and $Pd(Ph_3P)_2Cl_2$ (0.037 g, 0.05 mmol in THF)) were sequentially added **8d** (0.50 g, 1.2 mmol) and **12f** (0.211 g, 1.0 mmol) at room temperature. The homogeneous reaction mixture turned black in 24 h. The reaction mixture was diluted with ether and stirred with saturated KF. After filtration of Bu_3SnF, the reaction was worked up as usual, and the crude product purified by column chromatography (hexane as eluant) to give 0.14 g (88%) of **12g**: ^1H NMR ($CDCl_3$) δ 0.86 (t, 6 H, CH_3, J = 7.0 Hz), 1.02–1.4 (m, 16 H, CH_2), 1.9 (s, 3 H), 2.3 (dt, 2 H, C=CCH_2, J = 7.0, 1.6 Hz), 2.9 (dq, 2 H, C=CCH_2, J = 7.0, 1.6 Hz), 5.5 (ddt, 1 H, HC=C*H*C, J = 18.0, 10.0, 1.6 Hz), 5.8 (dt, 1 H, C=C*H*HC=C, J = 10.0, 1.6 Hz), 6.0 (ddt, 1 H, C*H*=CHC, J = 18.0, 10.0, 7.0 Hz); ^{13}C NMR δ 142.6 (*C*=CHCH=C), 132.7 (C=CHCH=*C*), 129.6 (C=*C*HCH=C), 123.5 (C=CH*C*H=C), 33.2, 32.7, 31.9, 29.9, 29.3, 22.6, 17.6, 14.1; GC/MS, m/e (rel intensity) 280 (M^+, 35.0). The spectral data matched the published results.[36]

Preparation of 1-Hexynyltributylstannane[37] (12h). To a solution of 1-hexyne (0.82 g, 10.0 mmol) in Et_2O (15 mL) was added dropwise *n*-BuLi (3.8 mL, 10.0 mmol) at −30 °C. After 30 min Bu_3SnCl (3.25 g, 10.0 mmol) was added. The reaction was warmed to room temperature and then subjected to the normal workup. Bulb-to-bulb distillation (bath temperature, 65 °C (0.03 mmHg)) gave 3.5 g (95%) of **12h**: ^1H NMR ($CDCl_3$) δ 0.86 (t, 9 H, CH_3, J = 7.0 Hz), 0.89 (t, 3 H, CH_3, J = 7.0 Hz), 1.2–1.4 (m, 12 H, CH_2), 1.4–1.5 (m, 10 H, CH_2), 2.20 (t, 2 H, CH_2, J = 7.0 Hz); ^{119}Sn δ −68.2; GC/MS, m/e (rel intensity) 315 (M^+ − 56, 100).

Preparation of 8-Methyl-7(*E*)-hexadecen-5-yne (12i). To a solution of **8d** (0.211 g, 1.0 mmol, prepared as described earlier) and **12h** (0.44 g, 1.2 mmol) at room temperature was added "$Pd(Ph_3P)_2$" (0.05 mmol) in 5 mL of THF (generated *in situ* by the reaction of 2 equiv of DIBALH and 1 equiv of $Pd(Ph_3P)_2Cl_2$ in THF). The homogeneous reaction mixture turned black within an hour. The black reaction mixture was added to 25 mL of water, and this aqueous mixture was extracted with ether (3 × 25 mL) which was back extracted with brine (1 × 25 mL) and dried over potassium carbonate. The dried extracts were filtered through alumina and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane as eluant) to give 0.155 g (88%) of **12i**: ^1H NMR ($CDCl_3$) δ 0.87 (t, 6 H, CH_3, J = 6.7 Hz), 1.26–1.4 (m, 12 H, CH_2), 1.54–1.64 (m, 4 H, CH_2), 1.9 (s, 3 H, CH_3), 2.1 (dt, 2 H, C≡CCH_2, J = 6.7, 1.8 Hz), 2.23 (dt, 2 H, C=CCH_2, J = 6.7, 1.9 Hz), 5.7 (t, 1 H, C=C*H*C=C, J = 1.9 Hz); ^{13}C NMR δ 142.9 (*C*=CHC≡C), 120.1 (C=*C*H), 110.1, 88.6, 79.3, 39.1, 32.7, 32.5, 31.0, 22.1, 22.0, 19.0, 13.7, 13.5; GC/MS, m/e (rel intensity) 278 (M^+, 23.0).

Reaction of 1-Decynyldiethylaluminum with Tributylstannyl Hydride. To a solution of 1-decynyldiethylaluminum in THF (prepared from 1-decyne (0.138 g, 1.0 mmol) in 5 mL of THF, *n*-BuLi (0.40 mL, 1.04 mmol), and Et_2AlCl (1.0 mL, 1.0 mmol); 0 °C, 0.5 h), Bu_3SnH (0.291 g, 1.0 mmol) was added dropwise, and the reaction stirred overnight at 0 °C. Only 1-decyne and Bu_3SnH were recovered. Vinylstannane products were not detected by gas chromatographic analysis after the normal workup.

Reaction of $Bu_3SnAlEt_2$ and Tributylstannyl Hydride. To a THF solution of $Bu_3SnAlEt_2$ (1.0 mmol) prepared by method b was added Bu_3SnH (0.291 g, 1.0 mmol) at 0 °C, and the reaction was stirred at this temperature. Only Bu_3SnH was obtained upon the usual workup. Formation of hexabutylditin was not observed even after 24 h.

Reaction of $Bu_3SnAlEt_2$ with Tributylstannyl Hydride in the Presence of Catalyst. $Bu_3SnAlEt_2$ (1.0 mmol) was prepared according to method b. Bu_3SnH (0.291 g, 1.0 mmol) and CuCN (0.004 g, 0.05 mmol) in 5 mL of THF were added to this solution at 0 °C. After stirring for 0.5 h, the reaction was quenched with 1 N HCl and subjected to the normal workup. Hexabutylditin (0.04 g, 69%) was obtained as the only product after bulb-to-bulb distillation.

Reaction of Tributylstannyl Hydride with CuCN. No reaction was observed when Bu_3SnH was reacted with CuCN in THF under argon at 0 °C for 12 h.

Reaction of $Bu_3SnAlEt_2$ with CuCN. CuCN (0.004 g, 0.05 mmol) was added to a solution of $Bu_3SnAlEt_2$ (1.0 mmol, method b) in 5 mL of THF. The solution immediately turned brick red. Workup after 30 min yielded 69% of hexabutylditin.

Reaction of 1-Decynyldiethylaluminum with $Bu_3SnAlEt_2$. Decynyldiethylaluminum (vide supra) was transferred via a canula to a THF solution of $Bu_3SnAlEt_2$ (1.0 mmol, vide supra) while the temperature was maintained at 0 °C. The reaction was stirred overnight at 0 °C, after which it was subjected to the normal workup to give 1-decyne.

Acknowledgment. This work was supported through a Natural Sciences and Engineering Research Council of Canada Operating Grant to A.C.O. and an S.F.U. Open Graduate Scholarship to S.S.

Registry No. **4**, 28688-36-0; **5**, 92074-24-3; **6**, 764-93-2; **7a**, 112164-71-3; **7b**, 122593-83-3; **7c**, 122593-85-5; **7d**, 122593-86-6; **7e**, 122593-88-8; **7f**, 122593-89-9; **8a**, 112164-72-4; **8b**, 122593-84-4; **8d**, 122593-87-7; **9a**, 928-90-5; **9b**, 68274-83-9; **9c**, 1720-37-2; **9d**, 66977-99-9; **10a**, 119288-35-6; **10b**, 122593-90-2; **10c**, 119288-42-5; **10d**, 119288-37-8; **11a**, 119288-45-8; **12a**, 122593-91-3; **12b**, 122593-92-4; **12c**, 122593-93-5; **12d**, 122593-94-6; **12e**, 122593-95-7; **12f**, 16644-98-7; **12g**, 122593-96-8; **12h**, 35864-20-1; **12i**, 122593-97-9; Bu_3SnLi, 4226-01-1; Bu_3SnMe, 1528-01-4; Bu_3SnCl, 1461-22-9; Me_3SnCl, 1066-45-1; Me_4Sn, 594-27-4; Bu_3SnH, 688-73-3; Bu_4Sn, 1461-25-2; $Me_3SnSnMe_3$, 661-69-8; CuCN, 544-92-3; $Pd(Ph_3P)_2Cl_2$, 13965-03-2; $Pd(Ph_3P)_4$, 29032-53-9; $CuBr{\cdot}Me_2S$, 54678-23-8; CuI, 7681-65-4; $Pd(Ph_3P)_2$, 31989-57-8; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; iodobenzene, 591-50-4; dihydropyran, 110-87-2; 1-hexyne, 693-02-7; hexabutylditin, 813-19-4.

Scope of Tandem Cycloaddition/Radical Cyclization Methodology

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Tandem cycloaddition/radical cyclization is an effective strategy for the rapid assembly of a wide variety of ring systems. To set up the reagents for this sequence, it is necessary to include a potential radical site in one of the two cycloaddition partners, located at an appropriate distance from a new double bond that will be formed in the cycloaddition step. Examples in which the cycloaddition step is [4 + 2] or [3 + 2] and in which the radical cyclization creates 5-, 6-, or 7-membered rings are described. Examples of the tandem methodology carried out in a completely intramolecular mode are also described.

Introduction

The construction of polycyclic systems from acyclic precursors with a minimum number of steps and with regio- and stereochemical control remains a synthetic challenge. Two of the most important ring-forming reactions currently in use for this purpose are cycloadditions

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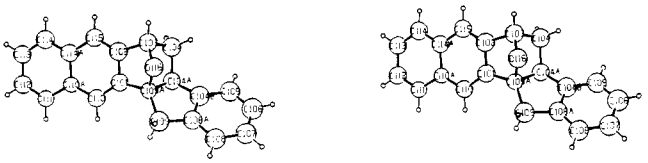
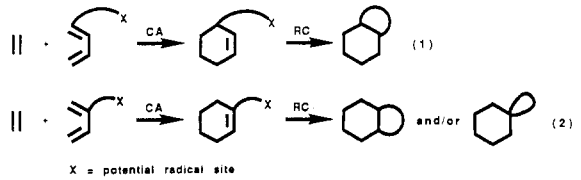


Figure 1. Stereoview of 8 showing that radical cyclization occurs with exo stereochemistry.

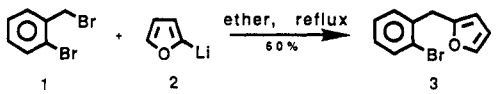
(CA)[1] and radical cyclizations (RC).[2] In this paper we will demonstrate that the *tandem* use of these two reaction types enhances the utility of each and constitutes a widely applicable strategy for the rapid assembly of polycyclic systems.[3]

The idea is quite simple. In many cycloaddition reactions, a new double bond is formed. If one of the two reacting partners in a cycloaddition were to carry a potential radical site located at an appropriate position with respect to the newly formed double bond, then a second ring could be formed by treating the cycloadduct with a radical initiator. Equations 1 and 2 illustrate schematically the possibilities for a Diels–Alder reaction in which the diene component carries a potential radical site at C1 or C2. Despite the intense current interest in using radical cyclizations in synthesis, we are unaware of previous examples in which the two reactions, cycloaddition and radical cyclization, are coupled in this way.

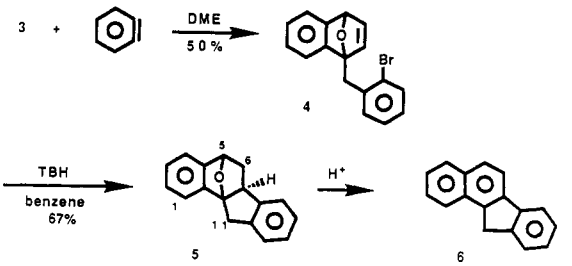


Results and Discussion

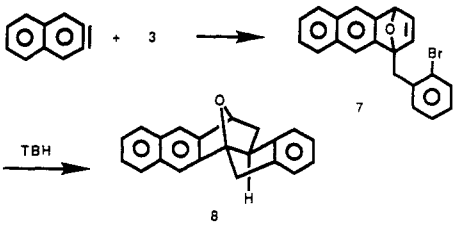
Tandem [4 + 2] Cycloaddition/Radical Cyclization. (a) Five-Membered Ring Formation. As the first diene with a strategically located potential radical site we selected furan **3**. The reasons for this choice were that the diene moiety is cisoid, the radical site is five atoms away from one of the carbon atoms that becomes part of the double bond after cycloaddition to the furan, and the molecule can be assembled in one step from readily available precursors. Treatment of 2-bromobenzyl bromide[4] with 2-lithiofuran in ether at reflux gave **3** in 60% yield.[5]



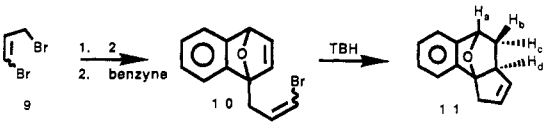
Addition of benzyne (generated from anthranilic acid and isoamyl nitrite) to **3** gave cycloadduct **4** in 50% yield. The ^{1}H NMR spectrum of **4** showed diastereotopic methylene protons at δ 3.63 and 4.10, the bridgehead proton at δ 5.68 coupled (J = 5 Hz) to the adjacent vinyl proton, as well as peaks for the remaining vinyl and aryl protons. Subsequent heating of **4** with tri-*n*-butyltin hydride (TBH, 1 equiv) in refluxing benzene gave a single cyclized product **5**. Proof of the carbon framework came from the fact that **5** was easily dehydrated (HCl, ethanol) to the known benzo[a]fluorene **6** (identical melting points and spectra[6]).



The ^{1}H NMR spectrum showed **5** to be a single stereoisomer, with a bridgehead proton at δ 5.43, two geminally coupled benzylic methylene protons at δ 3.78, 3.37 (J = 17 Hz), a methine proton at δ 3.17, and remaining methylene protons at δ 2.30 and 2.03. Unfortunately, the NMR spectrum did not permit an unambiguous assignment of stereochemistry. An X-ray structure determination on the similarly prepared naphtho analogue **8** solved the problem and clearly established the exo geometry of the new C–C bond formed in the radical cyclization step (Figure 1). Since the nonaromatic portion of the ^{1}H NMR spectra of **5** and **8** were virtually identical we conclude that **5** also has the exo structure as drawn.



The vinyl analogue of **5** was similarly prepared. 1,3-Dibromopropene and 2-lithiofuran gave 2-(3-bromoallyl)furan as a cis/trans mixture. When this furan was subjected to the tandem CA/RC sequence using benzyne as the dienophile in the first step, **11** was obtained in reasonable yield. The ^{1}H NMR spectrum showed that



only one isomer was formed, and by analogy with **5** and **8** we place the methine proton H_d endo. The NMR spectrum is fully consistent with this assignment. In particular, H_a appears as a doublet (δ 5.37), coupled only with H_b (δ 2.00, J = 5 Hz), which, in turn, is also coupled with H_d (δ 2.65, J = 5 Hz) and H_c (δ 1.72, J = 12 Hz). Finally, H_d is coupled with cis proton H_c by a larger coupling constant (J = 8.5 Hz) than with trans proton H_b (J = 5 Hz), consistent with the rigid geometry shown. Other peaks were readily assigned to the vinyl (δ 5.90), allylic methylene (δ 3.15, 2.77), and aromatic (δ 7.20) protons. Compound **11** is a potentially useful functionalized tetracyclic synthon.

(b) Six-Membered Ring Formation. In the above examples there is a two-atom tether between the radical site (the bromine-bearing carbon) and C1 of the diene

(1) For a list of reviews, see: *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol 6, p 880. For more recent reviews, see: *Index of Reviews in Organic Chemistry*, Royal Society of Chemistry.

(2) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883–887. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553–565. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541–3676. Curran, D. P. *Synthesis* **1988**, 417–439, 489–513.

(3) For a preliminary account, see: Ghosh, T.; Hart, H. *J. Org. Chem.* **1988**, *53*, 2396–2398.

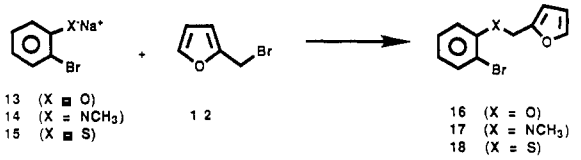
(4) Aldrich Chemical Co.

(5) For the analogous reaction of **2** with benzyl chloride, see: Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216–1219.

