Studies on the Use of Bidentate Ligands in the Directed Pauson-Khand Reaction

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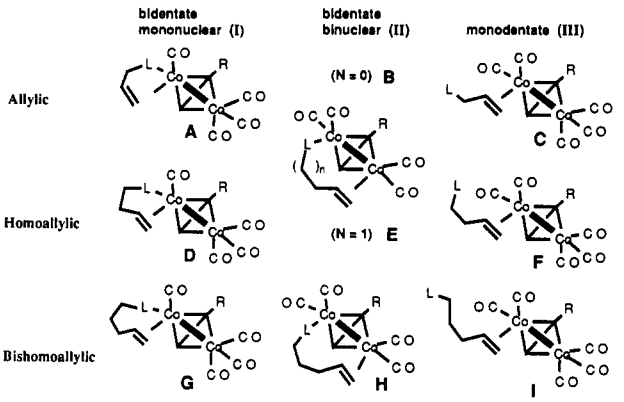
The use of bidentate ligands in the directed Pauson-Khand reaction was investigated. Substrates with a three-carbon linkage between the two heteroatoms gave better results than substrates containing two-carbon tethers. Higher yields and better regioselectivities were observed with thioamines and bisthioethers compared to diamines. Overall, only a few bidentate substrates showed marked improvements over previous results obtained with analogous monodentate compounds. Rationalizations based on the possible modes of cycloaddition operative for the various substrates studied are presented.

Introduction

The Pauson-Khand reaction[1] is a convenient synthetic route to cyclopentenones from olefins and acetylenes catalyzed by octacarbonyldicobalt. The reaction has been the subject of numerous studies and has enjoyed widespread use in synthesis.[2] The proposed mechanism of the reaction[3] (Scheme I) involves coordination of the olefin to the pre-formed (alkyne)hexacarbonyldicobalt complex from the less hindered face followed by carbon-carbon bond formation via generation of a metallacycle (step 1). Migratory insertion of a carbonyl group (step 2) followed by reductive elimination (step 3) and decomplexation of the alkene yields the cyclopentenones.

The regioselectivity of the intermolecular reaction with respect to the acetylenic component is high and dependent on steric factors, supporting the premise that the olefin coordinates to cobalt from the less hindered side of the alkyne-cobalt complex.[4] Conversely, regiocontrol with respect to the alkene is limited.[5] Since the regiochemical outcome of the reaction is presumably determined in the carbon-carbon bond forming step in the proposed mechanism (step 1 in Scheme I),[3] the generation of a "preferred orientation" of the olefin in the initial complex could be expected to improve the regioselectivity of the reaction. Recently, we reported improved regioselectivity in reactions of unactivated olefins upon use of tethered heteroatoms as directing groups.[6] A modified mechanism involving the formation of a bidentate coordinated initial complex which leads to preferential carbon-carbon bond formation between the termini of the alkene and the acetylene has been presented to rationalize the observed regioselectivity.[6] Directed Pauson-Khand reactions of representative substrates with (phenylacetylene)hexacarbonyldicobalt (1) and (1-hexyne)hexacarbonyldicobalt (2) are shown in Table I.[6]

Chart I. Modes of Cycloaddition in the Directed Pauson-Khand Reaction[6]



The effect of the length of the methylene chain between the olefinic moiety and the heteroatom on the degree of regioselectivity observed was rationalized in terms of the modes of coordination available to each substrate (Chart I).[6] Only the monodentate mode depicted by complex **C** is accessible to allylic substrates, while bidentate modes **G** (which gives the 2,5-disubstituted cyclopentenone) and **H** (which yields the 2,4-disubstituted product) are possible for bishomoallylic substrates; hence, low regioisomer ratios are observed with these derivatives. For homoallylic substrates, bidentate mononuclear mode **D** appears to be favored, which would explain the higher regioisomeric ratios obtained with these compounds.

