178.0449.

4-(Phenylsulfenyl)but-3-yn-2-one (25). Oxalyl chloride (2.83 mL, 32.40 mmol) was added dropwise to a solution of DMSO (3.07 mL, 43.20 mmol) in CH_2Cl_2 (125 mL) at −78 °C. After the addition was complete, the reaction was stirred at −78 °C for 30 min. A solution of the alcohol **24** (3.85 g, 21.60 mmol) in CH_2Cl_2 (25 mL) was then added dropwise, and after the addition was complete, the reaction was stirred at −78 °C for an additional 30 min. Et_3N (15.00 mL, 108.62 mmol) was added and the mixture stirred for an additional 15 min at −78 °C. The reaction was poured into CH_2Cl_2, and the organic layer was washed with a 1 M HCl solution (2×) and brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (hexanes−EtOAc 9:1) yielded **25** (3.23 g, 85%) as a colorless oil: $R_f = 0.47$ on silica gel (hexanes−EtOAc 9:1); IR (neat) 3065, 3002, 2924, 2137, 2095, 1667, 1580, 1479, 1441, 573 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48−7.25 (5H, m), 2.37 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.2, 129.2, 127.5, 126.6, 100.6, 84.6, 31.2; HRMS calcd for $C_{10}H_8O_1S_1$ $[M]^+$ 176.0296, found 176.0301.

2-Methyl-1-*p*-tolyl-1*H*-pyrrole (30). A solution of *tert*-butyllithium (14.6 mL, 1.7 M solution in pentane, 24.86 mmol) was added dropwise to a solution of 1-*p*-tolyl-1*H*-pyrrole[39] (**29**) (5.0 g, 22.60 mmol) in THF (120 mL) at −78 °C. The mixture was stirred for 10 min at −78 °C, 10 min at 0 °C, and 20 min at rt. The mixture was cooled to 0 °C prior to the slow addition of iodomethane (7.0 mL, 112 mmol). After the addition was complete, the mixture was stirred for 1 h at rt, and the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ether (3×), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized from MeOH to yield **30** as a white solid (4.29 g, 81%): $R_f = 0.43$ on silica gel (hexanes−EtOAc 9:1); mp 87−88 °C (MeOH); IR (KBr) 3142, 3107, 2966, 2924, 1595, 1490, 1455, 1358, 1174 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.67 (2H, d, $J = 8.5$ Hz), 7.31−7.26 (3H, m), 6.16 (1H, t, $J = 3.3$ Hz), 5.96−5.93 (1H, m), 2.41 (3H, s), 2.29 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.7, 136.2, 130.7, 129.8, 126.8, 121.9, 113.0, 111.1, 21.5, 13.5. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.25; H, 5.79; N, 5.85.

1-Methyl-7-*p*-tolyl-7-azabicyclo[2.2.1]hepta-2,5-diene (31). A solution of **30** (4.29 g, 18.25 mmol) and DMAD (12.95 g, 91.13 mmol) in xylenes (30 mL) was heated at reflux for 7 h. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (hexanes−EtOAc 2:1) to yield **31** (2.25g, 33%) as a white crystalline solid: $R_f = 0.28$ on silica gel (hexanes:EtOAc 2:1); mp 112−115 °C (CH_2Cl_2); IR (KBr) 3100, 3002, 2945, 2847, 1724, 1700, 1635, 1439, 1345, 1161 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.59 (2H, d, $J = 8.4$ Hz), 7.26 (2H, d, $J = 8.2$ Hz), 7.06 (1H, dd, $J = 5.2$, 2.9 Hz), 6.78 (1H, d, $J = 5.5$ Hz), 5.46 (1H, d, $J = 2.9$ Hz), 3.72 (3H, s), 3.68 (3H, s), 2.40 (3H, s), 1.87 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.1, 161.6, 155.8, 148.5, 148.0, 143.7, 143.5, 135.4, 129.6, 128.3, 79.0, 69.0, 52.1 (2C), 21.5, 13.6. Anal. Calcd for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71. Found: C, 57.18; H, 5.13; N, 3.73.