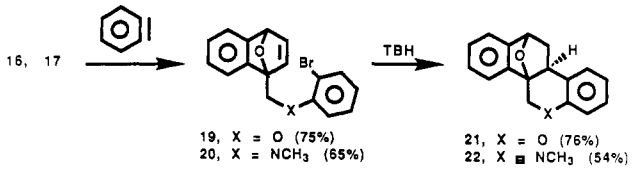
(6) Cook, J. W.; Hewett, C. L. *J. Chem. Soc.* **1934**, 365–377. Datta, B. B.; Bardhan, J. C. *J. Chem. Soc.* **1962**, 3974–3977.

moiety, and this results in five-membered ring formation in the radical cyclization step. If the tether length is increased to three atoms, a six-membered ring can be formed in this step. The following examples are illustrative and also incorporate a heteroatom in the tether.

Treatment of 2-furfuryl bromide **12** (generated in situ from furfuryl alcohol and PBr_3) and nucleophiles **13–15** gave the required starting materials **16–18**.[7] Treatment

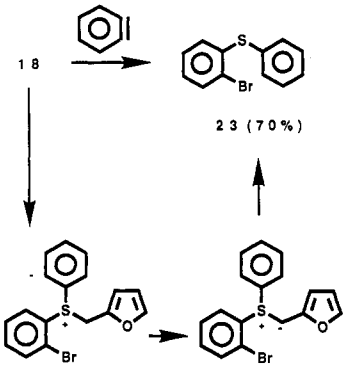


of **16** or **17** with benzyne gave the corresponding cycloadducts **19** and **20** in good yield. The ^1H NMR spectra of **19** and **20** were similar. In the aliphatic region, the bridgehead proton appeared as a doublet (J = 2.8 Hz) at δ 5.75 and 5.65 in **19** and **20**, respectively, and the methylene protons appeared as an AB quartet at δ 4.80 in **19**, and as two doublets at δ 3.65, 4.25 (J = 14.8 Hz) in **20**.



Radical cyclization gave **21** and **22**, respectively, each as a single stereoisomer.[8] Due to the saturation of the double bond, the bridgehead protons moved upfield slightly (to δ 5.50 in **21** and δ 5.43 in **22**) and though still doublets, had a larger coupling constant (J = 4.5 Hz) due to coupling with the adjacent exo methylene proton. The endo methine proton appeared as a doublet of doublets at δ 3.00 in both compounds, coupled to each adjacent methylene proton (J = 8, 4.5 Hz). The isolated methylene protons appeared as an AB quartet at δ 4.85 in **21**, whereas in **22** they appeared as two doublets (J = 12.8 Hz) at δ 3.75 and 4.05. The similarity of the aliphatic portions of the ^1H NMR spectra of **21** and **22** to that of **8** is consistent with cyclization on the exo face of the double bond, as depicted.

Reaction of **18** with benzyne did not furnish a cycloadduct; instead, the product was sulfide **23**, presumably formed via ylid intermediates. Sulfides are known to react



(7) For preparation of the analogues, but lacking the bromine substituent, see for **16**: Paul, R.; Normant, H. *Bull. Soc. Chim. Fr.* **1938**, *5*, 1148–1153. For **17**: Eliel, E. L.; Peckham, P. E. *J. Am. Chem. Soc.* **1950**, *72*, 1209–1212. For **18**: Lapkin, I. I.; Bogoslovskii, N. V.; Saitkulova, F. G. *J. Org. Chem., U.S.S.R. (Engl.)* **1966**, *2*, 150–152. Katritzky, A. R.; Abdel-Megeed, M. F.; Lhomett, G.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 426–429.

(8) Structures related to **21** and **22** were recently synthesized using intramolecular Diels–Alder methodology: Tsuge, O.; Ueno, K.; Kanemasa, S. *Heterocycles* **1986**, *24*, 629–632.

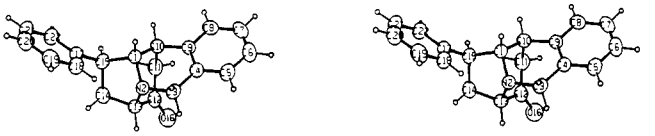
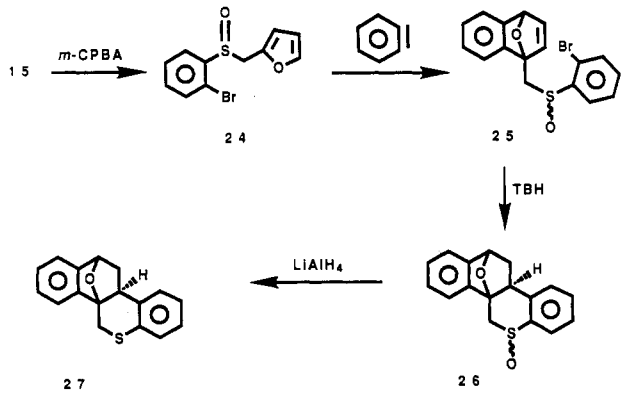


Figure 2. Stereoview of **43** (Table I) showing the regio- and stereochemistry of styrene cycloaddition to **40′**.

with benzyne to give ylids.[9] This difficulty was overcome by oxidizing **15** to sulfoxide **24**, which then readily underwent the benzyne CA/RC sequence to give **26**. Benzyne adduct **25** was obtained as a mixture of diastereomeric sulfoxides formed in unequal amounts, as was **26**. Thus **25** showed two peaks for the bridgehead protons (major at δ 5.73 J = 2 Hz, minor at δ 5.68) and for the methylene protons (major at δ 3.55 and 4.05, doublets, J = 14 Hz, minor at δ 3.65 and 3.93). Similarly **26**, with an additional chiral center, was a mixture of *two* isomers which were separated (see the Experimental Section for details). That the isomerism was due to the sulfoxide moiety was proved by reduction to a single sulfide **27**. The ^1H NMR spectrum of **27** showed only one bridgehead signal (δ 5.44, d, J = 4.5 Hz) and only one methine proton (δ 2.90, dd, J = 8, 4.5 Hz, coupled with each adjacent methylene proton). These data confirm that the six-membered radical cyclizations also occur stereospecifically from the exo face of the oxanorbornene double bond.



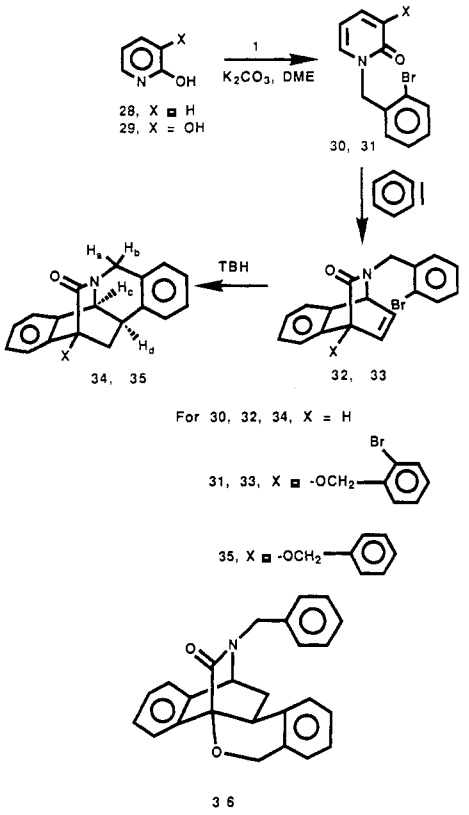
All examples presented so far use a five-membered cyclic diene. To extend the scope of the CA/RC sequence, we used pyridones as the diene moiety, with a three-carbon tether to the radical site. Pyridones **30** and **31** were readily prepared by alkylation of 2-hydroxy- or 2,3-dihydroxypyridine with 2-bromobenzyl bromide.[10] Reaction with benzyne[11] gave the corresponding cycloadducts **32** and **33**, whose ^1H NMR spectra were consistent with the structures. Radical cyclization of **32** gave a single product **34** in 73% yield. Bridgehead proton H_c appears as a doublet at δ 4.72 with only small coupling (J = 2.3 Hz) to H_d at δ 3.27, confirming the endo geometry of the latter.

Radical cyclization of **33** could involve either the nitrogen tether to give **35** or the oxygen tether to give **36**.

(9) Franzen, V.; Joschek, H.-I.; Mertz, C. *Justus Liebigs Ann. Chem.* **1962**, *654*, 82–91.

(10) Giam, C. S.; Hauck, A. E. *Org. Prep. Proc.* **1977**, *9*, 5–8. Nedenskov, P.; Clauson-Kaas, N.; Lei, J.; Heide, H.; Olsen, G.; Jansen, G. *Acta Chem. Scand.* **1969**, *23*, 1791–1796.

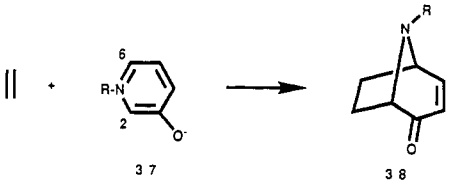
(11) Bauer, L.; Muellner, F. W. *J. Heterocycl. Chem.* **1983**, *20*, 1581–1584. Muellner, F. W.; Abdel-Sayed, A. N.; Bauer, L. *J. Heterocycl. Chem.* **1985**, *22*, 1055–1060. Sheinin, E. B.; Wright, G. E.; Bell, C. L.; Bauer, L. *J. Heterocycl. Chem.* **1968**, *5*, 859–862. Paquette, L. A.; Meisinger, R. H. *Tetrahedron Lett.* **1970**, 1479–1482. Kuzuya, M.; Ishikawa, M.; Okuda, T.; Hart, H. *Tetrahedron Lett.* **1979**, 523–526. Kuzuya, M.; Mano, E.; Ishikawa, M. Okuda, T.; Hart, H. *Tetrahedron Lett.* **1981**, *22*, 1613–1616.



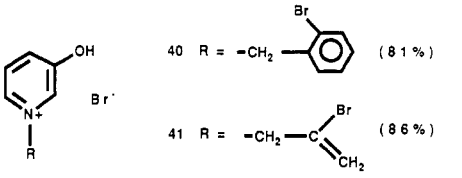
Two equivalents of TBH were used, sufficient to reduce both bromines. Although ^1H NMR signals due to a minor product (**36**) could be seen in the crude mixture, the major product, isolated pure, was **35**. Its ^1H NMR spectrum showed many similarities to that of **34**. In particular, H_c appeared as a doublet at δ 4.70 (J = 2.0 Hz) coupled to H_d at δ 3.26; also, the chemical shifts of H_a and H_b were nearly identical in **34** and **35** (δ 5.20 and 4.27, J = 16.3 Hz in **34**, δ 5.27 and 4.34, J = 16.5 Hz in **35**). Preferred cyclization from the nitrogen tether may be a consequence of less strain in the resulting six-membered ring and a reflection of that difference in the two cyclization transition states.

Tandem [3 + 2] Cycloaddition/Radical Cyclization. Several years ago Katritzky and co-workers showed that betaines **37** derived from 3-hydroxypyridine undergo useful [3 + 2] cycloadditions with a variety of dipolarophiles.[12] Addition occurs across C2 and C6 of **37**, and the product **38** is a bicyclic enone. We though that if R were to contain a potential radical site, cyclization could subsequently be induced onto the enone double bond, thus incorporating the nitrogen atom in another ring.

Alkylation of 3-hydroxypyridine with 2-bromobenzyl bromide **1** or 2,3-dibromopropene **39** gave in good yield the quaternary bromides **40** and **41**, respectively. For reaction with long-lived dipolarophiles, betaines **40′** and **41′** were generated from these precursors in situ using triethylamine. The cycloadducts thus obtained are shown in Table



I. For benzyne as dipolarophile (entry 2), the betaine was preformed and benzyne was generated in its presence from anthranilic acid.



The regioisomer shown (phenyl or methoxycarbonyl group remote from the ketone) predominated by a large factor, and, in the case of entry 1, only adduct **42** with phenyl exo, was obtained. The ^1H NMR spectrum of **42** clearly supported this assignment. For example, H_6 appeared as a doublet at δ 3.75, coupled to H_{7n} (J = 8 Hz) and *not* coupled to bridgehead H_5 or H_{7x}. Other features of the spectrum are consistent with this assignment, which was ultimately confirmed by an X-ray structure on a single crystal of the corresponding cyclized product **43** (Figure 2). Structures of the remaining cycloadducts in Table I were assigned from their spectra. With entries 3 and 4, the exo isomers predominated. This was deduced by integrating the H_5 protons, which appeared as a doublet at δ 4.15 for *exo*-**46** (coupled only to H_4) but a doublet of doublets at δ 4.05 for *endo*-**46** (coupled to H_4 and H_6); similarly, H_5 was a doublet at δ 4.21 for *exo*-**48**, but a doublet of doublets at δ 4.10 for *endo*-**48**.

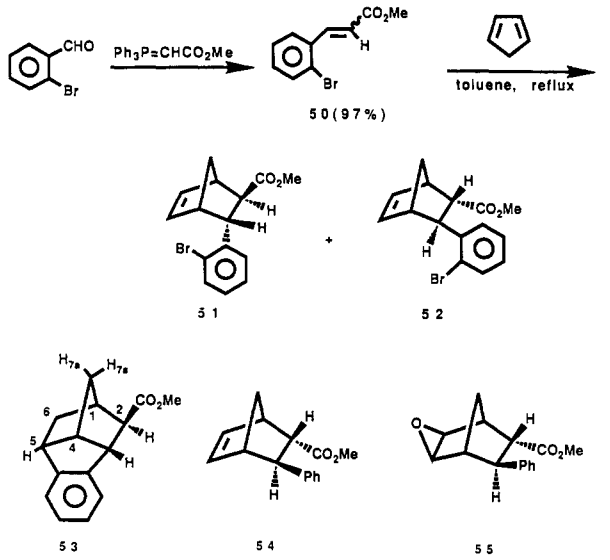
Each cycloadduct, when treated with tributyltin hydride under the usual radical cyclization conditions, gave the corresponding cyclized product shown in the last column of Table I. That cyclization had occurred in each case was evident from the absence of signals due to the vinyl protons in the ^1H NMR spectra of **43**, **45**, and **47** and the presence of only two vinyl proton signals in the spectrum of **49**. The IR carbonyl frequency also showed absence of conjugation. In the case of entries 3 and 4, exo/endo mixtures of the cycloadducts were cyclized, but through chromatography the predominant exo cyclization products (*exo*-**47** and *exo*-**49**) were obtained pure. Salient features of the ^1H NMR spectra, upon which structural assignments are based, are summarized in Table II.

Tandem [4 + 2] Cycloaddition/Radical Cyclization with the Radical Site in the Dienophile. In all examples of [4 + 2] CA/RC reactions presented above, the potential radical site required for the second step was incorporated in the diene. Incorporation in the dienophile is also useful, as illustrated by the following example.

Methyl *o*-bromocinnamate **50** was obtained as a trans/cis = 6 mixture from a Wittig reaction with *o*-bromobenzaldehyde. Cycloaddition with cyclopentadiene gave (70%) a 1:1 inseparable mixture of **51** and **52**, derived from the trans precursor. The mixture was treated with TBH to give cyclized product **53** from endo-aryl adduct **51** and the reduction product **54** from the exo-aryl adduct **52** which cannot cyclize. These products were still not easily separated, so this mixture was treated with *m*-CPBA to convert **54** to epoxide **55**; the separation of **53** from **55** was easily accomplished chromatographically.

Several homodecoupling experiments enabled a complete chemical shift assignment for the aliphatic protons

(12) Katritzky, A. R.; Takeuchi, Y. *J. Am. Chem. Soc.* **1970**, *92*, 4134–4136. Dennis, N.; Ibrahim, B.; Katritzky, A. R.; Taulov, I. G.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1883–1887. Banerji, J.; Dennis, N.; Frank, J.; Katritzky, A. R.; Matsuo, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2334–2338. Katritzky, A. R.; Banerji, J.; Boonyarakvanich, A.; Cutler, A. T.; Dennis, N.; Rizvi Abbas, S. Q.; Sabongi, G. J.; Wilde, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 399–407. Katritzky, A. R.; Dennis, N.; Sabongi, G.; Turker, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1525–1535. Katritzky, A. R.; Banerji, J.; Dennis, N.; Ellison, J.; Sabongi, G.; Wurthwein, E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2528–2534. Katritzky, A. R.; Abdallah, M.; Bayyuk, S.; Bolouri, A. A.; Dennis, N.; Sabongi, J. *Pol. J. Chem.* **1979**, *53*, 57–72.

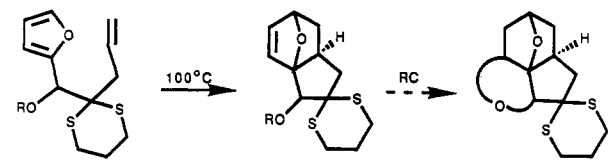


in **53** (see the Experimental Section for details). This spectrum, and the molecular weight of 228, clearly establish the tricyclic nature of **53**.