Contrary to the explanation in our previous report,[6] molecular models constructed with correct bond angles at cobalt derived from X-ray data[7] show that the bidentate binuclear mode **E** could be operative depending on the site of ligand substitution. However, the high regioselectivity exhibited by homoallylic substrates suggests that this mode of cycloaddition is not favorable, as it would lead to the opposite regioisomer.

Since the structure and stability of the initial complex(es) formed between the cobalt-alkyne complex and the reacting olefin evidently affects the regiochemical outcome of the reaction, we investigated the use of directing groups containing two heteroatoms L_1 and L_2, positioned in such a way that both groups could simultaneously coordinate to cobalt (eq 1). The bidentate co-

(1) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1971**, 36. (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 975. (c) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.

(2) For reviews on the Pauson-Khand reaction, see: Pauson, P. L.; Khand, I. U. *Ann. N. Y. Acad. Sci.* **1977**, *295*, 2. Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. Pauson, P. L. In *Organometallics in Organic Synthesis*; de Meijere, A., tom Dieck, H., Ed.; Springer-Verlag: Berlin, 1987; p 234. Schore, N. E. *Org. React.* **1991**, *40*, 1. Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 1037.

(3) (a) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477. (b) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. (c) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483.

(4) (a) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 30. (b) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 9.

(5) (a) Khand, I. U.; Pauson, P. L. *J. Chem. Res., Miniprint* **1977**, 168. (b) Billington, D. C.; Kerr, W. J.; Pauson, P. L.; Farnocchi, C. F. *J. Organomet. Chem.* **1988**, *356*, 213. (c) Krafft, M. E. *Tetrahedron Lett.* **1988**, *29*, 999.

(6) (a) Krafft, M. E.; Juliano, C. A.; Scott, I. L.; Wright, C.; McEachin, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 1693. (b) Krafft, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 968.

(7) Gregson, D.; Howard, J. A. K. *Acta Crystallogr.* **1983**, *C39*, 1024.

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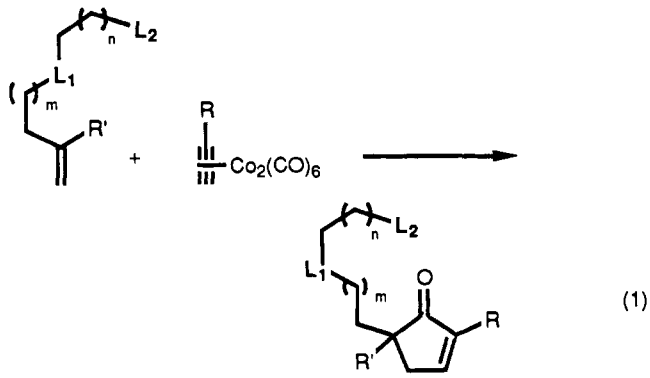


(1)

ordination of the two heteroatoms was expected to result in the formation of a more stable initial complex and possibly a stronger ligand-directing effect, which could result in higher yields and increased regioselection.