General Procedure for the Diels−Alder Reaction in Et_2O. Method A. *exo,exo*-1,6-Dimethyl-11,12-dioxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic Acid (33). Acetylenedicarboxylic acid (15 g, 132 mmol) and 2-methylfuran (28 mL, 310 mmol) were dissolved in Et_2O (75 mL), and the solution was left for 3 weeks at rt with daily stirring, during which time the product crystallized out. The crystals were isolated by filtration and washed with Et_2O to yield the cycloadduct **33** (22.6 g, 62%) as a white solid: mp 141−143 °C (Et_2O); IR (KBr) 3459−2453, 1750, 1729 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 6.66 (2H, dd, $J = 5.5$, 1.7 Hz), 6.38 (2H, d, $J = 5.5$ Hz), 5.07 (2H, d, $J = 1.8$ Hz), 1.64 (6H, s); ^{13}C NMR (50 MHz, CD_3OD) δ 173.9, 143.8, 140.1, 91.5, 81.9, 75.2, 15.1. Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.19; H, 5.34.

3-(Benzenesulfonyl)-1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxyxlic Acid Methyl Ester (34). Freshly prepared **21**[35] (513 mg, 2.29 mmol) and **27** (1.0 mL, 11.08 mmol) in Et_2O (5 mL) were stirred at rt for 15 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (hexanes−EtOAc 3:1) to give the cycloadduct **34** (432 mg, 62%) as a colorless oil: $R_f = 0.26$ on silica gel (hexanes−EtOAc 3:1); IR (neat) 3066, 2988, 2953, 1730, 1631, 1443, 1311, 1262, 1160, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94−7.90 (2H, m), 7.68−7.64 (1H, m), 7.58−7.55 (2H, m), 7.06 (1H, dd, $J = 5.2$, 1.9 Hz), 6.93 (1H, d, $J = 5.1$ Hz), 5.48 (1H, d, $J = 1.9$ Hz), 3.82 (3H, s), 1.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 158.5, 155.6, 145.0, 143.8, 138.4, 134.1, 129.3, 128.0, 95.0, 83.5, 52.6, 14.8; HRMS calcd for $C_{15}H_{14}O_5S$ $[M]^+$ 306.0562, found 306.0570.

General Procedure for the Diels−Alder Reaction in 5 M $LiClO_4$/Et_2O. Method B. Cycloadduct 36. The cycloadduct[28b,c] **28** (900 mg, 4.01 mmol) and the furan derivative[30] **10** (580 mg, 4.01 mmol) were dissolved in a solution of 5 M $LiClO_4$ in Et_2O (5 mL) and allowed to stand at rt for 6 weeks in a sealed flask with daily stirring. The mixture was diluted with EtOAc (100 mL), and the organic layer was washed (3×) with water and brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (hexanes−EtOAc 3:1) yielded the cycloadduct **36** (503 mg, 34%) as a pale yellow oil: $R_f = 0.13$ on silica gel (hexanes−EtOAc 3:1); IR (neat) 3095, 3014, 2953, 2873, 1716, 1457, 1436, 1387, 1242, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (2H, dd, $J = 5.5$, 1.4 Hz), 6.34 (1H, d, $J = 5.5$ Hz), 6.28 (1H, d, $J = 5.5$ Hz), 5.12 (1H, d, $J = 1.8$ Hz), 5.11 (1H, d, $J = 1.8$ Hz), 3.65−3.48 (2H, m), 3.60 (3H, s), 3.59 (3H, s), 2.17−1.95 (3H, m), 1.89−1.78 (1H, m), 1.62 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 142.4, 140.8, 139.2, 139.0, 93.1, 90.0, 80.5(2C), 74.6, 74.3, 52.0, 51.9, 45.0, 28.0, 26.4, 14.9; HRMS calcd for $C_{18}H_{21}ClO_6$ $[M]^+$ 368.1027, found 368.1021.