Although in this particular CA/RC example half of the cycloaddition product has the wrong stereochemistry for the cyclization step, one can imagine other examples (intramolecular, or with acyclic dienes) that do not suffer this defect.

Tandem Intramolecular Cycloaddition/Radical Cyclization. In all examples of CA/RC reactions presented thus far, the cycloaddition step was performed in the *inter*molecular mode. If *both* steps are carried out *intra*molecularly, one can construct three fused rings with a high degree of stereoselectivity in just two steps. We present here several examples.

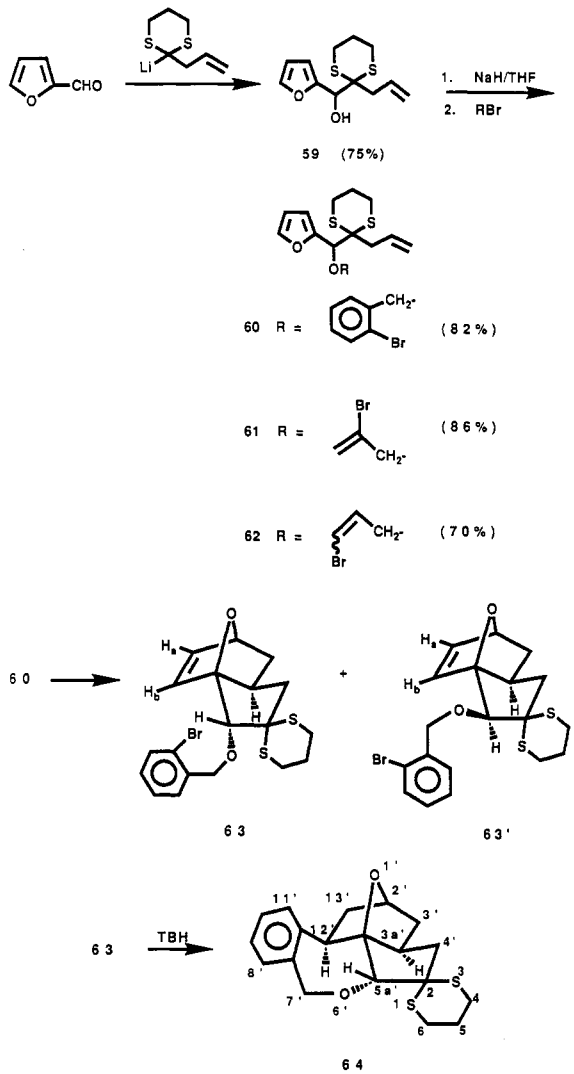
Intramolecular Diels–Alder additions to a furan moiety have been known for some time.[13] One example suitable for adaptation to the CA/RC strategy is the conversion of **56** to **57** at 100 °C.[14] If R were to contain a suitable radical site, cyclization to the novel ring system in **58** could be envisioned.



Three CA/RC precursors **60–62** were readily synthesized from furfural via the known alcohol **59**.[14]

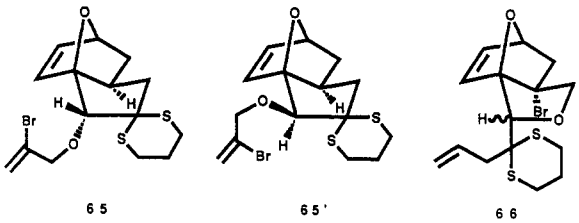
On heating at reflux in benzene for 4 days, **60** gave a 70% yield of the two expected cycloadducts, **63** and **63′**, in a 10:1 ratio. Stereochemical assignments are based on the chemical shifts of the vinyl protons. In particular, H_b is deshielded in **63** (δ 6.63) relative to its chemical shift (δ 6.08) in **63′**, due to the *O*-aryl group. This observation has been used previously for such assignments.[14]

Treatment of **63** with TBH (1.5 equiv) gave **64** in 53% yield. Although the ^1H NMR spectrum of **64** is complex, homodecoupling experiments permitted some features to be distinguished. The methine $H_{5a'}$ signal is a singlet at



δ 4.66. Bridgehead proton $H_{2'}$ (δ 4.60) is coupled to $H_{3'x}$ (δ 1.60, J = 4 Hz) and $H_{13'x}$ (δ 2.15, J = 4 Hz) but *not* to the corresponding endo protons. Methine proton $H_{12'}$ (δ 3.62) is coupled to both $H_{13'x}$ (J = 4 Hz) and $H_{13'n}$ (δ 2.35, J = 9 Hz), and the $H_{13'}$ methylenes are also geminally coupled (J = 13 Hz). Similarly, the methylene protons that are both benzylic and α to an oxygen appear as an AB quartet (δ 4.97, J = 24.5 Hz). An X-ray structure unequivocally verified the structure as drawn, with oxygen endo at $C_{5a'}$ and the aromatic ring exo at $C_{12'}$ (Figure 3). The seven-membered benzoxepin ring is formed with complete stereocontrol in the radical cyclization. Careful examination of the ^1H NMR spectrum of the crude product revealed no other isomer. Overall, application of the intramolecular CA/RC strategy to **60** creates three new rings to afford **64** in two steps with a high degree of stereoselectivity at three tertiary centers ($C_{3a'}$, $C_{5a'}$, and $C_{12'}$).

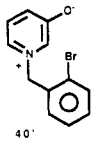
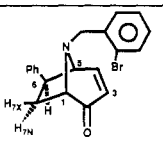
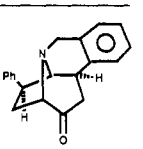
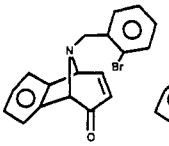
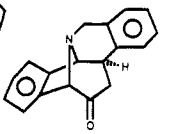
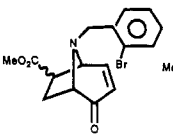
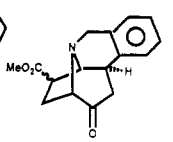
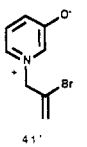
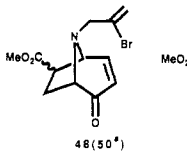
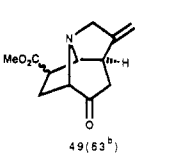
Heating 61 gave the expected cycloadducts **65** and **65′** (72%, ratio 10:1) as well as about 8% of cycloadducts **66** derived from the vinyl bromide moiety acting as the dienophile. Although the total yield of cycloadducts or



(13) For a review, see: Ciganek, E. *Org. React.* **1984**, *32*, 38, 77–78, 258–273.

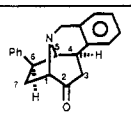
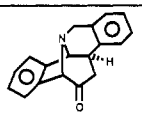
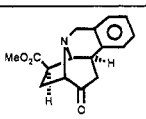
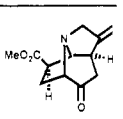
(14) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1982**, *23*, 303–306.

Table I. Tandem 1,3-Dipolar Cycloadditions/Radical Cyclizations

entry	betaine	dipolarophile	cycloadduct (yield, %)	cyclized product (yield, %)
1	 40	$PhCH=CH_2$	 42(34)	 43(45)
2			 44(32)	 45(37)
3		$MeO_2CCH=CH_2$	 46(65[a])	 47(55[b])
4	 41	$MeO_2CCH=CH_2$	 48(50[a])	 49(63[b])

[a] The regioisomer was also formed, but constituted less than 15% of the total cycloadduct yield. [b] The exo adduct was isolated pure.

Table II. Chemical Shifts of the Aliphatic Protons in the NMR Spectra of the Final Products in Table I

proton	 **43**	 **45**	 *exo*-**47**	 *exo*-**49**
H_1	3.70 (d, J = 4.8)	4.31 (d, J = 1.8)	3.90 (br, s)	3.80
H_{3x}	2.20–2.40	2.41 (dd, J = 16, 6.7)	2.12 (dd, J = 14, 10)	2.03 (dd, J = 10, 9)
H_{3n}	2.20–2.40	1.90 (dd, J = 16, 1.8)	2.74 (m)	2.70 (m)
H_4	3.08 (dd, J 14, 8.5)	3.33 (d, J = 6.7)	3.29 (dd, J = 10, 6)	3.30 (dd, J = 9, 6)
H_5	3.43 (d, J = 5)	4.40 (s)	3.59 (d, J = 6)	3.55 (d, J = 6)
H_{6n}	3.55 (d, J = 5)		3.38 (d, J = 6.5)	3.05
H_{7x}	3.55		2.90 (dd, J = 16, 6.5)	2.70 (m)
H_{7n}	2.40		2.24 (dd, J = 16, 1.5)	2.29 (dd, J = 9, 2)
NCH_2	4.28, 4.55 (d, J = 18.5)	4.25, 4.55 (d, J = 20)	4.20, 4.55 (d, J = 18.5)	3.80, 3.67
$=CH_2$				4.90, 5.10 (m)

their ratio did not vary, the cyclization time for **61** could be reduced from 5 days (in refluxing benzene) to 8 h at 90 °C by carrying out the reaction in water containing 1 equiv of β-cyclodextrin.[15]

Standard radical cyclization of **65** gave (68%) a single product **67**. The yield was somewhat better for six-membered cyclization (to **67**) compared with seven-membered cyclization (to **64**). The structure of **67** was assigned based

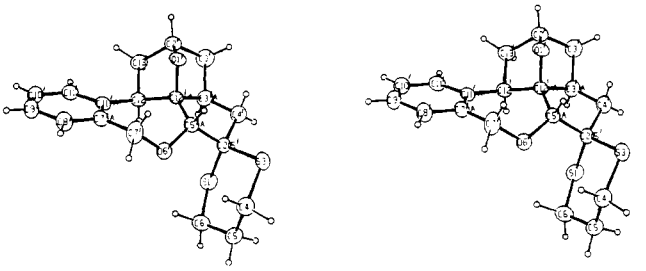
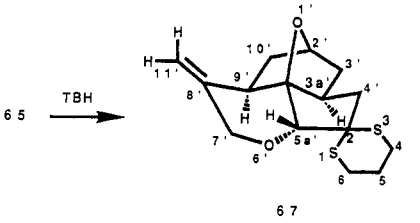
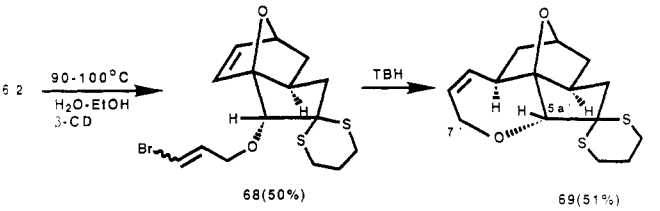


Figure 3. Stereoview of **64** showing the stereochemistry at 3a′, 5a′, and 12′.



on its ^1H NMR spectrum [including homodecoupling and a 2D NMR (COSY) experiment] and by analogy with **64**. For example, the protons at $C_{2'}$, $C_{3'}$, and $C_{10'}$ show almost the same chemical shifts in **67** as the corresponding protons in **64**. The vinyl protons (at $C_{11'}$) appeared as multiplets at δ 4.75 and 4.95, and the allylic methylenes (at $C_{7'}$) were at slightly higher field (δ 4.25, 4.65) than the corresponding benzylic protons in **64** and also exhibited long range coupling with the vinyl protons as expected. Other details of the spectrum (see the Experimental Section) are fully consistent with structure **67**.

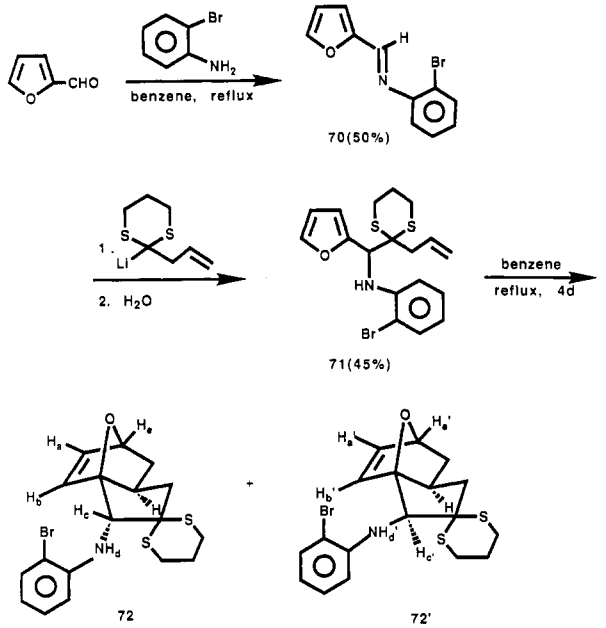
In an analogous manner, intramolecular CA/RC applied to **62** gave successively **68** and **69**. In the first step the epimeric ether and the isomer in which cycloaddition at the bromine-substituted double bond were also formed in low yield. Cyclization product **69** exhibited ^1H NMR features similar in several respects to those of **67** and **64** (singlet for $H_{5a'}$ at δ 4.40, methylenes α to oxygen at δ 4.60) as well as vinyl protons at δ 5.10, 5.40. The structural assignment is thus based on spectra and analogy.



Next we describe a related but not exactly analogous example in which the oxygen atom in the tether to the radical site is replaced by nitrogen. Imine **70** was prepared from 2-bromoaniline and furfural and converted to the required precursor **71** by reaction with the lithio derivative of 2-allyl-1,3-dithiane.[16] On heating at reflux in benzene (48 h), **71** gave an inseparable mixture of two epimeric intramolecular cycloadducts, **72** and **72′** in a 3:1 ratio, the reaction being appreciably less stereoselective than the oxygen analogues described above. The ^1H NMR spectra of **72** and **72′** were quite similar; for example H_d (δ 5.95) and $H_{d'}$ (δ 5.80), coupled (J = 7 Hz) with H_c or $H_{c'}$ at δ 4.51, H_a (δ 5.61) as a doublet of doublets, coupled with H_b (δ

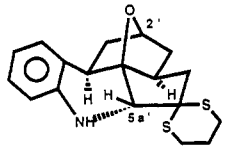
(15) Sternbach, D. D.; Rossana, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 5853–5854.

(16) For related examples, see: Klepo, Ž.; Jakopčič, K. *J. Heterocycl. Chem.* **1987**, *24*, 1787–1791.



6.11, J = 5.8 Hz) and H_e (δ 4.63, J = 1.8 Hz), and $H_{a'}$ (δ 5.78) similarly coupled with $H_{b'}$ (δ 5.90) and $H_{e'}$ (δ 4.60). The appearance of H_b in the major isomer at lower field than $H_{b'}$ in the minor isomer is consistent with NMR assignments of the oxygen analogs.

The mixture of epimers was subjected to radical cyclization. Chromatography gave the major product **73**, mp 208–210 °C, in 50% yield. Features of its ^{1}H NMR spectrum were analogous to that of oxygen analogs ($H_{2'}$ as a doublet of doublets at δ 4.65, $H_{5a'}$ as a singlet at δ 3.75); indeed, the general pattern in the aliphatic region is very similar for all of these final products (**64**, **67**, **69**, and **73**).

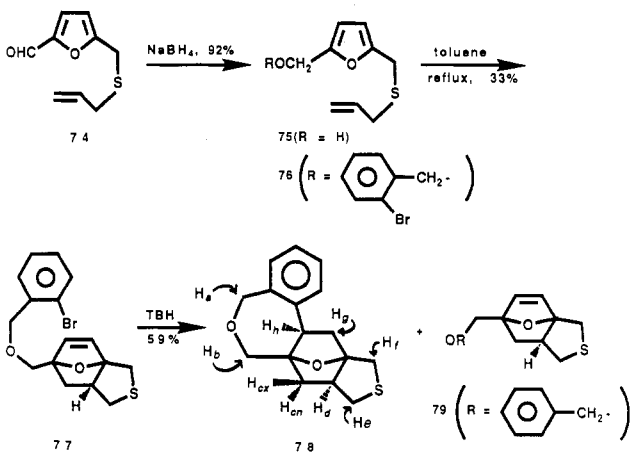


73

In the final example, a 2,5-disubstituted furan **76** with the dienophile in one arm and the radical site in the other arm permits, via tandem CA/RC, the synthesis of a linearly fused polycyclic system **78**. The known[17] furfural **74** was reduced with sodium borohydride to alcohol **75**, which was converted to the alkoxide and alkylated with 2-bromobenzyl bromide to give **76**, the desired precursor for the CA/RC sequence. On heating at reflux in toluene for 24 h, **76** gave a single intramolecular cycloadduct **77** in 33% yield. The yield and stereochemistry are comparable to several examples in the literature,[17] and the ^{1}H NMR spectrum is fully consistent with the structure (see the Experimental Section for details).