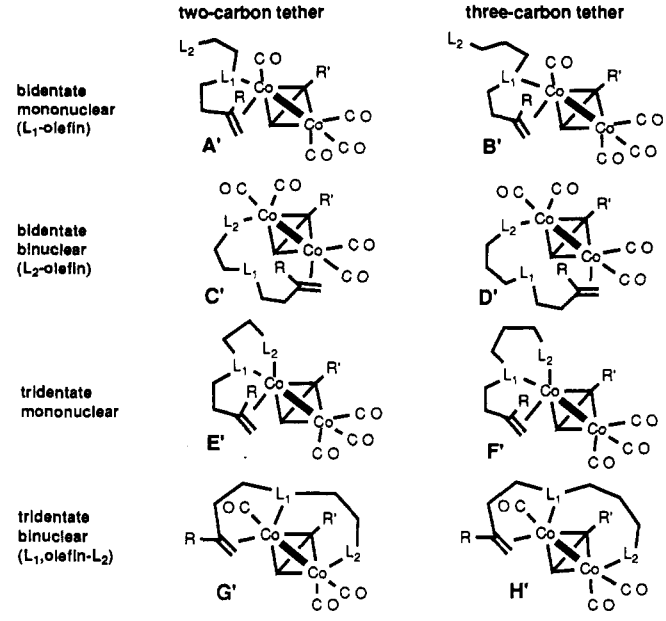
Results and Discussion

Effect of the Length of the Carbon Tether. The low reactivity of 1,1-disubstituted olefins in the Pauson–Khand reaction, which is presumably due to the formation of a quaternary center in the course of the reaction, could be enhanced by the presence of a directing group, such that good yields of cyclopentenones could be obtained from 3-methyl-3-butenyl amines and sulfides, with the 2,5,5-trisubstituted cyclopentenones formed exclusively (see entries 8–10 in Table I).[6] Studies on the effect of the length of the carbon tether between the heteroatoms were thereby conducted using 3-methyl-3-butenyl derivatives since the regiochemical bias present[5,6] would allow focus on possible effects on the yield and rate of reaction. Since the directing ability of amines and sulfides had been demonstrated,[6] diamines, thioamines, and bisthioethers were employed.

The Pauson–Khand reactions of bidentate 3-methyl-3-butenyl derivatives with (phenylacetylene)hexacarbonyldicobalt (1), shown in Table II, produced only the regioisomeric product with the directing group adjacent to the carbonyl moiety. These results are consistent with the behavior of substrates with monodentate directing groups (see entries 8–10 in Table 1). The reactions of bidentate substrates with a propylene link between the heteroatoms gave higher yields of cyclopentenones compared to reactions of substrates with an ethylene linkage (compare entries 4–6 with entries 1–3 in Table II). Diamines **9** and **15** (entries 1 and 4) gave lower yields of enones than analogous thioamines **11** and **17** (entries 2 and 5) and bisthioethers **13** and **19** (entries 3 and 6). Yield enhancements were noted with substrates **17** and **19** compared to analogous monodentate sulfide **7** (see entry 10 in Table I). In general, no significant rate accelerations were noted over reactions of substrates with monodentate directing groups (see Table I, entries 8–10).

The above results could be explained based on the possible modes of cycloaddition of bidentate homoallylic substrates (Chart II with R = CH_3). Bidentate mononuclear (L_1-olefin) modes **A′** and **B′**, which have the homoallylic functional group L_1 and the olefinic moiety both coordinated to cobalt, are similar and analogous to the homoallylic bidentate mononuclear mode **D** for substrates with monodentate directing groups (see Chart I). The bidentate binuclear (L_2-olefin) modes **C′** and **D′** are analogous to the bishomoallylic bidentate binuclear mode **H** in Chart I. Tridentate mononuclear modes **E′** and **F′** have the olefin and both functional groups coordinated to a single cobalt atom, while tridentate binuclear modes **G′** and **H′** have L_1 and the olefin coordinated to one cobalt

Chart II. Modes of Cycloaddition of Bidentate Homoallylic Substrates



atom and L_2 coordinated to the other cobalt atom of the complex. Based on our previous studies (see Chart I and accompanying discussion), mode **G′** appears to be less favorable than modes **E′** or **A′** for substrates with two-carbon tethers between coordinating groups. It is hard to rule out any of the tridentate modes for substrates with three carbon tethers between the heteroatoms.

Three other possible modes of cycloaddition were omitted. The bidentate mononuclear (L_2-olefin) mode, in which L_2 and the double bond are coordinated to the same cobalt atom, is unlikely since the carbon tether is too long and the possibility of both ends coordinating to a single cobalt atom with simultaneous noncoordination of L_1 is low. The bidentate binuclear (L_1-olefin) mode, with the homoallylic functional group L_1 and the olefin simultaneously coordinated to different cobalt atoms, would not be operative in homoallylic substrates containing bidentate directing groups if the analogy could be drawn to our previous results with monodentate directing groups (see Table I), where mode **E** in Chart I is possible based on molecular models but is apparently not a favored pathway (based on lower observed yields of the resulting regioisomer).[6] The tridentate binuclear (L_1,L_2-olefin) mode, with both heteroatoms coordinated to one cobalt atom and the olefinic moiety coordinated to the other cobalt, would be unlikely due to the same reasons given for the bidentate binuclear (L_1-olefin) mode.