Cycloadduct 37. The reaction was carried out as in the general procedure B using the dienophile **28** (918 mg, 4.09 mmol) and 4,5,6,7-tetrahydro-4-benzofuran (**19**) (500 mg, 4.09 mmol) in a solution of 5 M $LiClO_4$ in Et_2O (5 mL) for 6 weeks. Purification by flash chromatography (hexanes−EtOAc 1:1) yielded the cycloadduct **37** (702 mg, 50%) as a white solid: R_f = 0.44 on silica gel (hexanes−EtoAc 1:1); mp 107−110 °C (Et_2O); IR (neat) 3016, 2945, 2861, 1742, 1715, 1435, 1241 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (1H, dd, $J = 5.5$, 1.8 Hz), 6.26 (1H, d, $J = 5.5$ Hz), 6.25−6.23 (1H, m), 5.12 (1H, d,

J = 1.8 Hz), 4.93 (1H, d, J = 1.8 Hz), 3.57 (6H, s), 2.48−2.34 (2H, m), 1.97−1.57 (4H, m), 1.52 (3H, s), 1.32−1.03 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.5, 150.7, 143.4, 137.7, 132.3, 90.0, 80.5, 78.7, 77.2, 73.4, 72.9, 51.7, 51.5, 27.6, 26.7, 23.7, 22.5, 14.6. Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.79; H, 6.36.

Cycloadduct 38. The reaction was carried out as in the general procedure B using the dienophile **31** (2.70 g, 7.16 mmol) and 2-methylfuran (3.23 mL, 35.80 mmol) in a solution of 5 M $LiClO_4$ in Et_2O (25 mL) for 6 weeks. Purification by flash chromatography (CH_2Cl_2−EtOAc 9:1) yielded the cycloadduct **38** (840 mg, 26%) as a white solid: R_f = 0.45 on silica gel (CH_2Cl_2−EtOAc 9:1); mp 44−46 °C (CH_2Cl_2); IR (neat) 3094, 2988, 2952, 2847, 1743, 1716, 1599, 1436, 1348, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (2H, d, J = 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz), 6.61 (1H, dd, J = 5.5, 1.8 Hz), 6.35 (1H, dd, J = 5.1, 2.2 Hz), 6.24 (1H, d, J = 5.5 Hz), 5.95 (1H, d, J = 5.5 Hz), 5.11 (1H, d, J = 2.2 Hz), 5.00 (1H, d, J = 1.8 Hz), 3.59 (3H, s), 3.56 (3H, s), 2.37 (3H, s), 1.64 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.7, 143.1, 142.8, 142.5, 139.5, 138.2, 137.7, 129.3, 127.9, 90.3, 80.4, 76.5, 74.9, 72.6, 65.7, 52.1, 52.0, 21.5, 14.8, 13.6. Anal. Calcd for $C_{23}H_{25}NO_7S$: C, 60.12; H, 5.48; N, 3.05. Found: C, 60.10; H, 5.37; N, 3.25.

Cycloadduct 39. The reaction was carried out as in the general procedure A using acetylenedicarboxylic acid (325 mg, 2.85 mmol) and **6** (500 mg, 2.84 mmol) in Et_2O (1.5 mL) for 1 week to yield the cycloadduct **39** (608 mg, 74%) as a white solid: mp 156−160 °C (Et_2O); IR (KBr) 3416−2488, 2988, 2938, 1721, 1384 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 6.58 (2H, dd, J = 5.5, 1.7 Hz), 6.47 (2H, d, J = 5.6 Hz), 5.00 (2H, d, J = 1.7 Hz), 2.37−2.22 (2H, m), 2.08−1.79 (3H, m), 1.71−1.60 (1H, m); ^{13}C NMR (50 MHz, CD_3OD) δ 173.8, 173.7, 142.9, 139.6, 91.3, 84.7, 74.4, 69.7, 26.5, 18.1. Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.86. Found: C, 61.95; H, 4.79.