Radical cyclization of **77** gave a single cyclized product **78**, mp 107–109 °C, as well as reduction product **79** in a nearly 3:4 ratio and combined yield of 56%. The ^{1}H NMR spectrum of **78** in C_6D_6 is well resolved at 250 MHz, and all the aliphatic protons can be uniquely assigned (see the Experimental Section for details). Particularly pertinent as a consequence of cyclization is the absence of vinyl protons and the presence of H_h as a doublet of doublets at δ 2.89 coupled with both methylene protons H_g (J = 8.2 Hz), which appear at δ 1.80 and 1.60, geminally coupled (J = 12 Hz) in addition to the coupling with H_h.

(17) Klein, L. L.; Shanklin, M. S. *J. Org. Chem.* **1988**, *53*, 5202–5209.



In conclusion, we have presented here examples of [4 + 2] and [3 + 2] inter- and intramolecular cycloadditions coupled with radical cyclizations, as a strategy for the rapid assembly of polycyclic systems, often with considerable regio- and stereochemical control. With proper design, the radical site can be located in either cycloaddition partner (for example in either the diene or the dienophile if the cycloaddition is a Diels–Alder reaction). The radical site need only be located in such a manner that radical cyclization is possible on the double bond that is newly formed in the cycloaddition step. We are currently extending this strategy to [2 + 2] cycloadditions and to double bond forming reactions other than cycloadditions. Finally, we note that even in this exploratory study, almost all of the polycyclic ring systems created by the CA/RC sequence are new.

Experimental Section

General Procedures. IR spectra were recorded on a Perkin Elmer 599 and Nicolet IR/42 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ solution (except where mentioned otherwise) containing $(CH_3)_4Si$ as an internal standard. Chemical shifts are reported in δ units and coupling constants in hertz. Mass spectra were recorded at 70 eV on a Finnigan 4000 spectrometer. High-resolution mass spectral data were obtained at the Michigan State University mass spectrometry facility which is supported, in part, by a grant (DRR-00480) from the Biotechnology Resources Branch, division of research resources, NIH. High-resolution mass spectral analyses for compounds **3**, **17**, **61**, and **62** were performed by Midwest Center for Mass Spectroscopy, University of Nebraska, Lincoln, NE. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI. Melting points, taken on a Melt-Temp apparatus, are uncorrected. Silica gel for chromatography was 230–400 mesh. Plates used for preparative TLC were 20 cm × 20 cm (1000 μm) from Analtech. The drying agent throughout was anhydrous $MgSO_4$. The following compound abbreviations are used in the Experimental Section: AIBN = azobisisobutyronitrile, *m*-CPBA = *m*-chloroperbenzoic acid, DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane, DMSO = dimethyl sulfoxide, DZA = *o*-benzenediazonium carboxylate hydrochloride, TBH = tri-*n*-butyltin hydride, THF = tetrahydrofuran.

2-(2′-Bromobenzyl)furan (3). To a solution of furan (3.4 g, 50 mmol) in ether (100 mL) at 0 °C was added 29 mL of *n*-BuLi (1.6 M in hexane). The solution was then allowed to warm to room temperature and heated at reflux for 4 h. The solution was cooled to 0 °C, and a solution of 2-bromobenzyl bromide (11 g, 44 mmol) in ether (30 mL) was added dropwise. The reaction mixture was then heated at reflux for 16 h. After cooling, the mixture was poured onto crushed ice. The ether layer was separated, washed with brine, and dried. The yellow oil obtained after removal of the ether was distilled (80–83 °C/0.4 Torr) to give 6.2 g (60%) of **3**: ^{1}H NMR δ 7.55 (m, 1 H), 7.33 (m, 1 H), 7.00–7.22 (m, 3 H), 6.30 (m, 1 H), 6.05 (m, 1 H), 4.10 (s, 2 H); ^{13}C NMR δ 34.69, 106.97,

110.32, 124.43, 127.49, 128.19, 130.61, 132.78, 137.69, 141.57, 152.81; mass spectrum m/e (relative intensity) 238 (47), 236 (48), 171 (20), 169 (19), 129 (79), 128 (100), 102 (14), 89 (18), 81 (24); high-resolution mass spectrum calcd for $C_{11}H_9OBr$ 235.9837, obsd 235.9844. Anal. Calcd: C, 55.75; H, 3.81. Found: C, 56.08; H, 3.81.

Cycloadduct 4. To a refluxing solution of **3** (960 mg, 4 mmol) and anthranilic acid (610 mg, 4.5 mmol) in dimethoxyethane (DME, 15 mL) was added a solution of isoamyl nitrite (0.8 mL) in DME (5 mL). Heating at reflux was continued for 3 h. After the mixture was cooled and the solvent was removed, the resulting dark oil was chromatographed over silica gel using hexane–CH_2Cl_2 (60:40) as eluent to give 630 mg (50%) of **4** as a colorless oil which solidified: mp 53–55 °C; ^{1}H NMR δ 7.60 (dd, J = 6.8, 1.3, 1 H), 7.55 (dd, J = 6.8, 1.3, 1 H), 7.25 (m, 3 H), 7.10 (m, 1 H), 6.85–7.03 (m, 4 H), 5.68 (d, J = 2.8, 1 H, bridgehead), 4.10 (d, J = 17, 1 H, methylene), 3.63 (d, J = 17, 1 H, methylene); ^{13}C NMR δ 34.76, 81.50, 92.32, 119.20, 119.90, 124.93 (2), 124.98, 127.37, 128.28, 132.43 (2), 132.69, 136.49, 143.84, 144.25, 150.48; mass spectrum, m/e (relative intensity) 314 (2), 312 (2), 288 (3), 286 (3), 203 (11), 202 (15), 171 (96), 169 (100), 115 (50), 89 (35), 77 (10). Anal. Calcd for $C_{17}H_{13}BrO$: C, 65.19; H, 4.18. Found: C, 65.22; H, 4.12.

Cyclization of 4 (Typical Procedure for All Radical Cyclizations). A solution of **4** (80 mg, 0.25 mmol), tributyltin hydride (TBH, 0.3 mmol), and azobisisobutyronitrile (AIBN, 3 mg) in benzene (10 mL) was heated at reflux for 9 h. The benzene was removed under reduced pressure, ether (25 mL) was added, and the solution was stirred with aqueous KF solution. The mixture was filtered; the ether layer was separated and washed with brine and dried. The crude product obtained after removal of the ether was chromatographed over silica gel using hexane–CH_2Cl_2 (55:45) as eluent to give 45 mg (67%) of **5** as a gum which solidified: mp 113–115 °C; ^{1}H NMR δ 7.19–7.36 (m, 8 H), 5.43 (d, J = 5, 1 H, bridgehead), 3.78 (d, J = 17, 1 H, methylene at C11), 3.37 (d, J = 17, 1 H, methylene at C11), 3.17 (m, 1 H, methine), 2.30 (m, 1 H, exo methylene at C6), 2.03 (dd, J = 12.5, 10, 1 H, endo methylene at C6); ^{13}C NMR δ 33.30, 34.42, 52.28, 79.55, 96.44, 117.37, 119.70, 125.34, 125.47, 126.55, 126.67, 126.86, 127.10, 141.84, 144.62, 145.24; mass spectrum, m/e (relative intensity), 234 (55), 216 (45), 215 (100), 202 (28), 189 (13), 116 (13), 90 (13), 77 (12). Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 86.97; H, 5.85.

A solution of **5** (25 mg) in ethanol (95%, 5 mL) was treated with HCl (3 drops) and the solution heated at reflux for 24 h. The ethanol was removed under reduced pressure and ether (20 mL) was added. The ether layer was washed with water and dried. Removal of the ether gave 20 mg of **6** as a white solid: mp 178–180 °C (lit.[6] mp 182 °C); ^{1}H NMR δ 7.77 (m, 4 H), 7.29–7.49 (m, 6 H), 4.11 (s, 2 H).

Preparation of 8. To a refluxing solution of **3** (900 mg, 4 mmol) and 3-amino-2-naphthoic acid (1.2 g, 6 mmol) in DME (40 mL) was added a solution of isoamyl nitrite (2 mL). Heating was continued for 5 h. After the mixture was cooled, the solvent was removed and the residual dark oil was chromatographed over silica gel using hexane–CH_2Cl_2 (1:1) as eluent to give 260 mg (20%) of **7** as an oil. For **7**: ^{1}H NMR δ 7.40–7.80 (m, 9 H), 7.25 (m, 1 H), 7.15 (m, 1 H), 6.85 (m, 1 H, vinyl), 5.75 (br s, 1 H, bridgehead), 4.17 (d, J = 17, 1 H, methylene), 3.68 (d, J = 17, 1 H, methylene); mass spectrum, m/e (relative intensity), 364 (18), 362 (16), 281 (17), 265 (24), 252 (28), 165 (100), 126 (48), 113 (25), 71 (63).

A solution of **7** (60 mg, 0.17 mmol), TBH (0.3 mmol), and AIBN (8 mg) in benzene (15 mL) was heated under reflux for 48 h. Chromatography of the crude product over silica gel using hexane–CH_2Cl_2 (1:1) as eluent gave 40 mg (80%) of **8**: mp 152–157 °C; ^{1}H NMR δ 7.85 (m, 2 H), 7.65 (m, 2 H), 7.45 (m, 2 H), 7.35 (m, 1 H), 7.33 (m, 3 H), 5.45 (d, J = 5, 1 H, bridgehead), 3.87 (d, J = 17, 1 H, methylene), 3.45 (d, J = 17, 1 H, methylene), 3.30 (m, 1 H, methine), 2.40 (m, 1 H, exo oxanorbornane methylene), 2.17 (dd, J = 13, 10, 1 H, endo oxanorbornane methylene); mass spectrum, m/e (relative intensity), 284 (79), 265 (65), 239 (21), 149 (44), 133 (37). A single crystal of **8** was subjected to X-ray structure determination (vide infra).

Preparation of 11. To a solution of furan (2.8 g, 40 mmol) in THF (60 mL) at −20 °C was added n-BuLi (30 mmol, 12 mL of a 2.5 M solution). After 2 h of stirring at −10 °C, a solution of 2,3-dibromopropene (3 g, 15 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at 0 °C for 16 h, quenched with aqueous NH_4Cl solution, and extracted with ether. The ether layer was separated and dried. Removal of the ether followed by chromatography of the crude residue over silica gel using hexane as eluent gave 600 mg of 2-(3-bromoallyl)furan as a light yellow oil: ^{1}H NMR δ 7.35 (m, 1 H), 6.02–6.40 (m, 4 H), 3.35–3.60 (m, 2 H). Without further purification, 600 mg (3 mmol) of this oil was heated with the diazonium hydrochloride of anthranilic acid (DZA, 1 g, 5 mmol) in 1,2-dichloroethane (DCE) at reflux for 2 h. Removal of the solvent and chromatography of the resulting dark gum over silica gel using hexane–ether (80:20) as eluent gave 350 mg of the benzyne cycloadduct **10** (cis–trans mixture) as an oil: ^{1}H NMR δ 7.25 (m, 2 H), 7.00 (m, 3 H), 6.80 (m, 1 H), 6.35 (m, 2 H), 5.65 (m, 1 H, bridgehead), 3.02–3.25 (m, 2 H, methylene); ^{13}C NMR δ 30.04, 32.83, 81.79 (2), 90.88, 91.26, 107.55, 110.35, 119.11, 119.20 (2), 119.98 (2), 120.05, 124.91 (4), 129.55, 132.05, 143.64, 144.02, 144.69 (2), 149.61, 150.43.

Without purification, 160 mg (0.61 mmol) of **10** was heated with TBH (150 μL, 0.56 mmol) and AIBN (30 mg) in benzene at reflux for 40 h. Chromatography of the crude product over silica gel using pentane–ether (9:1) as eluent gave 80 mg (70%) of **11** as a colorless oil: ^{1}H NMR δ 7.20 (m, 4 H, arom), 5.90 (s, 2 H, vinyls), 5.37 (d, J = 5, 1 H, H_a), 3.15 (d with str, J = 16, 1 H, allylic methylene), 2.77 (d with str, J = 16, 1 H, allylic methylene), 2.65 (dd, J = 8.5, 5, 1 H, H_d), 2.00 (ddd, J = 12,5,5, 1 H, H_b), 1.72 (dd, J = 12, 8.5 1 H, H_c); ^{13}C NMR δ 31.98, 33.04, 53.12, 78.94, 81.67, 95.62, 116.99, 119.73, 126.20, 126.55, 129.37, 133.67, 144.34; mass spectrum calcd for $C_{13}H_{12}O$ 184.0888, obsd 184.0891.

Preparation of 2-Bromophenyl 2-Furylmethyl Ether (16). Typical Procedure for the Preparation of 17 and 18. To a suspension of NaH (46 mmol) in ether (100 mL) was added dropwise a solution of 2-bromophenol (8 g, 46.2 mmol) in ether (10 mL). After the addition was complete, the mixture was heated at reflux for 1 h. After the mixture was cooled to room temperature, a fresh solution of furfuryl bromide (prepared from 10 g of furfuryl alcohol and 10 g of PBr_3 in ether) was added. After the addition the reaction mixture was heated at reflux for 15 h. The mixture was poured into water, and the ether layer was separated and washed thoroughly with 2 M NaOH until the aqueous layer was basic. The ether layer was then washed with water and brine and dried. The dark oil obtained after removal of the solvent was chromatographed over silica gel using hexane–CH_2Cl_2 (65:35) as eluent to give 2.5 g (22%) of **16** as a yellow oil: ^{1}H NMR δ 7.53 (dd, J = 8.5, 1.5, 1 H), 7.43 (m, 1 H, furyl H_5), 7.23 (dd, J = 8, 1.5, 1 H), 7.02 (dd, J = 8, 1.5 1 H), 6.85 (dt, J = 8, 1.5, 1 H), 6.44 (m, 1 H, furyl H_4), 6.36 (m, 1 H, furyl H_3), 5.06 (s, 2 H, methylene).

Preparation of 17. To a solution of **14** [prepared from 2-bromo-N-methylaniline[18] (3.7 g, 20 mmol) and NaH (25 mmol)] in ether (75 mL) was added furfuryl bromide [freshly prepared from furfuryl alcohol (5 g) and PBr_3 (5 g)] in ether (70 mL). Chromatography of the crude product over basic alumina using hexane–ether (75:25) as eluent gave 1.7 g (35%) of **17** as a colorless liquid: ^{1}H NMR δ 7.58 (dd, J = 6.8, 1.3, 1 H), 7.35 (m, 1 H), 7.20 (dt, J = 6.8, 1.3, 1 H), 7.00 (dd, J = 6.8, 1.3, 1 H), 6.90 (dt, J = 6.8, 1.3, 1 H), 6.28 (m, 1 H), 6.15 (m, 1 H), 4.25 (s, 2 H, methylene), 2.75 (s, 3 H, NCH_3); ^{13}C NMR δ 40.55, 53.45, 109.00, 109.95, 120.00, 122.78, 125.30, 128.00, 134.30, 142.90, 150.00, 153.20; mass spectrum, m/e (relative intensity) (no M^+), 201 (2), 200 (2.6), 199 (2.2), 198 (2.3), 187 (89), 186 (86), 185 (100), 184 (92), 148 (19), 105 (22), 104 (17), 91 (35), 81 (14), 77 (48); high-resolution mass spectrum calcd for $C_{12}H_{12}BrNO$ 265.0102, obsd 265.0094. Anal. Calcd: C, 54.16; H, 4.57. Found: C, 54.27; H, 4.56.

Preparation of 18. To a solution of **15** [prepared from 2-bromothiophenol (3.8 g, 20 mmol) and NaH (25 mmol)] in ether (70 mL) was added furfuryl bromide [freshly prepared from furfuryl alcohol (5 g) and PBr_3 (5 g) in ether (70 mL)]. Chromatography of the crude product over basic alumina using hexane–CH_2Cl_2 (65:35) as eluent gave 2.01 g (40%) of **18** as a light yellow oil: ^{1}H NMR δ 7.55 (dd, J = 7.0, 1.5, 1 H), 7.20–7.35 (m, 3 H), 7.05 (dt, J = 7.0, 1.5, 1 H), 6.25 (m, 1 H), 6.15 (m, 1 H), 4.15 (s, 2 H, methylene); mass spectrum, m/e (relative intensity) 270 (7), 268 (8), 189 (3), 187 (3), 108 (14), 81 (100), 53 (16).

(18) Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 795–802.