If the heteroatoms coordinate to cobalt more readily than the olefinic moiety, the bidentate modes illustrated in Chart II (R = CH_3) would be less significant since they involve coordination of the olefinic moiety and one heteroatom with simultaneous noncoordination of the second heteroatom. Cycloaddition could then be expected to proceed via the tridentate complexes. Substrates with two-carbon tethers between the coordinating groups could initially form tridentate mononuclear complex **E′**, while substrates with three-carbon tethers between the heteroatoms could form mononuclear and binuclear complexes **F′** and **H′**. In view of the lower yields observed with reactants that have a two-carbon chain between heteroatoms, it is plausible that the formation of tridentate mononuclear complex **E′** (tridentate mononuclear) hinders or retards the reactions of substrates **9**, **11**, and **13** (entries 1–3 in Table II), or even results in the breakdown of the

Scheme I. Proposed Mechanism: Reaction with a Terminal Acetylene[3,6]

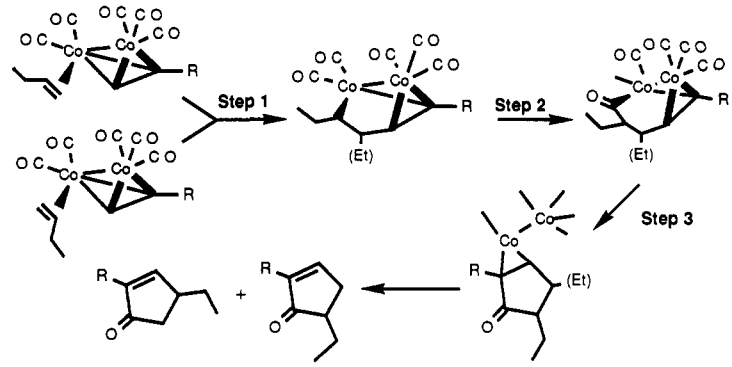
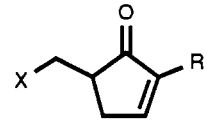
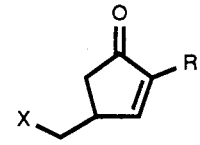
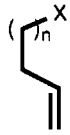
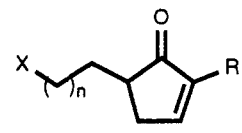
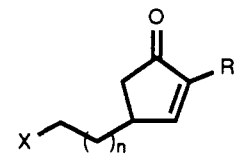
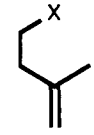
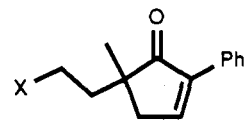


Table I. Ligand Direction with Allylic, Homoallylic, and Bishomoallylic Substrates[6]

entry	substrates	cobalt complex	products			reaction time	isolated yields
							
1	X=SMe	1		2 : 1	R=Ph	24 h	29%
							
2	$X=NMe_2$	1	n=1	5 : 1	R=Ph	24 h	72%
3	X=SMe	2	n=1	8 : 1	R=Bu	36 h	60%
4	X=SMe	1	n=1	18 : 1	R=Ph	26 h	61%
5	$X=NMe_2$	1	n=2	3 : 1	R=Ph	24 h	69%
6	X=SMe	2	n=2	3 : 1	R=Bu	26 h	52%
7	X=SMe	1	n=2	3 : 1	R=Ph	32 h	30%
							
8	**3**, $X=NMe_2$	1	**4**, $X=NMe_2$			24 h	78%
9	**5**, X=NMeBu	1	**6**, X=NMeBu			72 h	37%
10	**7**, X=SEt	1	**8**, X=SEt			24 h	70%

cobalt complexes. Facile decomposition may occur prior to carbonyl insertion upon cyclization from **E'** since carbon monoxide must migrate from the other cobalt nucleus for insertion to occur (refer to step 2 in Scheme I).[3,6]