Cycloadduct 40. The reaction was carried out as in the general procedure A using DMAD (500 mg, 2.63 mmol) and **6** (444 mg, 3.12 mmol) in Et_2O (2.0 mL) for 3 weeks to yield the cycloadduct **40** (644 mg, 71%) as a white solid: R_f = 0.39 on silica gel (hexanes−EtOAc 1:1); mp 151−153 °C (CH_2Cl_2); IR (KBr) 3002, 2959, 2924, 2861, 1736, 1708, 1434, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (2H, dd, J = 5.5, 1.8 Hz), 6.42 (2H, d, J = 5.5 Hz), 4.99 (2H, d, J = 1.5 Hz), 3.56 (3H, s), 3.55 (3H, s), 2.13−2.10 (4H, m), 1.98−1.86 (1H, m), 1.65 (1H, dquintet, J = 13.6, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 142.0, 138.1, 89.9, 83.4, 73.3, 68.5, 51.9, 51.8, 25.6, 17.0. Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 63.72; H, 5.80.

Cycloadduct 41. The reaction was carried out as in the general procedure A using acetylenedicarboxylic acid (453 mg, 4.0 mmol) and **12** (1.00 g, 4.0 mmol) in Et_2O (5 mL) for 6 weeks to yield the cycloadduct **41** (1.15 g, 79%) as a white solid: mp 186−189 °C (acetone); IR (KBr) 3416−2545, 2959, 1727, 1695, 1683, 1408, 699 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 6.65 (1H, dd, J = 5.5, 1.9 Hz), 6.47−6.43 (2H, m), 6.37 (1H, d, J = 5.5 Hz), 5.12 (1H, d, J = 1.8 Hz), 3.67−3.57 (2H, m), 2.39 (1H, td, J = 14.0, 4.9 Hz), 2.23−1.86 (8H, m), 1.68−1.64 (1H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 174.1, 173.8, 142.7, 142.4, 142.1, 140.5, 93.8, 91.4, 90.6, 82.1, 76.2, 72.6, 45.9, 29.6, 27.5, 26.6 (2), 18.1. Anal. Calcd for $C_{18}H_{19}O_6Cl_1$: C, 58.94; H, 5.22. Found: C, 58.67; H, 5.17.

Cycloadduct 42. The reaction was carried out as in the general procedure A using DMAD (2.31 g, 16.25 mmol) and **13** (2.63 g, 14.77 mmol) in Et_2O (20 mL) for 3 weeks. The filtrate was concentated and the residue purified by flash chromatography (hexanes−EtOAc 1:2) to yield the cycloadduct **42** in a combined yield of 76% (3.59 g) as a white crystalline solid: R_f = 0.33 on silica gel (hexanes−EtOAc 1:2); mp 178−181 °C (Et_2O); IR (KBr) 3012, 2966, 1736, 1727, 1717, 1428, 1255, 1080 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 6.67 (2H, dd, J = 5.7, 1.7 Hz), 6.43 (2H, d, J = 5.5 Hz), 5.14 (2H, d, J = 1.5 Hz), 4.25 (2H, d, J = 13.2 Hz), 4.13 (2H, d, J = 13.2 Hz), 3.60 (3H, s), 3.58 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 171.6, 171.5, 141.4, 138.5, 89.0, 85.1, 72.4, 68.5, 65.7, 52.6, 52.5. Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 59.61; H, 4.94.

Cycloadduct 43. The reaction was carried out as in the general procedure A using DMAD (1.7 g, 11.7 mmol) and **15** (3.0 g, 10.6 mmol) without solvent for 6 weeks to yield the cycloadduct **43** (2.82g, 63%) as a white solid: R_f = 0.40 on silica gel (hexanes−EtOAc 1:2); mp 128−131 °C (Et_2O); IR (neat) 3077, 2997, 2891, 2836, 1716, 1513, 1444, 1399, 1265, 1183, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02−6.98 (2H, m), 6.82−6.78 (2H, m), 6.65 (2H, dd, J = 5.5, 1.9 Hz), 6.49 (2H, d, J = 5.5 Hz), 5.13 (2H, d, J = 1.8 Hz), 3.90 (2H, d, J = 13.6 Hz), 3.74 (3H, s), 3.61 (3H, s), 3.59 (3H, s), 3.58 (2H, d, J = 13.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.3, 154.0, 145.2, 139.7, 139.2, 119.6, 114.2, 88.1, 83.8, 71.9, 67.6, 55.5, 52.1 (2C), 49.9; HRMS calcd for $C_{23}H_{23}NO_7$ $[M]^+$ 425.1475, found 425.1457.