Preparation of 19 and 21. To a solution of **16** (600 mg, 2 mmol) and anthranilic acid (600 mg, 4.5 mmol) in DME (30 mL) heated at reflux was added a solution of isoamyl nitrite (1 mL in 10 mL of DME). After addition, heating was continued for 2 h. After removal of the solvent the residual dark gum was chromatographed over silica gel using hexane–CH_2Cl_2 (60:40) as eluent to give **19** (480 mg, 75%) as a yellow gum: ^1H NMR δ 7.60 (dd, J = 8, 1.5, 1 H), 6.85–7.45 (series of m, 9 H), 5.75 (d, J = 2.8, 1 H, bridgehead), 4.80 (AB q, δ_A = 4.89, δ_B = 4.69, J = 15, 2 H, methylene); ^{13}C NMR δ 67.45, 82.43, 91.20, 112.60, 113.97, 120.08, 122.70, 125.18 (2), 128.55, 133.49, 142.75, 144.08 (2), 148.72, 149.96, 155.18; mass spectrum, m/e (relative intensity) 330 (4), 328 (5), 221 (12), 157 (27), 129 (100), 128 (97), 127 (39), 115 (36), 77 (22), 63 (24). Anal. Calcd for $C_{17}H_{13}BrO_2$: C, 62.03; H, 3.98. Found: C, 62.00; H, 3.94.

A solution of 19 (240 mg, 0.73 mmol), TBH (240 μL, 0.90 mmol), and AIBN (8 mg) in benzene (10 mL) in a sealed tube was heated at 135 °C for 24 h. Chromatography of the crude product gave unreacted **19** (30 mg) and **21** (70 mg, 50%). For **21**: mp 108–111 °C; ^1H NMR δ 6.90–7.35 (m, 8 H), 5.50 (d, J = 4.5, 1 H, bridgehead), 4.85 (AB q, J = 15, 2 H, methylene next to the oxygen), 3.00 (dd, J = 8, 4.5, 1 H, methine), 2.25 (m, 2 H); ^{13}C NMR δ 38.04, 39.15, 63.91, 79.23, 83.88, 117.26, 117.38, 119.43, 121.61, 125.96, 126.70, 127.23(2), 129.99, 144.43, 146.34, 152.42; IR (neat film) 3030, 2940, 1583, 1491, 1458, 1305, 1292, 1269, 1240, 1051, 970, 736 cm^{-1}; mass spectrum calcd for $C_{17}H_{14}O_2$ 250.0994, obsd 250.0991. Anal. Calcd: C, 81.58; H, 5.64. Found: C, 81.76; H, 5.50.

Preparation of 20 and 22. To a solution of **17** (530 mg, 2 mmol) in DCE (30 mL) was added DZA (512 mg, 2.8 mmol) and propylene oxide (1 mL), and the mixture was heated at reflux for 1.5 h. After removal of the solvent the residual dark gum was chromatographed over silica gel using hexane–CH_2Cl_2 (60:40) as eluent to give **20** (440 mg, 65%) as a viscous oil: ^1H NMR δ 7.60 (dd, J = 8, 1.5, 1 H), 7.15–7.35 (m, 5 H), 6.90–7.02 (m, 4 H), 5.65 (d, J = 2.8, 1 H, bridgehead), 4.25 (d, J = 14.8, 1 H, methylene), 3.65 (d, J = 14.8, 1 H, methylene), 2.92 (s, 3 H, NCH_3); IR (neat) 3070, 2950, 1600, 1541, 1383, 1280, 812, 766 cm^{-1}; mass spectrum calcd for $C_{18}H_{16}BrNO$ 341.0415, obsd 341.0420.

A solution of **20** (100 mg, 0.3 mmol), TBH (107 μL, 0.4 mmol), and AIBN (15 mg) in benzene (20 mL) was heated at reflux for 12 h. Chromatography of the crude product over silica gel using hexane–ether (70:30) as eluent gave **22** (40 mg, 54%) as a light yellow solid: mp (hexane) 105–107 °C; ^1H NMR δ 7.05–7.35 (m, 5 H), 6.95 (d, 1 H), 6.75 (d, 2 H), 5.43 (d, J = 4.5, 1 H, bridgehead), 4.05 (d, J = 12.8, 1 H, methylene next to N), 3.75 (d, J = 12.8, 1 H, methylene next to N), 3.05 (s, 3 H, NCH_3), 3.00 (dd, J = 8.2, 4.5, 1 H, methine), 2.25 (m, 2 H, methylene); ^{13}C NMR δ 39.71, 39.91 (2), 50.86, 78.47, 84.82, 112.29, 117.23, 118.21, 119.28, 126.38, 126.55 (2), 126.97 (2), 129.84, 145.64, 146.43; IR (neat) 2900–3070, 1603, 1504, 1221–1354, 974, 924, 752 cm^{-1}; mass spectrum calcd for $C_{18}H_{17}NO$ 263.1310, obsd 263.1320. Anal. Calcd: C, 82.10; H, 6.50. Found: C, 81.95; H, 6.42.

Reaction of 18 with Benzyne. To a solution of **18** (540 mg, 2 mmol) in DCE (20 mL) was added DZA (600 mg, 32 mmol) and propylene oxide (1 mL), and the mixture was heated at reflux for 1.5 h. After removal of the solvent the residual dark gum was chromatographed over silica gel using hexane and hexane–CH_2Cl_2 (3:2) as eluent to give **23** (370 mg, 70%) as a colorless oil which solidified: mp 35 °C (lit.[19] mp 35 °C); ^1H NMR δ 7.55 (d, J = 7.5, 1 H), 7.40 (m, 5 H), 7.15 (t, J = 7.5, 1 H), 6.95 (d, J = 7.5, 1 H); mass spectrum, m/e (relative intensity) 266 (55), 264 (51), 185 (88), 184 (100), 152 (17), 139 (15), 108 (27), 92 (21), 81 (41).

Preparation of Sulfoxide 24. To a solution of **15** (800 mg, 3 mmol) in CH_2Cl_2 (20 mL) containing $NaHCO_3$ (340 mg) cooled by an ice bath was added a solution of m-CPBA (650 mg, 3.7 mmol) in CH_2Cl_2 (10 mL). After addition, stirring was continued for 1 h. The solution was filtered and washed successively with $NaHCO_3$ (10%) and brine and dried. Removal of the solvent gave **24** (700 mg, 83%). No further purification was necessary: ^1H NMR δ 7.28 (series of m, 5 H), 6.30 (m, 2 H), 4.28 (AB q, J = 15, 2 H, methylene); IR (neat) 3120, 3060, 2980, 2920, 1500, 1450, 1330, 1250, 1150, 1060, 1020, 750 cm^{-1}; mass spectrum calcd for $C_{11}H_9BrO_2S$ 283.9507, obsd 283.9503.

Preparation of 25 and 26. A mixture of **24** (700 mg, 2.5 mmol), DZA (560 mg, 4.4 mmol), and propylene oxide (1 mL) in DCE (30 mL) was heated under reflux for 45 min. The solvent was removed, and the crude oil was chromatographed over silica gel using hexane–ethyl acetate (60:40) as eluent. The cycloadduct **25** was obtained as a 60:40 (see text) mixture (640 mg, 71%). Major isomer: ^1H NMR δ 8.05 (m, 1 H), 7.63 (m, 2 H), 7.43 (m, 2 H), 7.20 (m, 3 H), 6.95 (m, 2 H), 5.73 (d, J = 2, 1 H, bridgehead), 4.05 (d, J = 14, 1 H, methylene), 3.55 (d, J = 14, 1 H, methylene). Minor isomer: ^1H NMR aromatic region same as above, δ 5.86 (d, J = 2, 1 H, bridgehead), 3.93 (d, J = 14, 1 H, methylene), 3.65 (d, J = 14, 1 H, methylene); IR of mixture (neat) 3060, 3020, 1450, 1320, 1280, 1250, 1120, 1040, 940, 750 cm^{-1}; mass spectrum calcd for $C_{17}H_{13}BrO_2S$ 359.9820, obsd 359.9826.

A solution of **25** (200 mg, 0.55 mmol), TBH (200 μL, 0.76 mmol) and AIBN (30 mg) in benzene (40 mL) was heated under reflux for 10 h. Chromatography of the crude product over silica gel using hexane–ethyl acetate (45:55) as eluent gave 45 mg of one isomer **26** and 35 mg of another isomer **26′** (total yield 67%). For **26**: ^1H NMR δ 7.85 (dd, J = 5, 1.8, 1 H), 7.10–7.50 (series of m, 7 H), 5.45 (m, 1 H, bridgehead), 3.90 (AB q, δ_A = 3.98, δ_B = 3.70, J_{AB} = 5, 1.8, J = 13, 2 H, methylene next to sulfur), 3.35 (dd, J = 7, 7, 1 H, methine), 2.30 (m, 2 H, methylene); ^{13}C NMR δ 37.09, 41.98, 49.80, 79.17, 83.85, 118.05, 119.14, 127.20(2), 127.29, 127.34, 129.40, 131.78, 138.16, 139.43, 144.84, 146.22; mass spectrum calcd for $C_{17}H_{14}O_2S$ 282.0715, obsd 282.0717. For **26′**: mp 170–175 °C; ^1H NMR δ 7.92 (m, 1 H), 7.52 (m, 7 H), 5.52 (d, J = 4.5, 1 H, bridgehead), 4.30 (d, J = 12, 1 H, methylene next to sulfur), 3.30 (d, J = 12, 1 H, methylene next to sulfur), 2.72 (m, 2 H), 2.15 (m, 1 H); ^{13}C NMR δ 33.30, 41.95, 52.98, 78.97, 83.56, 117.55, 119.49, 123.90, 126.62, 127.48, 127.61, 130.58, 146.60 (some aromatic peaks overlapped); mass spectrum calcd for $C_{17}H_{14}O_2S$ 282.0715, obsd 282.0710. Anal. Calcd: C, 72.31; H, 5.00. Found: C, 72.09; H, 4.91.

Reduction of 26 and 26′. To a solution of **26** + **26′** (35 mg, 0.12 mmol) in ether (20 mL) was added lithium aluminum hydride (10 mg, 0.26 mmol). The mixture was stirred for 1 h at room temperature, then aqueous NH_4Cl was added. The ether layer was separated, washed with brine, and dried. Removal of the ether gave **27** (20 mg, 67%) as an oil: ^1H NMR δ 7.21–7.31 (m, 5 H), 7.04–7.10 (m, 3 H), 5.44 (d, J = 4.5, 1 H, bridgehead), 3.86 (d, J = 13.5, 1 H, methylene next to sulfur), 3.29 (d, J = 13.5, 1 H, methylene next to sulfur), 2.90 (dd, J = 8, 4.5, 1 H, methine), 2.27 (m, 2 H, methylene); ^{13}C NMR δ 28.59, 38.80, 42.27, 78.12, 85.56, 117.46, 119.35, 125.73, 126.02 (2), 126.87 (2), 127.11, 127.76, 130.20, 131.31, 146.90; IR (neat) 3040, 2953, 2922, 1475, 1462, 1286, 1261, 929–1008, 754 cm^{-1}; mass spectrum calcd for $C_{17}H_{14}OS$ 266.0766, obsd 266.0774.

Preparation of *N*-(2-Bromobenzyl)-2(1*H*)-pyridone (30). A suspension of 2-hydroxypyridine (5 g, 0.05 mol) and K_2CO_3 (15 g) in DME (70 mL) was heated under reflux for 1 h. To the refluxing solution was added dropwise a solution of 2-bromobenzyl bromide (15 g, 0.06 mol) in DME (20 mL). Reflux was continued for 10 h. The mixture was filtered hot, and the white cake (inorganic) was washed with DME. Removal of the solvent under reduced pressure gave a yellow solid, which was triturated with petroleum ether to give 12.2 g (78%) of **30** as a white solid: mp 94–96 °C; ^1H NMR δ 7.75 (d, 1 H), 7.35 (m, 3 H), 7.22 (m, 2 H), 6.65 (d, J = 12, 1 H), 6.20 (dt, J = 12, 1.5, 1 H), 5.28 (s, 2 H, methylene); ^{13}C NMR δ 162.3, 139.5, 137.3, 135.3, 132.9, 129.7, 129.4, 127.9, 123.4, 121.1, 106.2, 51.7; mass spectrum, m/e (relative intensity) 265 (0.6), 263 (0.6), 184 (100), 171 (27), 169 (27), 90 (11), 89 (12). Anal. Calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82. Found: C, 54.65; H, 3.71.

Preparation of *N*-(2-Bromobenzyl)-3-[(2-bromobenzyl)oxy]-2(1*H*)-pyridone (31). A suspension of 2,3-dihydroxypyridine (2.3 g, 0.03 mol) and potassium carbonate (15 g) in DME (70 mL) was heated at reflux for 1 h. To this solution was added 15 g (0.06 mol) of 2-bromobenzyl bromide and heating was continued for 16 h. The mixture was filtered hot, and the inorganic cake was washed with DME. Removal of the solvent gave a brown solid that was chromatographed over silica gel using hexane–ethyl acetate (7:3) as eluent to give 8 g (60%) of **31** as a white solid: mp 88–91 °C; ^1H NMR δ 7.56 (m, 3 H), 7.24 (m, 5 H), 6.99 (dd, J = 7.5, 1.5, 1 H), 6.17 (dd, J = 7.5, 1.5, 1 H), 6.00 (t, J = 7, 1

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H), 5.31 (s, 2 H, methylene next to O), 5.17 (s, 2 H, methylene next to N); mass spectrum, *m/e* (relative intensity) 447 (0.5), 370 (14), 368 (11), 252 (10), 250 (10), 171 (100), 169 (99), 90 (61), 89 (53), 63 (21). Anal. Calcd for $C_{19}H_{15}Br_2NO_2$: C, 50.80; H, 3.37. Found: C, 50.87; H, 3.22.

Benzyne Adduct 32. A suspension of **30** (1.1 g, 4 mmol), DZA (1 g, 6 mmol), and propylene oxide (5 mL) in DCE (30 mL) was heated under reflux for 8 h. The dark gum obtained after removal of the solvent under reduced pressure was chromatographed over silica gel using hexane–ethyl acetate (7:3) as eluent to give 300 mg (25%) of **32** as a viscous oil: ^{1}H NMR δ 7.35–7.60 (m, 3 H), 7.05–7.20 (m, 4 H), 6.90–7.00 (m, 2 H), 6.82 (m, 1 H), 5.05 (dd, J = 7.5, 1.7, 1 H, bridgehead) 4.73 (dd, J = 7.5, 1.7, 1 H, bridgehead), 4.55 (AB q, J = 20, 2 H, methylene); IR (neat) 3020, 2950, 1680, 1440, 1157, 751 cm^{-1}; mass spectrum, *m/e* (relative intensity) 260 (M^+ – Br, 1), 171 (2), 169 (2), 139 (4), 128 (100), 105 (9).

Benzyne Adduct 33. A suspension of **31** (1.2 g, 2.5 mmol), DZA (900 mg, 5 mmol), and propylene oxide (3 mL) in DCE (20 mL) was heated under reflux for 15 h. The solvent was removed under reduced pressure, and the resulting dark oil was chromatographed over silica gel using hexane–ethyl acetate (4:1) as eluent to give **33** (1 g, 75%) as a light yellow gum: ^{1}H NMR δ 7.92 (d, J = 7.8, 1 H), 7.67 (d, J = 7.8, 1 H), 7.56 (m, 2 H), 7.40 (m, 1 H), 6.99–7.20 (m, 8 H), 6.82 (dd, J = 8, 5.8, 1 H), 5.50 (d, J = 13.8, 1 H, methylene next to O), 5.16 (d, J = 13.8, 1 H, methylene next to O), 5.01 (dd, J = 5.8, 1.8, 1 H, bridgehead), 4.61 (AB q, J = 15, 2 H, methylene next to N); IR (neat) 3020, 2950, 1688, 1465, 1440, 1409, 1241, 1157, 1026, 751 cm^{-1}; mass spectrum, *m/e* (relative intensity) (no M^+) 314 (7), 312 (7), 233 (10), 171 (100), 169 (92), 115 (21), 90 (25), 89 (22).

Radical Cyclization of 32. A solution of **32** (250 mg, 0.74 mmol), TBH (221 μL, 0.83 mmol), and AIBN (30 mg) in benzene (20 mL) was heated at 160 °C in a sealed tube for 18 h. Chromatography using hexane–ethyl acetate (7:3) as eluent gave 140 mg (73%) of **34** as a light yellow gum which solidified on standing: mp 118–122 °C; ^{1}H NMR δ 7.07–7.37 (series of m, 8 H), 5.20 (d, J = 16.3, 1 H, methylene next to N), 4.72 (d, J = 2.3, 1 H, bridgehead H_c), 4.27 (d, J = 16.3, 1 H, methylene next to N), 3.87 (m, 1 H, bridgehead), 3.27 (d, with structure, J = 9.5, 1 H, H_d), 2.15 (ddd, J = 12.5, 10, 2, 1 H, endo methylene), 1.92 (ddd, J = 12.5, 3, 3, 1 H, exo methylene); IR (neat film) 3034, 2937, 1687, 1487, 1398, 1257, 758 cm^{-1}; mass spectrum calcd for $C_{18}H_{15}NO$ 261.1154, obsd 261.1143. Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79. Found: C, 82.59; H, 5.74.