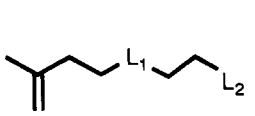
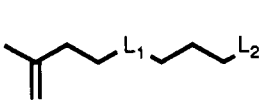
For substrates with propylene linkages between heteroatoms, decomposition may also occur upon reaction via tridentate mononuclear mode **F'** but tridentate binuclear complex **H'** could also form to give a metallacycle with carbon monoxide available for insertion. Possible complications arising from the reaction proceeding predominantly via tridentate mononuclear mode **F'** are apparently reduced, and enones are formed in higher yield (see entries 4–6 in Table II). The predominance of cycloadditions occurring via mode **H'** over reactions via mode **F'** would be consistent with the observed results of reactions of bishomoallylic derivatives with monodentate directing groups (see Table I, entries 5–7),[6] in which more of the 2,4-disubstituted cyclopentenone was formed presumably through bidentate binuclear mode **H** (Chart I).

Since increased yields were noted when nitrogen was replaced by sulfur as a directing ligand, it is possible that the complexes formed initially between diamines **9** and **15** and the alkyne cobalt complexes were too stable. Products **10** and **16** may have remained coordinated to cobalt and were lost in the workup (see entries 1 and 4 in Table II).

Based on the results in Table II, regioselectivity studies were conducted with substrates having three-carbon tethers between the corresponding heteroatoms.

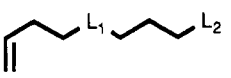
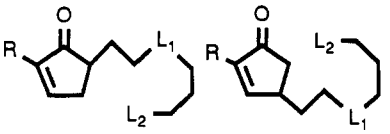
Regioselectivity Studies. The results of Pauson–Khand reactions of 3-butenyl derivatives with cobalt complexes **1** and **2** are outlined in Table III. Reactions of diamine **21** showed no improvements in yield and regioselectivity (entry 1 in Table III) over reactions of its monodentate analog (entry 2 in Table I).[6] The behavior of substrates **24** and **27** was erratic. With complex **1**, thioamine **24** (entry 2 in Table III) gave a ratio of regioisomeric products similar to that obtained with the corresponding monodentate sulfide (see entry 4 in Table I) but higher than that observed with bisthioether **27** (entry 3 in Table III). With complex **2**, bisthioether **27** gave >40:1 ratio of regioisomers (entry 4 in Table III), compared to the ratio of 8:1 obtained with a monodentate directing group (see entry 3 in Table I).[6] All reactions of substrates **24** and **27** were marked by rate accelerations and yield

Table II. Pauson–Khand Reactions of Bidentate 3-Methyl-3-butenyl Substrates with Complex 1

entry	substrates	products	reaction time	yields
				
1	**9** L_1= -NMe-, L_2= -NMe_2	**10**	5-7 days	10%[a]
2	**11** L_1= -S-, L_2= -NMe_2	**12**	2 days	30%[b]
3	**13** L_1= -S-, L_2=-SEt	**14**	6 hours	30%[b]
				
4	**15** L_1= -NMe-, L_2= -NMe_2	**16**	2 days	46%[a]
5	**17** L_1= -S-, L_2= -NMe_2	**18**	1 day	86%[a]
6	**19** L_1= -S-, L_2= -SEt	**20**	1.5 days	89%[b]

[a] Yield after acid–base workup. [b] Yield of product purified by flash chromatography.[8]

Table III. Pauson–Khand Reactions of Bidentate 3-Butenyl Substrates

entry	substrates	cobalt complex	products		reaction time	yields
						
1	**21** L_1= -NMe-, L_2= -NMe_2	1	**22 : 23**	2 : 1 (R=Ph)	2 days	52%[a]
2	**24** L_1= -S-, L_2= -NMe_2	1	**25 : 26**	15 : 1 (R=Ph)	6 hrs	85%[a]
3	**27** L_1= -S-, L_2=-SEt	1	**28 : 29**	8 : 1 (R=Ph)	1.5 hrs	70%[b]
4	**27**	2	**30 : 31**	>40 : 1 (R=Bu)	1.75 hrs	85%[b]

[a] Yield after acid–base workup. [b] Yield after flash chromatography.[8]

enhancements over the analogous monodentate cases[6] (compare entries 2–4 in Table III with entries 3 and 4 in Table I).