Cycloadduct 44. The reaction was carried out as in the general procedure A using DMAD (234 mg, 1.65 mmol) and **16** (400 mg, 1.50 mmol) in Et_2O (5 mL) for 6 weeks to yield the cycloadduct **44** (443 mg, 72%) as a white solid: R_f = 0.40 on silica gel (hexanes−EtOAc 1:1); mp 162−165 °C (Et_2O); IR (KBr) 3030, 3000, 2950, 2850, 2790, 1735, 1708, 1465, 1437 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (5H, m), 6.57 (2H, dd, J = 5.5, 1.8 Hz), 6.41 (2H, d, J = 5.5 Hz), 5.11 (2H, d, J = 1.9 Hz), 3.77 (2H, s), 3.58 (3H, s), 3.53 (3H, s), 3.29 (2H, d, J = 13.2 Hz), 2.96 (2H, d, J = 12.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 139.7, 139.1, 136.9, 129.3, 128.2, 127.1, 88.4, 83.7, 72.0, 67.8, 62.5, 52.0, 51.9, 50.8. Anal. Calcd for $C_{23}H_{23}N_1O_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.08; H, 5.80; N, 3.67.

Cycloadduct 45. The reaction was carried out as in the general procedure A using DMAD (2.3 g, 16.4 mmol) and **17** (4.4 g, 14.9 mmol) in Et_2O (15 mL) for 6 weeks to yield the cycloadduct **45** (4.26 g, 65%) as a white solid: R_f = 0.14 on silica gel (hexanes−EtOAc 1:1); mp 159−163 °C (acetone); IR (CCl_4) 3066, 3000, 2952, 2936, 2836, 2786, 1723, 1558, 1458, 1436, 1248, 1103, 1085, 1042, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.22 (2H, m), 6.84−6.80 (2H, m), 6.57 (2H, dd, J = 5.5, 1.9 Hz), 6.41 (2H, d, J = 5.5 Hz), 5.10 (2H, d, J = 1.5 Hz), 3.77 (3H, s), 3.71 (2H, bs), 3.59 (3H, s), 3.53 (3H, s), 3.28 (2H, d, J = 13.2 Hz), 2.92 (2H, d, J = 13.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 158.7, 139.8, 139.0, 130.6, 128.9, 113.6, 88.5, 83.7, 72.0, 67.8, 61.9, 55.2, 52.0, 51.9, 50.7. Anal. Calcd for $C_{24}H_{25}N_1O_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.50; H, 5.84; N, 3.15.

Cycloadduct 47. The reaction was carried out as in the general procedure A using DMAD (2.19 g, 15.4 mmol) and furfuryl sulfide (**46**) (3.00 g, 15.4 mmol) in Et_2O (10 mL) for 3 weeks to yield the cycloadduct **47** (3.68 g, 71%) as a white solid: R_f = 0.33 on silica gel (hexanes−EtOAc 1:2); mp 191−194 °C (Et_2O); IR (KBr) 2997, 2958, 1740, 1705, 1440, 1430, 1278, 1010, 685 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.57 (2H, dd, J = 5.5, 1.8 Hz), 6.41 (2H, d, J = 5.5 Hz), 5.09 (2H, d, J = 1.7 Hz), 3.58 (3H, s), 3.57 (3H, s), 3.52 (2H, d, J = 15.1 Hz), 2.87 (2H, d, J = 15.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.2, 170.0, 141.3, 138.9, 87.1, 83.3, 73.4, 67.2, 52.1, 52.0, 27.1. Anal. Calcd for $C_{16}H_{16}O_6S_1$: C, 57.13; H, 4.79. Found: C, 57.43; H, 4.80.