Radical Cyclization of 33. A solution of **33** (500 mg, 0.96 mmol), TBH (520 μL 1.95 mmol), and AIBN (50 mg) in benzene (30 mL) was heated at 150 °C in a sealed tube for 16 h. Chromatography using hexane–ethyl acetate (4:1) as eluent gave **35** (160 mg, 45%) as a white solid, which was recrystallized from petroleum ether: mp 55–60 °C; ^{1}H NMR δ 7.00–7.70 (m, 12 H), 5.27 (d, J = 16.5, 1 H), 5.14 (AB q, J = 15, 2 H, methylene next to O), 4.70 (d, J = 2, 1 H, H_c), 4.34 (d, J = 16.5, 1 H), 3.26 (m, 1 H, H_d), 2.16 (m, 2 H); mass spectrum calcd for $C_{25}H_{21}NO_2$ 367.1572, obsd 367.1563. Anal. Calcd: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.34; H, 5.74; N, 3.74. Removal of the solvent from the mother liquor gave a gum whose ^{1}H NMR signals were mainly due to **35**, but there were signals due to another compound, probably **36**.

Preparation of *N*-(2-Bromobenzyl)-3-hydroxypyridinium Bromide (40). A solution of 3-hydroxypyridine (2 g, 20 mmol) and **1** (5 g, 20 mmol) in THF (30 mL) was heated under reflux for 2.5 h. The white solid was filtered and dried to give **40** (5.7 g, 80%): mp 185–188 °C; ^{1}H NMR (DMSO-d_6) δ 8.60 (m, 2 H), 8.05 (m, 2 H), 7.75 (m, 1 H), 7.45 (m, 3 H), 5.93 (s, 2 H, methylene), 3.45 (br, 1 H, hydroxyl). Anal. Calcd. for $C_{12}H_{11}Br_2NO$: C, 41.77; H, 3.21. Found: C, 41.81; H, 3.23.

Preparation of *N*-(2-Bromo-3-propenyl)-3-hydroxypyridinium Bromide (41). A solution of 3-hydroxypyridine (4 g, 40 mmol) and 2,3-dibromopropene (8 g, 40 mmol) in THF (70 mL) was heated under reflux for 20 h. The solution was filtered to give 9.5 g (79%) of **41** as a beige solid: mp 146–150 °C; ^{1}H NMR (DMSO-d_6) δ 8.63 (m, 2 H), 8.10 (m, 2 H), 6.43 (d, 1 H, vinyl), 5.95 (d, 1 H, vinyl), 5.65 (s, 2 H, methylene), 3.45 (br, 1 H, hydroxyl). Anal. Calcd for $C_8H_9Br_2NO$: C, 32.65; H, 3.08. Found: C, 32.71; H, 3.07.

General Procedure for 1,3-Dipolar Cycloaddition. Except for **44**, where the preformed betaine was used, a mixture of the salt (**40** or **41**), Et_3N, and the dipolarophile was heated under reflux for the designated period of time. A small amount of hydroquinone was added to retard polymerization. The precipitated solids were filtered, and the gum remaining after solvent removal was triturated with CH_3CN or benzene to precipitate any polymer. After filtration and removal of solvent (in vacuo) the crude material was chromatographed over silica gel to obtain the pure cycloadducts.

Preparation of 42. A mixture of **40** (700 mg, 2 mmol), Et_3N (0.8 mL), styrene (10 mL), and hydroquinone (150 mg) in THF (20 mL) was heated under reflux for 72 h. The adduct **42** was obtained as yellow gum (250 mg, 35%): ^{1}H NMR δ 7.25 (m, 9 H), 6.65 (dd, J = 10, 5.5, 1 H, H_4), 6.20 (dd, J = 10, 1.5, 1 H, H_3), 4.00 (AB q, J = 13, 2 H, methylene next to N), 3.75 (d, J = 8, 1 H, H_6), 3.68 (d, J = 4.8, 1 H, H_5), 3.25 (dd, J = 9.3, 3.3, 1 H, H_1), 2.23 (dd, J = 14, 8.5, 1 H, H_{7x}), 1.95 (dd, J = 14, 8, 1 H, H_{7n}); IR (neat) 3020, 2940, 1680, 1440, 1030, 750, 700 cm^{-1}; mass spectrum calcd for $C_{20}H_{18}BrNO$ 367.0572, obsd 367.0550.

Preparation of 44. A solution of betaine **40′** was prepared as follows. To a suspension of **40** (3 g, 87 mmol) in CH_3CN (40 mL) was added Et_3N (1 g), and the mixture stirred at room temperature for 1 h. The resulting solution was filtered. Concentration of the filtrate precipitated **40′** (800 mg, 35%): mp 165–170 °C; ^{1}H NMR δ 8.28 (d, 1 H), 8.15 (m, 1 H), 7.75 (dd, 1 H), 7.63 (m, 3 H), 7.35 (m, 2 H), 5.95 (s, 2 H); mass spectrum, *m/e* (relative intensity) 265 (5), 263 (5), 171 (84), 169 (100), 95 (19), 90 (62), 89 (56), 64 (11), 63 (39), 62 (15).

A mixture of betaine **40′** (1.1 g, 4 mmol) and anthranilic acid (700 mg, 5 mmol) in DME (20 mL) was heated under reflux, and a solution of isoamyl nitrite (2 mL) was added dropwise. Heating at reflux was continued for 12 h. The dark gum obtained after removal of solvent was chromatographed using hexane–ether (75:25) as eluent. The adduct **44** was obtained as a yellow gum (430 mg, 32%); ^{1}H NMR δ 7.52 (m, 3 H), 7.10–7.35 (m, 6 H), 5.55 (d, J = 12.5, 1 H, vinyl next to carbonyl), 4.48 (m, 2 H, methylene), 3.85 (s, 2 H, bridgeheads); ^{13}C NMR δ 55.56, 65.15, 77.00, 122.87(2), 124.43, 125.82, 127.17, 127.43, 127.58, 128.76, 130.61, 132.73, 136.90, 138.43, 145.78, 151.10, 194.27; IR (neat) 3040, 2950, 1689, 1367, 1026, 750 cm^{-1}; mass spectrum calcd for $C_{18}H_{14}BrNO$ 339.0259, obsd 339.0268.

Preparation of 46. A mixture of **40** (5 g, 14.5 mmol), Et_3N (15 mL), and hydroquinone (300 mg) in methyl acrylate (40 mL) was heated under reflux for 20 h. After cooling the solution was filtered. Excess methyl acrylate was removed under reduced pressure, and the resulting yellow gum was chromatographed using hexane–ethyl acetate (7:3) as eluent. There was obtained **46** (2.8 g) as a mixture of isomers: ^{1}H NMR (mixture) δ 7.25–7.58 (m, 3 H), 7.15 (m, 1 H), 6.95–7.10 (m, 1 H), 6.00–6.20 (m, 1 H), 3.60–4.18 (series of multiplets with two singlets, 7 H), 2.55–3.00 (m, 2 H), 1.99–2.20 (m, 1 H); IR (neat) 3060, 2950, 1730, 1685, 1440, 1350, 1200, 1030, 756, 740 cm^{-1}; mass spectrum calcd for $C_{16}H_{16}BrNO_3$ 349.0313, obsd 349.0328.

Preparation of 48. A mixture of **41** (1.5 g, 5 mmol), Et_3N (6 mL), hydroquinone (300 mg), and methyl acrylate (20 mL) was heated under reflux for 20 h. The excess methyl acrylate was removed under reduced pressure, and the residual dark oil was chromatographed using hexane–ethyl acetate (65:35) as eluent. The first fractions gave a mixture of *exo*- and *endo*-**48** (60:40) (550 mg). The later fractions gave a mixture of *exo*- and *endo*-**48** together with its regioisomer. For *exo*-**48**: ^{1}H NMR δ 7.03 (dd, J = 9.8, 5, 1 H, H_3), 6.08 (dd, J = 9.8, 1.5, 1 H, H_2), 5.85 (m, 1 H, vinyl methylene), 5.55 (m, 1 H, vinyl methylene), 4.21 (d, J = 5.3, 1 H, H_5), 3.78 (s, 3 H, OCH_3), 3.65 (m, 1 H), 3.45 (m, 2 H, methylene next to N), 2.95 (m, 1 H, methine next to ester), 2.65 (m, 1 H, H_{7x}), 1.93 (dd, J = 13, 9, 1 H, H_{7n}). For *endo*-**48**: ^{1}H NMR δ 6.92 (dd, J = 9.8, 5, 1 H), 6.12 (dd J = 9.8, 1.5, 1 H), 5.80 (m, 1 H), 5.55 (m, 1 H), 4.10 (dd, J = 6, 6, 1 H, H_5), 3.68 (s, 3 H), 3.65 (m, 1 H), 3.40 (m, 2 H), 2.85 (m, 1 H), 2.60 (m, 1 H), 2.05 (dd, J = 14, 5.8, 1 H); IR (neat) 2953, 1736, 1687, 1437, 1205, 904 cm^{-1}; mass spectrum calcd for $C_{12}H_{14}BrNO_3$ 299.0157, obsd 299.0151.

Radical Cyclization of 42. A solution of **42** (280 mg, 0.76 mmol), TBH (280 μL 1.04 mmol), and AIBN (40 mg) was heated under reflux in benzene (50 mL) for 8 h. The product **43** (100

mg, 45%) was isolated by chromatography using pentane–ether (70:30) as eluent: mp 145–150 °C; ^{1}H NMR δ 7.50 (m, 2 H), 7.10–7.40 (m, 5 H), 7.00 (m, 2 H); for the remaining peaks and their assignments, see Table II; mass spectrum calcd for $C_{20}H_{19}NO$ 289.1467, obsd 289.1473. A single crystal of **43** was subjected to X-ray structure determination (vide infra).

Radical Cyclization of 44. A solution of **44** (250 mg, 0.73 mmol), TBH (340 μL, 1.3 mmol), and AIBN (50 mg) in benzene (40 mL) was heated at 150 °C in a sealed tube for 24 h. The product **45** (70 mg, 37%) was isolated by chromatography, using hexane–ethyl acetate (70:30) as eluent, as a gum; ^{1}H NMR δ 6.95 (series of m, 8 H), for the remaining peaks and their assignments, see Table II; ^{13}C NMR δ 41.43, 41.94, 49.29, 60.76, 77.27, 122.82, 122.94, 126.38, 127.40, 127.95, 128.12, 128.36, 129.36, 130.53, 138.71, 139.89, 142.37, 206.39; IR (neat) 3060, 2920, 1720, 1500, 1270, 1190, 750 cm^{-1}; mass spectrum calcd for $C_{18}H_{15}NO$ 261.1154, obsd 261.1167.

Radical Cyclization of 46. A mixture of **46** (170 mg, 0.48 mmol), TBH (170 μL 0.63 mmol), and AIBN (40 mg) was heated under reflux in benzene (40 mL) for 48 h. Chromatography of the crude product using hexane–ethyl acetate (70:30) gave a fraction (20 mg) consisting of a mixture of *exo*-**47** and its regioisomer followed by a fraction (50 mg) consisting of a mixture of *exo*- and *endo*-**47**. Preparative TLC of the second fraction using hexane–ethyl acetate (4:6) gave pure *exo*-**47**: mp 123–125 °C; ^{1}H NMR δ 7.26 (m, 2 H), 6.98 (m, 2 H), 3.77 (s, 3 H, methoxyl), for the remaining peaks and their assignments, see Table II; mass spectrum calcd for $C_{16}H_{17}NO_3$ 271.1209, obsd 271.1218. Anal. Calcd: C, 70.82; H, 6.32. Found: C, 70.39; H, 6.40.

Radical Cyclization of 48. A solution of **48** (exo and endo isomer, 300 mg, 1 mmol), TBH (350 μL, 1.3 mmol), and AIBN (50 mg) was heated under reflux in benzene (20 mL) for 18 h. The products were isolated by chromatography using hexane–ethyl acetate (65:35) as eluent. First to elute was unreacted **48** (60 mg, exo and endo). Next to elute was pure *exo*-**49** (40 mg) followed by a mixture of *exo*- and *endo*-**49** (40 mg). For *exo*-**49**: ^{1}H NMR see Table II; ^{13}C NMR δ 32.69, 42.06, 43.39, 48.50, 52.62, 52.67, 68.06, 73.44, 106.46, 151.54, 173.83, 211.45; IR (neat) 2953, 1734, 1437, 1205, 918, 731 cm^{-1}; mass spectrum calcd for $C_{12}H_{15}NO_3$ 221.1052, obsd 221.1058.

Preparation of Methyl *o*-Bromocinnamate (50). A mixture of the ylid derived from [(methoxycarbonyl)methylene]triphenylphosphonium bromide (10 g, 30 mmol) and 2-bromobenzaldehyde (5.5 g, 30 mmol) in CH_2Cl_2 (70 mL) was heated under reflux for 16 h. After cooling, the reaction mixture was filtered to give 8.2 g of triphenylphosphine oxide. Removal of the solvent from the filtrate gave 7 g (97%) of methyl *o*-bromocinnamate as a mixture of trans and cis isomers (trans/cis = 6). For *trans*-**50**: ^{1}H NMR δ 8.05 (d, J = 20, 1 H), 7.60 (m, 2 H), 7.30 (m, 2 H), 6.40 (d, J = 20, 1 H), 3.80 (s, 3 H). For *cis*-**50**: ^{1}H NMR δ 7.60 (m, 2 H), 7.30 (m, 2 H), 7.10 (d, J = 13, 1 H), 6.05 (d, J = 13, 1 H), 3.65 (s, 3 H); mass spectrum, *m/e* (relative intensity) 242 (3), 240 (2), 211 (5), 209 (5), 183 (3), 181 (4), 161 (100), 146 (8), 118 (9), 102 (26), 75 (9), 51 (9).

Diels–Alder Reaction of 50 with Cyclopentadiene. A solution of **50** (4 g, 15 mmol) and freshly distilled cyclopentadiene (6 g, 90 mmol) in toluene (30 mL) was heated at reflux for 48 h. After removal of the toluene the residual yellow oil was chromatographed over silica gel using hexane and then hexane–ethyl acetate (4:1) as eluent. First to elute was dicyclopentadiene followed by a mixture of cycloadducts and unreacted **50**. This liquid was then subjected to fractional distillation at 0.5 Torr. The fraction boiling at 140–143 °C (3 g, 68%) was found to consist of a 1:1 mixture of **51** and **52**. For **51**: ^{1}H NMR δ 7.51 (d, 1 H), 7.32 (t, 1 H), 7.16 (d, 1 H), 7.03 (d, 1 H), 6.42 (m, 1 H, vinyl), 5.84 (m, 1 H, vinyl), 4.15 (m, 1 H, bridgehead), 3.68 (s, 3 H, methoxyl), 3.21 (m, 1 H), 3.15 (m, 1 H), 2.56 (dd, J = 5.5, 1.5, 1 H, methine next to ester), 1.94 (d, J = 8.8, 1 H, C_7 methylene), 1.55 (dd, J = 8.8, 1.5, 1 H, C_7 methylene). For **52**: ^{1}H NMR δ 7.62 (d, 1 H), 7.32 (t, 1 H), 7.20 (t, 1 H), 7.03 (d, 1 H), 6.49 (m, 1 H, vinyl), 6.15 (m, 1 H, vinyl), 3.63 (s, 3 H, methoxyl), 3.39 (dd, J = 5.2, 1.3, 1 H, bridgehead), 3.29 (m, 1 H, bridgehead), 3.21 (m, 1 H, methine next to aryl), 2.90 (br s, 1 H, methine next to ester), 1.70 (d, J = 8.8, 1 H, C_7 methylene), 1.50 (dd, J = 8.8, 1.8, 1 H, C_7 methylene); mass spectrum calcd for $C_{15}H_{15}BrO_2$ 306.0255, obsd 306.0245.