The modes of cycloaddition illustrated in Chart II (with R = H) would also apply to the substrates listed in Table III, such that modes **B′** [bidentate mononuclear (L_1-olefin)], **F′** (tridentate mononuclear), and **H′** (tridentate binuclear) could be operative in the given reactions. The behavior of diamine **21** is consistent with that of 3-methyl-3-butenyl diamine **15** (see entry 4 in Table II), which appears to support the premise that complexes formed from diamino derivatives are quite stable, giving lower yields of enones. The significant rate accelerations and similar-to-better regioselectivities observed in reactions of substrates **24** and **27** could be due to the accessibility of tridentate complexes **F′** and **H′** in addition to bidentate complex **B′**. Also the presence of terminal heteroatoms which could fill in the vacant coordination sites necessarily generated in steps 1 and 2 of the mechanistic hypothesis (see Scheme I) may be responsible for accelerating the reaction.[9]

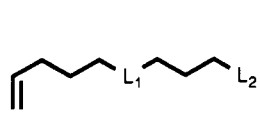
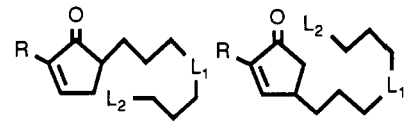
No rate enhancements were observed in the Pauson–Khand reactions of difunctionalized bishomoallylic derivatives shown in Table IV (compare with entries 5–7 in Table I). The product ratios observed were similar to those obtained from reactions of substrates with monodentate directing groups[6] (~3:1 in all cases). Bishomoallylic thioamine **35** gave a slightly higher ratio of regioisomers with phenylacetylene complex **1** than bisthioether **38** (entries 3 and 4 in Table III), which is consistent with the behavior of homoallylic substrates **24** and **27** with **1** (see entries 2 and 3 in Table III). Unlike bisthioether **27**, the ratio of products obtained from the reaction of alkene **38** with hexyne complex **2** was only slightly higher than the ratio observed from reaction with complex **1**.

The possible modes of cycloaddition in reactions of bishomoallylic substrates are illustrated in Chart III. The similarity in the product ratios observed with bidentate substrates compared to those observed with monodentate substrates suggest that *all* the modes given in Chart III may be operative. The modes that generate the "directed"

(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

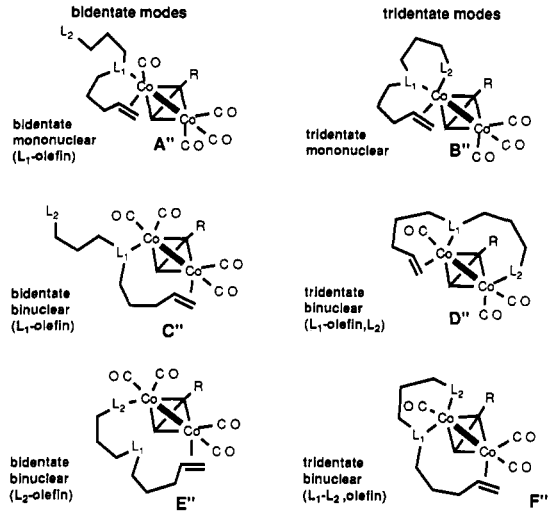
(9) Krafft, M. E.; Scott, I. L.; Romero, R. H. *Tetrahedron Lett.* **1992**, *33*, 3829.