Cycloadduct 48. The reaction was carried out as in the general procedure A using freshly prepared **21**[35] (424 mg, 1.89 mmol) and **6** (366 mg, 2.08 mmol) in Et_2O (10 mL) for 15 h. Recrystallization from CH_2Cl_2 yielded the cycloadduct **48** (525 mg, 69%) as a white solid: R_f = 0.38 on silica gel (hexanes−EtOAc 1:1); mp 181−183 °C (CH_2Cl_2); IR (KBr) 3002, 2952, 2931, 1715, 1574, 1448, 1321, 1279, 1152 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.83 (2H, m), 7.71−7.67 (1H, m), 7.63−7.59 (2H, m), 6.54 (4H, bs), 4.73 (2H, bs), 3.70 (3H, s), 2.21−2.08 (4H, m), 1.92−1.80 (1H, m), 1.68−1.61 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 142.1, 140.5, 138.6, 134.0, 129.4, 128.6, 91.5, 91.3, 83.4, 71.2, 52.3, 25.7, 16.7. Anal. Calcd for $C_{21}H_{20}O_6S_1$: C, 62.99; H, 5.03. Found: C, 62.73; H, 4.81.

Cycloadduct 49. A solution of **25** (500 mg, 2.84 mmol) in CH_2Cl_2 (35 mL) was treated with *m*-CPBA 50% (2.94 g, 8.52 mmol) at 0 °C and stirred for 3 h at rt. The mixture was diluted with CH_2Cl_2, washed with a saturated solution of $NaHCO_3$ (1×), a 5 M solution of NaOH (2×), and brine (1×), dried ($MgSO_4$), filtered, and concentrated. The crude keto sulfone **26** was dissolved in Et_2O (3 mL) and treated with **6**

(500 mg, 2.84 mmol). The mixture was stored for 24 h at rt, during which time the product crystallized out. The crystals were isolated by filtration and washed with Et_2O to yield the cycloadduct **49** (327 mg, 30%) as a white solid: $R_f = 0.38$ on silica gel (hexanes−EtOAc 1:1); mp 138−142 °C (CH_2Cl_2); IR (KBr) 3065, 2952, 1684, 1574, 1306 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88−7.85 (2H, m), 7.76−7.72 (1H, m), 7.68−7.64 (2H, m), 6.80 (2H, dd, J = 5.5, 1.8 Hz), 6.64 (2H, d, J = 5.5 Hz), 4.65 (2H, d, J = 1.5 Hz), 2.32 (3H, s), 2.18−2.05 (4H, m), 1.86−1.74 (1H, m), 1.64−1.59 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 142.4, 140.1, 139.3, 134.3, 129.7, 128.0, 92.0, 88.9, 83.2, 80.5, 32.3, 25.8, 16.6. Anal. Calcd for $C_{21}H_{20}O_5S_1$: C, 65.61; H, 5.24. Found: C, 65.28; H, 5.23.

Cycloadducts 50 and 51. The reaction was carried out as in the general procedure A using **22** (250 mg, 2.0 mmol) and **6** (352 mg, 2.0 mmol) in Et_2O (5 mL) for 2 weeks. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (hexanes:EtOAc 1:1) to yield a mixture of cycloadduct **50** (284 mg) and **51** (76 mg) in a 4:1 ratio as white solids in a combined yield of 60%. Cycloadduct **50**: $R_f = 0.43$ on silica gel (hexanes−EtOAc 1:1); mp 146−148 °C (CH_2Cl_2); IR (KBr) 3023, 3002, 2959, 2931, 2868, 1738, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.55−6.49 (4H, m), 5.04 (2H, bs), 3.60 (3H, s), 2.20−1.75 (5H, m), 1.82 (3H, s), 1.69−1.57 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.4, 171.1, 142.8, 138.4, 90.3, 83.2, 76.0, 71.2, 52.0, 31.9, 25.5, 16.9. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.25; H, 5.94. Cycloadduct **51**: $R_f = 0.26$ on silica gel (hexanes−EtOAc 1:1); mp 139−141 °C (CH_2Cl_2); IR (KBr) 3002, 2945, 2924, 2861, 1726, 1704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (2H, d, J = 5.5 Hz), 6.42 (2H, dd, J = 5.7, 1.9 Hz), 5.04 (2H, d, J = 1.8 Hz), 3.59 (3H, s), 2.17−2.04 (4H, m), 2.01−1.89 (1H, m), 1.98 (3H, s), 1.70−1.63 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 171.5, 144.6, 135.9, 90.5, 83.5, 82.6, 67.0, 52.0, 29.7, 25.6, 17.2. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.14; H, 5.97.