Radical Cyclization of 51 and Reduction of 52. A solution of the 1:1 mixture of **51** and **52** (650 mg, 2.1 mmol), TBH (0.8 mL, 3 mmol), and AIBN (50 mg) in benzene (30 mL) was heated at reflux for 16 h. The crude product was chromatographed using hexane–ethyl acetate (85:15) as eluent to give 390 mg (80%) of **53** and **54**. This mixture was dissolved in CH_2Cl_2 (20 mL), and sodium bicarbonate (200 mg) was added. To this well-stirred mixture was added *m*-CPBA (150 mg, 80%). Stirring was continued for 16 h. After filtration, the filtrate was washed with aqueous sodium bisulfite and brine. The organic layer was separated and dried. Removal of the solvent under reduced pressure gave an oil which was chromatographed using hexane–ethyl acetate (85:15) as eluent. First to elute was **53** (200 mg) followed by **55** (130 mg). For **53**: ^{1}H NMR δ 7.05–7.21 (m, 4 H), 3.69 (s, 3 H, methoxyl), 3.43 (br s, 1 H, H_3), 3.23 (dd, J = 4.5, 4.3, 1 H, H_4), 3.01 (dd, J = 10, 4.5, 1 H, H_5), 2.70 (d, J = 3, 1 H, H_1), 2.29 (dd, J = 2.5, 1.3, 1 H, H_2), 1.88 (m, 2 H, H_{6x}, H_{7s}), 1.59 (dd, J = 10.5, 1.3, 1 H, H_{7s}), 1.27 (ddd, J = 10.5, 2.5, 2.5, 1 H, H_{6n}); ^{13}C NMR δ 18.87, 37.06, 37.67, 43.95, 48.73, 51.71, 53.59, 53.87, 123.03, 123.15, 126.13, 126.49, 149.05, 151.06, 174.98; IR (neat) 2952, 1736, 1475, 1435, 1200, 1175, 749 cm^{-1}; mass spectrum calcd for $C_{15}H_{16}O_2$ 228.1150, obsd 228.1161. Anal. Calcd: C, 78.92; H, 7.04. Found: C, 78.88; H, 7.00. For **55**: ^{1}H NMR δ 7.30 (m, 5 H), 3.74 (s, 3 H), 3.33 (s, 2 H), 3.24 (d, J = 5, 1 H), 2.93 (s, 2 H), 2.78 (s, 1 H), 1.52 (d, J = 10.5, 1 H), 1.27 (d, J = 10.5, 1 H); mass spectrum calcd for $C_{15}H_{16}O_3$ 244.1099, obsd 244.1116.

The NMR assignments for **53** are based on the following analysis and homonuclear decoupling experiments. H_{6n} appears at highest field (δ 1.27), geminally coupled (J = 10.5) to H_{6x} (δ 1.88) and weakly coupled to H_{7s} (δ 1.88) and H_5 (δ 3.01). H_{7a} (δ 1.59) is geminally coupled to H_{7s} and weakly (J = 1.3) to H_2 (δ 2.29). Irradiation of the multiplet at δ 1.88 caused the peaks at δ 1.59 and 1.27 to collapse to weakly coupled doublets and the peak at δ 3.01 became a doublet (J = 4.5). Irradiation at δ 3.01 (H_5) changed the multiplet pattern at δ 1.88 and transformed the peak at δ 3.23 (H_4) to a doublet (J = 4.3). Finally, irradiation at δ 3.23 transformed the peak at δ 3.01 to a doublet (J = 10) and the broad singlet at δ 3.43 (H_3) to a sharper singlet.

Preparation of 59.[14] To a solution of 2-allyl-1,3-dithiane (1 g, 6.25 mmol, prepared in 93% yield from 1,3-dithiane) in THF (20 mL) at −30 °C was added dropwise *n*-BuLi (6.5 mmol). The solution was stirred at −30 °C for 1.5 h, after which a solution of 2-furancarboxaldehyde (600 mg, 6.25 mmol) in THF (5 mL) was added. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by pouring the contents of the flask into aqueous NH_4Cl solution. Ether (100 mL) was added, and the organic layer was separated and dried. Removal of the solvent under reduced pressure gave a yellow oil, which was chromatographed over silica gel using hexane–ethyl acetate (85:15) as eluent to give 1.2 g (75%) of **59** as an oil which solidified on standing: mp 75–79 °C; ^{1}H NMR δ 7.42 (m, 1 H), 6.42 (m, 2 H), 6.00 (m, 1 H), 5.15 (m with a s, 3 H), 3.10 (m, 2 H), 2.60–2.93 (m, 4 H), 2.45 (m, 1 H), 2.10 (m, 1 H), 1.85 (m, 1 H).

General Procedure for the Synthesis of Ethers 60, 61, and 62. To a suspension of 60% NaH (4–7 mmol) in THF (20–50 mL) at room temperature was added slowly a solution of **59** (3–6 mmol) in THF (10 mL). The mixture was stirred for 3 h, and then a solution of the appropriate dibromide (3–6 mmol) was added. The mixture was stirred overnight and then poured into ice-cold NH_4Cl solution. Ether was added, and the ether layer was separated and dried. Removal of the solvent under reduced pressure followed by chromatography of the residue over silica gel using hexane–ethyl acetate (4:1) as eluent gave the pure product.

Preparation of 60. A suspension of NaH (160 mg, 4 mmol) in THF (20 mL) was treated with **59** (1 g, 3.9 mmol) followed by 2-bromobenzyl bromide (920 mg, 3.7 mmol). After workup and purification **60** (1.2 g, 82%) was obtained as a viscous oil: ^{1}H NMR δ 7.60 (dd, J = 9.3, 1.5, 1 H), 7.56 (dd, J = 9.3, 1.5, 1 H), 7.48 (d, J = 1.3, 1 H), 7.31 (dt, J = 7.5, 1, 1 H), 7.13 (dt, J = 7.5, 1, 1 H), 6.54 (d, J = 3.2, 1 H), 6.40 (dd, J = 3.2, 1.8, 1 H), 6.00 (m, 1 H), 5.15 (s, 1 H), 5.09 (d, J = 6, 1 H), 4.86 (s, 1 H), 4.50 (AB q, J = 20.7, 2 H), 3.03 (m, 1 H), 2.60–2.95 (m, 5 H), 1.95 (m, 2 H); mass spectrum calcd for $C_{19}H_{21}O_2S_2Br$ 424.0166, obsd 424.0154.

Preparation of 61. A suspension of NaH (140 mg, 3.5 mmol) in THF (20 mL) was treated with **59** (760 mg, 3 mmol) followed

by 2,3-dibromopropene (640 mg, 3.2 mmol). After workup and chromatography **61** (960 mg, 86%) was obtained as a colorless oil: ^{1}H NMR δ 7.45 (m, 1 H), 6.52 (m, 1 H), 6.42 (m, 1 H), 6.00 (m, 2 H), 5.63 (s, 1 H), 5.15 (m, 2 H), 4.86 (s, 1 H), 4.04 (AB q, J = 15.5, 2 H), 3.00–3.25 (m, 2 H), 2.50–2.80 (m, 4 H), 1.80–2.10 (m, 2 H); mass spectrum, m/e (relative intensity) 376 (0.1), 374 (0.1), 335 (0.2), 333 (0.2), 239 (0.5), 161 (11), 160 (12.5), 159 (100), 119 (12), 97 (13), 95 (12), 85 (26); high resolution mass spectrum calcd. for $C_{15}H_{19}BrO_2S_2$ 374.0009, obsd. 374.0002. Anal. Calcd: C, 48.00; H, 5.10. Found: C, 48.21, H, 5.11.

Preparation of 62. A suspension of NaH (280 mg, 3.5 mmol) in THF (30 mL) was treated with **59** (1.5 g, 6 mmol) followed by 1,3-dibromopropene (1.3 g, 6.4 mmol). After workup and chromatography **62** (1.54 g, 70%) was obtained as a mixture of stereoisomers: ^{1}H NMR δ 7.45 (m, 1 H), 6.51 (m, 1 H), 6.41 (m, 1 H), 6.31 (m, 2 H), 5.99 (m, 1 H), 5.17 (s, 1 H), 5.12 (m, 1 H), 4.74 (s, 1 H), 3.80–4.12 (m, 2 H), 2.85–3.20 (m, 2 H), 2.50–2.80 (m, 4 H), 1.85–2.10 (m, 2 H); mass spectrum, m/e (relative intensity) 376 (0.1), 374 (0.1), 335 (0.2), 333 (0.2), 239 (0.5), 161 (10), 160 (11), 159 (100), 121 (13), 119 (15), 95 (12), 85 (32); high-resolution mass spectrum calcd for $C_{15}H_{19}BrO_2S_2$ 374.0010, obsd 373.9997. Anal. Calcd: C, 48.00; H, 5.10. Found: C, 48.22; H, 5.18.

Intramolecular Diels–Alder Reaction of 60. A solution of **60** (1 g, 2.35 mmol) in benzene (40 mL) was heated under reflux for 5 days. The benzene was removed under reduced pressure, and the residual oil was chromatographed over silica gel using hexane–ethyl acetate (4:1) as eluent to give **63** (640 mg, 64%) and **63′** (60 mg, 6%). For **63**: ^{1}H NMR (C_6D_6) δ 7.72 (dd, J = 8, 1.5, 1 H), 7.31 (dd, J = 8, 1, 1 H), 6.97 (dt, J = 7.5, 1.5, 1 H), 6.68 (dt, J = 7.5, 1.5, 1 H), 6.63 (d, J = 5.8, 1 H, vinyl H_b), 5.81 (dd, J = 5.8, 1.5, 1 H, vinyl H_a), 4.98 (AB q, J = 13.2, 2 H, benzylic methylene), 4.69 (dd, J = 4.3, 1.5, 1 H, bridgehead), 4.55 (s, 1 H, methine next to O), 2.75 (m, 1 H), 2.65 (dd, J = 12.8, 6.3, 1 H), 2.50 (m, 3 H), 2.35 (m, 1 H), 1.90 (m, 1 H), 1.60 (m, 2 H), 1.35 (m, 1 H), 1.02 (dd, J = 11.2, 7.8, 1 H); mass spectrum calcd for $C_{19}H_{21}BrO_2S_2$ 424.0166, obsd 424.0157. Anal. Calcd: C, 53.64; H, 4.98. Found: C, 53.92; H, 5.13. For **63′**: ^{1}H NMR (C_6D_6) δ 7.96 (dd, J = 7.8, 1, 1 H), 7.27 (dd, J = 7.8, 1, 1 H), 7.00 (dt, J = 7.2, 1, 1 H), 6.70 (dt, J = 7.8, 1, 1 H), 6.08 (d, J = 5.8, 1 H, vinyl H_b), 5.83 (dd, J = 5.8, 1.5, 1 H, vinyl H_a), 4.86 (AB q, J = 13.2, 2 H, benzylic methylene), 4.68 (dd, J = 4.5, 1.5, 1 H, bridgehead), 4.52 (s, 1 H, methine next to O), 2.78 (m, 1 H), 2.35–2.58 (m, 4 H), 2.10 (m, 2 H), 1.64 (m, 2 H), 1.30–1.47 (m, 1 H), 0.96 (dd, J = 11.2, 7.2, 1 H).

Radical Cyclization of 63. A solution of **63** (350 mg, 0.88 mmol), TBH (350 μL, 1.3 mmol), and AIBN (70 mg) in benzene (30 mL) was heated under reflux for 18 h. The product **64** (130 mg, 53%) was isolated by chromatography using hexane–ethyl acetate (4:1) as eluent. For **64**: mp 130–133 °C; ^{1}H NMR δ 6.97–7.22 (m, 4 H), 4.97 (AB q, J = 24.5, 2 H, $H_{7'}$), 4.66 (s, 1 H, $H_{5a'}$), 4.60 (dd, J = 4, 4, 1 H, $H_{2'}$), 3.62 (dd, J = 9, 4, 1 H, $H_{12'}$), 3.13–3.22 (m, 2 H), 2.66–2.88 (m, 3 H), 2.45 (dd, J = 13, 7.5, 1 H, $H_{13'}$), 2.35 (dd, J = 13, 9, 1 H, H_{13n}), 2.15 (m, 1 H, $H_{13'x}$), 1.99–2.05 (m, 2 H), 1.85 (dd, J = 12, 8.2, 1 H, $H_{3'n}$), 1.75 (dd, J = 13, 7.5, 1 H, $H_{13'}$), 1.60 (m, 1 H, $H_{3'x}$); mass spectrum calcd for $C_{19}H_{22}O_2S_2$ 346.1061, obsd 346.1055. A single crystal of **64** was subjected to X-ray structure determination (vide infra).

The NMR assignments of **64** are based on the following analysis and homonuclear decoupling experiments. The AB quartet at δ 4.97 (J = 24.5) is clearly the benzylic protons $H_{7'}$. The singlet at δ 4.66 is assigned to the only isolated methine proton $H_{5a'}$. The bridgehead proton $H_{2'}$ (δ 4.60), a dd (J = 4, 4), is converted to a doublet (J = 4) when the peak at either δ 2.15 or δ 1.60 is irradiated; these are therefore assigned to $H_{13'x}$ and $H_{3'x}$, respectively. Irradiation at δ 2.15 ($H_{13'x}$) also converted the dd at δ 3.62 (J = 9, 4) to a doublet (J = 9), whereas irradiation at δ 2.35 converts it to a doublet (J = 4). Therefore δ 3.62 is $H_{12'}$ and δ 2.35 is $H_{13'n}$. Irradiation at δ 1.60 converts the dd (J = 12, 8.2) at δ 1.85 to a doublet (J = 8.2), indicating that the peaks at δ 1.60 and 1.85 are due to geminally coupled protons, $H_{3'x}$ and $H_{3'n}$, respectively. Irradiation at δ 2.45 converted the dd at δ 1.75 (J = 13, 7.5) to a doublet (J = 7.5) and irradiation at δ 1.75 converted the dd at δ 2.45 (J = 13, 7.5) to a doublet (J = 7.5). Hence these protons are geminally coupled and assigned $H_{4'x}$ and $H_{4'n}$, respectively, each also coupled to $H_{3a'}$. This absorption is probably buried in the three-proton multiplet at δ 2.60–2.88.

Intramolecular Diels–Alder Reaction of 61. A solution of **61** (950 mg, 2.53 mmol) in benzene (30 mL) was heated under reflux for 5 days. The solvent was removed under reduced pressure, and the residual oil was chromatographed over silica gel using hexane–ethyl acetate (85:15) as eluent to give **65** (460 mg, 67% yield, 49% conversion), **65′** (50 mg, 5%) together with **66** (40 mg) and recovered **61** (250 mg). For **65**: ^{1}H NMR (C_6D_6) δ 6.59 (d, J = 6, 1 H), 5.84 (m, 1 H), 5.78 (dd, J = 6, 1.5, 1 H), 5.40 (m, 1 H), 4.64 (dd, J = 4.5, 1.5, 1 H), 4.40 (AB q with a s, 3 H), 2.74 (m, 1 H), 2.38–2.65 (m, 4 H), 2.20–2.30 (m, 1 H), 1.78–1.88 (m, 1 H), 1.53–1.66 (m, 2 H), 1.32 (ddd, J = 11.5, 4, 4, 1 H), 0.98 (dd, J = 11.2, 7.8, 1 H); mass spectrum calcd for $C_{15}H_{19}BrO_2S_2$ 374.0010, obsd 373.9976. For **65′**: ^{1}H NMR (C_6D_6) δ 5.95 (d with a m, J = 6, 2 H), 5.76 (dd, J = 6, 1.5, 1 H), 5.42 (m, 1 H), 4.63 (dd, J = 4.5, 1.5, 1 H), 4.48 (s, 1 H), 4.45 (d, J = 15, 1 H), 4.23 (d, J = 15, 1 H), 3.05 (m, 1 H), 2.67 (m, 1 H), 2.20–2.52 (m, 4 H), 2.05 (m, 1 H), 1.65 (m, 2 H), 1.28 (m, 1 H), 0.93 (m, 1 H). An identical result was obtained when **61** was heated at 90–100 °C for 5 h with an equivalent of β-cyclodextrin in water.

Radical Cyclization of 65. A solution of **65** (350 mg, 0.94 mmol), TBH (270 μL, 1 mmol), and AIBN (50 mg) in benzene (30 mL) was heated under reflux for 16 h. The product **67** (190 mg, 68%) was isolated as a colorless gum by chromatography using hexane–ethyl acetate (4:1) as eluent. For **67**: ^{1}H NMR δ 4.93 (m, 1 H, H_{11}), 4.75 (m, 1 H, H_{11}), 4.65 (dd, J = 15, 1.5, 1 H, $H_{7'}$), 4.58 (dd, J = 5, 5, 1 H, $H_{2'}$), 4.25 (d with str, J = 15, 1 H, $H_{7'}$), 4.18 (s, 1 H, $H_{5a'}$), 2.70–3.20 (series of m, 4 H), 2.48–2.65 (m, 3 H, $H_{3'n}$, $H_{4'x}$, $H_{10'n}$), 1.85–2.18 (m, 5 H), 1.70 (m, 1 H), 1.60 (m, 1 H); mass spectrum calcd for $C_{15}H_{20}O_2S_2$ 296.0905, obsd 296.0903. Anal. Calcd: C, 60.77; H, 6.80. Found: C, 60.20; H, 6.84.