Cycloadduct 52. The reaction was carried out as in the general procedure B using methyl propiolate (**20**) (716 mg, 8.52 mmol) and **6** (1.0 g, 5.68 mmol) in a solution of 5 M $LiClO_4$ in Et_2O (7 mL) for 8 weeks. Purification by flash chromatography (hexanes−EtOAc 1:1) yielded the cycloadduct **52** (846 mg, 57%) as a white solid: $R_f = 0.27$ on silica gel (hexanes−EtOAc 1:1); mp 119−121 °C (CH_2Cl_2); IR (KBr) 3065, 3009, 2952, 2917, 2847, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (2H, dd, J = 5.7, 1.7 Hz), 6.12 (2H, d, J = 5.5 Hz), 4.82 (2H, d, J = 1.5 Hz), 3.55 (3H, s), 2.56 (1H, s), 2.35 (2H, dt, J = 14.0, 4.5 Hz), 2.11 (2H, dt, J = 14.2, .3.1 Hz), 1.99 (1H, qt, J = 13.4, .3.9 Hz), 1.75−1.68 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 140.5, 139.5, 87.4, 80.8, 63.8, 55.5, 51.9, 24.8, 17.3. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 68.86; H, 6.01.

Cycloadduct 54. The reaction was carried out as in the general procedure A using ethynyl *p*-tolylsulfone (**53**) (200 mg, 1.11 mmol) and **6** (235 mg, 1.33 mmol) in a solution of 5 M $LiClO_4$ in Et_2O (3 mL) for 4 weeks. Purification by flash chromatography (hexanes−EtOAc 1:1) yielded the cycloadduct **54** (328 mg, 83%) as a white solid: $R_f = 0.32$ on silica gel (hexanes−EtOAc 1:1); mp 165−167 °C (CH_2Cl_2); IR (KBr) 3092, 3070, 2977, 2938, 1590, 1282, 1293, 1144, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.4 Hz), 6.86 (2H, d, J = 5.5 Hz), 6.38 (2H, dd, J = 5.5, 1.8 Hz), 4.64 (2H, d, J = 1.8 Hz), 2.62 (2H, dt, J = 14.0, 4.5 Hz), 2.39 (3H, s), 2.26 (2H, dt, J = 14.2, 3.1 Hz), 2.00 (1H, tq, J = 13.5, 4.1 Hz), 1.84 (1H, s), 1.83−1.76 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 144.2, 137.8, 137.2, 129.2, 129.0, 89.8, 83.5, 81.1, 64.0, 26.3, 21.6, 17.1. Anal. Calcd for $C_{20}H_{20}O_4S_1$: C, 67.40; H, 5.66. Found: C, 67.27; H, 5.60.