The NMR assignments of **67** were based on chemical shifts and coupling constants, and homonuclear decoupling and a 2D NMR (COSY) experiment. Coupling of $H_{2'}$ (δ 4.58) with $H_{3'x}$ (δ 1.60) and $H_{10'x}$ (δ 1.95) was established by separately irradiating at δ 1.55 or δ 1.95, each of which transformed the $H_{2'}$ absorption to a doublet. From the COSY plot it was observed that the three-proton multiplet between δ 2.48 and 2.65 was strongly coupled to $H_{3'x}$, $H_{10'x}$, and a multiplet at δ 1.70. Thus the three-proton multiplet comprises of $H_{3'n}$, $H_{4'x}$, and $H_{10'n}$ and the multiplet at δ 1.70 is $H_{4'n}$. Since irradiation at δ 2.18 had a dramatic effect on the complex pattern between δ 2.80 and 3.20 we conclude that these represent the four protons of the dithiane moiety α to the sulfur atoms. The remaining two protons ($H_{9'}$ and $H_{3'}$) are buried in the multiplet between δ 1.85 and 2.18.

Intramolecular Diels–Alder Reaction of 62. To a suspension of **62** (700 mg, 1.86 mmol) in a water/ethanol (10:1) mixture (55 mL) was added β-cyclodextrin (2.2 g, 2 mmol), and the mixture was heated in an oil bath (90–100 °C) for 12 h. After cooling, ether (75 mL) was added, and the organic layer was separated. The ether layer was washed with brine and dried. Removal of the ether under vacuum gave a gum, which was chromatographed over silica gel using hexane–ethyl acetate (4:1) as eluent to give **68** (350 mg, 71% yield, 50% conversion) together with 90 mg of a mixture of other cycloadducts and 210 mg of recovered **62**. For **68**: ^{1}H NMR δ 6.23–6.58 (m, 4 H), 5.15 (m, 1 H), 5.02 (m, 1 H), 4.05–4.60 (series of m, 4 H), 2.70–3.15 (m, 6 H), 1.80 (m, 1 H), 1.65 (m, 1 H), 1.40 (m, 1 H); mass spectrum, m/e (relative intensity) 376 (0.3), 374 (0.3), 335 (0.7), 333 (0.7), 295 (0.4), 160 (10), 159 (100), 121 (14), 119 (19), 85 (25).

Radical Cyclization of 68. A solution of **68** (300 mg, 0.8 mmol), TBH (230 μL, 0.85 mmol) and AIBN (50 mg) in benzene (30 mL) was heated under reflux for 10 h. The product **69** (120 mg, 50%) was isolated as a gum (which solidified on standing) by chromatography using hexane–ethyl acetate (85:15) as eluent. For **69**: mp 135–138 °C; ^{1}H NMR δ 5.40 (m, 1 H, vinyl), 5.10 (m, 1 H, vinyl), 4.60 (m, 2 H, $H_{7'}$), 4.40 (s, 1 H, $H_{5a'}$), 4.25 (m, 1 H, $H_{2'}$), 3.15 (m, 1 H), 2.75–3.10 (m, 4 H), 2.55 (m, 2 H), 1.85–2.15 (m, 3 H), 1.55–1.80 (m, 4 H); mass spectrum calcd for $C_{15}H_{20}O_2S_2$, 296.0905, obsd 296.0914. Anal. Calcd: C, 60.77; H, 6.80. Found: C, 60.64; H, 6.99.

Preparation of Imine 70 and Amine 71. A solution of 2-bromoaniline (7.2 g, 42 mmol) and 2-furancarboxaldehyde (4 g, 41.6 mmol) in benzene (100 mL) was heated under reflux, with a water trap attached to the condenser, for 16 h. The gum obtained after removal of the benzene was triturated with pe-

troleum ether. The soluble portion was decanted. Removal of the solvent gave a yellow oil, which was distilled under vacuum. The imine **70** (5 g, 50%) was obtained as a yellow oil (140 °C/0.5 Torr): ^{1}H NMR (C_6D_6) δ 7.71 (s, 1 H), 7.45 (dd, J = 8, 1, 1 H), 6.99 (d, J = 1.5, 1 H), 6.85 (dt, J = 7.8, 1.3, 1 H), 6.72 (d, J = 3.5, 1 H), 6.61 (dt, J = 7.8, 1.3, 1 H), 6.49 (dd, J = 8, 1.5, 1 H), 5.95 (m, 1 H).

To a well-stirred solution of (2-allyl-1,3-dithianyl)lithium [prepared from 2-allyl-1,3-dithiane (1 g, 6 mmol) and *n*-BuLi (10 mmol) in THF (40 mL) at −35 °C] was added a solution of **70** (1.5 g, 6 mmol) in THF (20 mL). Stirring was continued for 2 h. The reaction was quenched at −35 °C by adding aqueous NH_4Cl solution dropwise. After the mixture was warmed to room temperature, ether (150 mL) was added. The ether layer was separated, washed with brine, and dried. The yellow gum obtained after removal of the solvent was triturated with hexane. This resulted in the precipitation of **71** as a white crystalline solid (1.1 g, 45%). For **71**: mp 123–125 °C; ^{1}H NMR δ 7.35 (dd, J = 7.5, 1.5, 1 H), 7.00 (m, 1 H), 6.82 (dt, J = 7.5, 1.5, 1 H), 6.50 (dd, J = 7.5, 1.5, 1 H), 6.30 (m, 2 H), 6.15 (m, 1 H), 6.05 (d, J = 7.5, 1 H), 5.95 (m, 1 H), 5.15 (m, 2 H), 4.92 (d, J = 7.5, 1 H), 2.88 (AB q each peak split into a d, J_{AB} = 14.8, J = 6.5, 2 H), 2.50 (m, 1 H), 2.18 (m, 2 H), 2.00 (m, 1 H), 1.35 (m, 2 H); mass spectrum, m/e (relative intensity) 411 (0.4), 409 (0.3), 252 (89), 250 (100), 159 (94), 85 (14). Anal. Calcd for $C_{18}H_{20}BrNOS_2$: C, 52.68; H, 4.91. Found: C, 52.88; H, 4.89.

Intramolecular Diels–Alder Reaction of 71. A solution of **71** (300 mg, 0.73 mmol) in benzene (30 mL) was heated under reflux for 48 h. The oil obtained after removal of the solvent was chromatographed over silica gel using hexane–ether (75:25) as eluent to give 180 mg (60%) of a 3:1 mixture of **72** and **72′**: ^{1}H NMR (C_6D_6) δ 7.36 (dd, J = 8, 1.5, 1 H), 6.99 (dt, J = 8.5, 1.5, 1 H), 6.91 (dt, J = 8, 1.5, 1 H), 6.35 (m, 1 H), 6.11 (d, J = 5.8, H_b), 5.95 (d, J = 7, H_d), 5.90 (d, J = 5.8, $H_{b'}$), 5.80 (d, J = 7, $H_{d'}$), 5.78 (dd, J = 5.8, 1.8, $H_{a'}$), 5.61 (dd, J = 5.8, 1.8, H_a), 4.63 (dd, J = 4.5, 1.5, H_e), 4.60 (dd, J = 4.5, 1.5, $H_{e'}$), 4.51 (d, J = 7, H_c, $H_{c'}$), 2.85 (m, 1 H), 2.55 (dd, J = 12.5, 6.3, 1 H), 2.22–2.50 (m, 3 H), 1.90–2.20 (m, 2 H), 1.25–1.55 (m, 3 H), 0.95 (dd, J = 11.3, 7.5, 1 H); mass spectrum, m/e (relative intensity) 411 (0.4), 409 (0.5), 252 (28.3), 250 (32.3), 159 (18.3), 158 (13), 84 (100), 82 (12.4).

Radical Cyclization of 72 and 72′. A solution of the above mixture of **72** and **72′** (250 mg, 0.61 mmol), TBH (220 μL, 0.82 mmol), and AIBN (50 mg) in benzene (30 mL) was heated under reflux for 18 h. After the usual workup, chromatography of the crude product over silica gel using hexane–ethyl acetate (85:15) as eluent gave **73** (70 mg, 50%) as a white solid: mp 208–210 °C; ^{1}H NMR δ 7.00 (m, 2 H), 6.78 (m, 2 H), 4.65 (dd, J = 5, 5, 1 H, $H_{2'}$), 3.75 (s, 1 H, $H_{5a'}$), 2.98–3.22 (series of m, 2 H), 2.89–2.97 (dd, J = 12.8, 6, 2 H), 2.63–2.83 (m, 4 H), 2.32 (m, 1 H), 2.00–2.17 (m, 2 H), 1.74–1.98 (m, 4 H); mass spectrum calcd for $C_{18}H_{21}NOS_2$ 331.1065, obsd 331.1055. Anal. Calcd: C, 65.22; H, 6.39. Found: C, 65.09; H, 6.47.

Preparation of 76. To a solution of aldehyde **74**[17] (7.0 g, 38.5 mmol) in methanol (100 mL) was added 6.0 g (158 mmol) of sodium borohydride, and the mixture was stirred at room temperature for 16 h. The rxn was quenched with 10% HCl and extracted with ether (100 mL), and the organic layer was washed with brine and dried. Removal of the ether (rotavap) gave 6.5 g (92%) of alcohol **75** as a colorless oil: ^{1}H NMR δ 6.21 (d, J = 3, 1 H), 6.10 (d, J = 3, 1 H), 5.77 (m, 1 H), 5.16 (m, 2 H), 4.57 (s, 2 H), 3.64 (s, 2 H), 3.12 (dt, J = 7.5, 1.3, 2 H), 1.95 (br s, 1 H); mass spectrum, m/e (relative intensity) 184 (6), 142 (33), 125 (10), 111 (100), 83 (21), 81 (9), 69 (8), 65 (8), 55 (19).

To a suspension of sodium hydride (80%, 750 mg, 25 mmol) in ether (80 mL) was slowly added a solution of alcohol **75** (3.7 g, 20 mmol) in 10 mL of ether. After the mixture was stirred at room temperature for 1 h, a solution of 2-bromobenzyl bromide (5.5 g, 22 mmol) in ether (20 mL) was added, and the mixture was heated at reflux for 20 h. The cooled mixture was poured into cold ammonium chloride solution and extracted with ether. The ether layer was dried, the solvent was removed (rotavap), and the residue was chromatographed over silica gel using hexane:ethyl acetate (4:1) as eluent to give 3.6 g (51%) of pure **76**: ^{1}H NMR δ 7.5 (m, 2 H), 7.30 (m, 1 H), 7.15 (m, 1 H), 6.30 (d, J = 3, 1 H), 6.13 (d, J = 3, 1 H), 5.30 (m, 1 H), 5.10 (m, 2 H), 4.65 (s, 2 H), 4.55 (s, 2 H), 3.70 (s, 2 H), 3.12 (dt, J = 7.5, 1.3, 2 H); mass spectrum, m/e (relative intensity) 354 (6), 352 (5), 281 (49), 279 (50), 251 (10), 171 (97), 169 (100), 125 (26), 95 (14), 94 (14), 81 (10).

Intramolecular Cycloaddition of 76. A solution of **76** (1.8 g, 5 mmol) in toluene (50 mL) containing 3 drops of pyridine was heated at reflux for 24 h. The solvent was removed (rotavap), and the residue was chromatographed over silica gel using hexane–ether (9:1) as eluent. The first fraction was unreacted **76** (1.1 g, 61%), followed by **77** (680 mg, 97% yield, 33% conversion): ^{1}H NMR δ 7.53 (dd, J = 7.5, 1.3, 1 H), 7.49 (dd, J = 7.5, 1.3, 1 H), 7.32 (dt, J = 7.5, 1.3, 1 H), 7.29 (dt, J = 7.5, 1.3, 1 H), 6.42 (s, 2 H, vinyls), 4.70 (s, 2 H, OCH_2Ar), 3.96 (s, 2 H, OCH_2C), 3.32 (ABq, J = 12.5, 2 H, SCH_2C), 3.05 (dd, J = 10.8, 7.5, 1 H, SCH_2CH), 2.75 (dd, J = 10.5, 10.5, 1 H, SCH_2CH), 2.35 (m, 1 H, SCHCH), 1.60 (m, 2 H), $OCCH_2CH$); mass spectrum, m/e (relative intensity) 354 (6), 352 (6), 281 (39), 279 (41), 171 (54), 169 (55), 149 (100), 125 (11), 121 (14), 111 (11), 109 (5), 97 (9), 95 (8), 91 (13). Anal. Calcd for $C_{16}H_{17}BrO_2S$: C, 54.39; H, 4.85. Found: C, 54.49; H, 4.89.

Radical Cyclization of 77. A solution of **77** (600 mg, 1.7 mmol), TBH (690 μL, 2.55 mmol), and AIBN (100 mg) in benzene (60 mL) was heated at reflux for 16 h. After the usual workup, the residue was chromatographed over silica gel using hexane–ether (3:1) as eluent to give **79** (150 mg, 32%) followed by **78** (110 mg, 24%). For **78**: mp (benzene) 107–109 °C; ^{1}H NMR δ 6.88–7.18 (m, 4 H), 4.57–4.69 (AB q, J = 11.8, 2 H, H_a), 3.63–3.73 (AB q, J = 11.8, 2 H, H_b), 3.21 (d, J = 12.5, 1 H, H_f), 2.89 (dd, J = 8.2, 8.2, H_b), 2.82 (d, J = 12.5, 1 H, H_f), 2.54–2.68 (m, 2 H, H_e), 2.20 (m, H_d), 2.10 (dd, J = 12, 6.5, H_{cn}), 1.80 (dd, J = 12, 8, 1 H, H_g), 1.60 (dd, J = 12, 8, 1 H, Hg), 1.25 (dd, J = 12, 3.8, H_{cx}); mass spectrum, m/e (relative intensity) 274 (100), 256 (8), 244 (56), 233 (12), 223 (19), 209 (32), 197 (38), 181 (50), 171 (33), 169 (40), 141 (45), 129 (68), 115 (85), 91 (45), 85 (38). Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61. Found: C, 70.07; H, 6.70. For **79**: ^{1}H NMR δ 7.30 (m, 5 H), 6.38 (m, 2 H), 4.63 (AB q, J = 12.2, 2 H), 3.85 (m, 2 H), 3.30 (d, J = 3.5, 2 H), 3.04 (dd, J = 10.7, 7.3, 1 H), 2.75 (dd, J = 10.7, 10.7, 1 H), 2.30 (m, 1 H), 1.60 (m, 2 H). Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61. Found: C, 70.11; H, 6.71.

X-ray Data for 8. Recrystallization of **8** from methylene chloride gave a colorless needlelike crystal, $C_{21}H_{16}O$: space group $P2_1/c$; a = 9.591 (3), b = 29.142 (9), and c = 10.633 (3) Å, β = 92.79 (2)°; Z = 8; M = 284.36; V = 2968.4 (15) Å^3; ρ = 1.27 g cm^{-3}. Preliminary examination and intensity data were measured by using Mo K_α radiation (λ = 0.710 73 Å) on a Nicolet P3F diffractometer ($2\theta_{max}$ = 40°) yielding 2776 unique reflections of which 818 were used in the refinement. The structure was solved by direct methods (SHELXS-86). The final R value was 0.072.

X-ray Data for 43. Recrystallization of **43** from methylene chloride gave a colorless rod crystal, $C_{20}H_{19}NO$: space group $P2_1/c$; a = 15.279 (2), b = 7.315 (1), and c = 13.542 (2) Å; β = 100.28 (1)°; Z = 4; M = 289.38; V = 1489.3 (3) Å^3; ρ = 1.29 g cm^{-3}. Preliminary examination and intensity data were measured as for **8** except that ($2\theta_{max}$ = 55°) yielding 3435 unique reflections of which 2067 were used in the refinement. The final R value was 0.041.

X-ray Data for 64. Recrystallization of **64** from ethyl acetate gave a colorless prism crystal, $C_{19}H_{22}O_2S_2$: space group $P2_1/c$; a = 19.909 (9), b = 6.430 (6), and c = 13.295 (18) Å; β = 108.73 (6)°; Z = 4; M = 346.51; V = 1611.9 (23) Å^3; ρ = 1.43 g cm^{-3}. Preliminary examination and intensity data were measured as for **43** yielding 3730 unique reflections of which 3483 were used in the refinement. The final R value was 0.045.

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Supplementary Material Available: Tables of atomic positional parameters, thermal parameters, bond lengths, and bond angles for **8**, **43**, and **64** (18 pages). Ordering information is given on any current masthead page.