1-(2-Furan-2-ylethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic Acid Dimethyl Ester (55) and Cycloadduct 56. The reaction was carried out as in the general procedure A using DMAD (105 mg, 0.74 mmol) and 1,2-bis(2-furyl)ethane[29] (**9**) (100 mg, 0.62 mmol) in Et_2O (1 mL) for 3 weeks. The solvent was removed in vacuo, and the residue was purified by flash chromatography (hexanes−EtOAc 3:1) to give the cycloadduct **55** (70 mg, 38%) as a colorless oil and the unreacted starting material **9** (19 mg, 19%). Further elution with hexanes−EtOAc (1:1) gave the cycloadduct **56** as a white solid (44 mg, 16%). Cycloadduct **55**: $R_f = 0.43$ on silica gel (hexanes−EtOAc 3:1); IR (neat) 3037, 3002, 2952, 2854, 1715, 1638, 1509, 1436, 1271, 1229, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, d, J = 1.8 Hz), 7.16 (1H, dd, J = 5.2, 1.9 Hz), 6.93 (1H, d, J = 5.1 Hz), 6.26 (1H, dd, J = 3.3, 1.9 Hz), 5.99 (1H, m), 5.64 (1H, d, J = 1.8 Hz), 3.82 (3H, s), 3.76 (3H, s), 2.82−2.70 (2H, m), 2.55−2.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.7, 155.6, 154.6, 151.8, 144.6, 144.5, 141.0, 110.1, 105.2, 96.8, 83.4, 52.4, 52.3, 27.5, 23.4; HRMS calcd for $C_{16}H_{16}O_6$ $[M]^+$ 304.0947, found 304.0943. Cycloadduct **56**: $R_f = 0.46$ on silica gel (hexanes−EtOAc 1:1); mp 189−192 °C (Et_2O); IR (KBr) 3093, 3016, 2959, 2854, 1739, 1710, 1650, 1440, 1429, 1279, 1261, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (2H, dd, J = 5.1, 1.8 Hz), 6.95 (2H, d, J = 5.1 Hz), 5.62 (2H, d, J = 2.2 Hz), 3.81 (6H, s), 3.76 (6H, s), 2.36−2.24 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.7, 155.5, 151.9, 144.8, 144.6, 97.0, 83.5, 52.4, 52.3, 24.3; HRMS calcd for $C_{22}H_{22}O_{10}$ $[M]^+$ 446.1213, found 446.1238.

1-(4-Furan-2-ylbutyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic Acid Dimethyl Ester (57) and Cycloadduct 58. The reaction was carried out as in the general procedure A using DMAD (411 mg, 2.89 mmol) and 1,4-bis(2-furyl)butane (**7**) (500 mg, 2.63 mmol) in Et_2O (2 mL) for 3 weeks. The solvent was removed in vacuo, and the residue was purified by flash chromatography (hexanes−EtOAc 3:1) to yield the cycloadduct **57** (330 mg, 38%) as a colorless oil and the unreacted starting material **7** (93 mg, 19%). Further elution with hexanes−EtOAc (1:1) gave the cycloadduct **58** as a clear oil (270 mg, 22%). Cycloadduct **57**: $R_f = 0.40$ on silica gel (hexanes−EtOAc 3:1); IR (neat) 3009, 2952, 2861, 1718, 1639, 1508, 1437, 1272, 1231, 1201, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, dd, J = 1.8, 0.7 Hz), 7.14 (1H, dd, J = 5.2, 1.9 Hz), 6.95 (1H, d, J = 5.5 Hz), 6.23 (1H, dd, J = 2.9, 1.8 Hz), 5.94 (1H, dd, J = 3.3, 0.7 Hz), 5.60 (1H, d, J = 1.8 Hz), 3.79 (3H, s), 3.74 (3H, s), 2.60 (2H, mt, J = 7.5 Hz), 2.22−2.08 (2H, m), 1.68 (2H, quintet, J = 7.5 Hz), 1.55−1.37 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 162.6, 156.1, 155.8, 151.3, 144.9, 144.5, 140.6, 110.0, 104.7, 97.6, 83.2, 52.3, 52.2, 28.5, 28.0, 27.6, 24.3; HRMS calcd for $C_{18}H_{20}O_6$ $[M]^+$ 332.1260, found 332.1263. Cycloadduct **58**: $R_f = 0.53$ on silica gel (hexanes−EtOAc 1:1); IR (neat) 3093, 3002, 2952, 2868, 1745, 1717, 1641, 1561, 1437, 1378, 1122, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (2H, dd, J = 5.3, 2.0 Hz), 6.95 (2H, d, J = 5.1 Hz), 5.61 (2H, d, J = 1.8 Hz), 3.81 (6H, s), 3.75 (6H, s), 2.19−2.08 (4H, m), 1.58−1.41 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 162.7, 156.2, 151.4, 144.9, 144.6, 97.6, 83.3, 52.3, 52.2, 28.6, 25.0; HRMS calcd for $C_{24}H_{26}O_{10}$ $[M]^+$ 474.1526, found 474.1526.

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Supporting Information Available: ORTEP drawings and details of the data acquisition are available for compounds **48** and **50** and for the derivative of **38** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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