Table IV. Pauson-Khand Reactions of Bidentate 4-Pentenyl Substrates

entry	substrates	cobalt complex	products	reaction time	yields
					
1	**32** L_1= -NMe-, L_2= -NMe_2	**1**	**33 : 34** 3 : 1 (R=Ph)	2 days	56%[a]
2	**35** L_1= -S-, L_2= -NMe_2	**1**	**36 : 37** 4.5 : 1 (R=Ph)	2 days	83%[a]
3	**38** L_1= -S-, L_2= -SEt	**1**	**39 : 40** 2.4 : 1 (R=Ph)	2 days	60%[b]
4	**38**	**2**	**41 : 42** 3 : 1 (R=Bu)	1.5 days	50%[b]

[a] Yield after acid–base workup. [b] Yield after flash chromatography.[8]

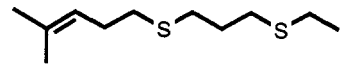
Chart III. Modes of Cycloaddition of Bidentate Bishomoallylic Substrates



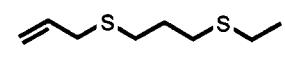
isomer (bidentate **A''** and tridentate **B''** and **D''**) are present together with (and appear to be offset by) modes that lead to the formation of the corresponding regioisomer (bidentate **C''** and **E''** and tridentate **F''**), such that the resulting ratios of regioisomeric cyclopentenones are the same *with or without* the influence of the second directing group.

Our rationales for the observed decrease in regioselectivity in the reactions of monodentate bishomoallylic derivatives and for the increase in yields upon employment of three-carbon instead of two-carbon tethers between coordinating ligands could be extended to explain the above results. With three-carbon tethers between both the olefin and L_1 and between L_1 and L_2, binuclear modes **C''**, **D''**, and **F''** would presumably be more favored, which would be consistent with the reactions of monodentate bishomoallylic substrates occurring via bidentate binuclear mode **H** in Chart I and with the cycloaddition reactions of three-carbon tethered bidentate homoallylic substrates proceeding via tridentate binuclear mode **H'** in Chart II. Cycloaddition via complexes **C''** and **F''** would account for the increased yields of 2,4-disubstituted regioisomeric cyclopentenones. Formation of the 2,5-disubstituted cyclopentenone would be due to cycloaddition via modes **A''**, **B''**, and **D''**.

The cycloaddition reactions of trisubstituted olefin **43** were characterized by the formation of many products in low yield and by slow reaction rates even in refluxing toluene. This suggests that the presence of a second



43



44

directing group does not result in the enhancement of the reactivity of a trisubstituted olefin under Pauson–Khand conditions. Allylic bisthioether **44** produced only minimal yields of a mixture of enones (17% from reaction with phenylacetylene complex **1** for 12 h at 93 °C and 0.2 M in toluene), together with other unidentified side-products.

In summary, our studies on the use of bidentate ligands in the Pauson–Khand reaction seem to suggest that the effect of the second tethered directing ligand is limited to enhancements of the yield and rate of the reaction in some cases. The presence of additional modes of cycloaddition did not generally result in marked improvements in regioselectivity since the new modes introduced led to the formation of both regioisomeric cyclopentenones. Enone formation appeared to be hindered in cases where tridentate coordination onto a single metal center was favored. Lower yields of products were also noted with diamines as bidentate ligands, presumably due to stronger complexation to cobalt which appeared to hinder cycloaddition. Our best results were obtained with homoallylic three-carbon tethered thioamines (such as **17** and **24**) and bisthioethers (such as **19** and **27**), which exhibited rate and yield enhancements. A moderate improvement in the regioselectivity of the cycloaddition was also noted with substrates **24** and **27**. Results on other modifications of the directed Pauson–Khand cycloaddition and related studies will be reported in due course.

Experimental Section

General experimental procedures are described in ref 6a. For NMR data, *J* values are given in Hz. Proton and carbon spectra were obtained in $CDCl_3$ unless otherwise noted. Chromatography refers to flash chromatography as reported by Still.[8]

Preparation of Cobalt Alkyne Complexes. All of the cobalt alkyne complexes were prepared according to reported procedures.[2,10,11] Dicobalt octacarbonyl obtained from Strem Chemical Co. gave the best results. The yields of the alkyne dicobalthexacarbonyl complexes were higher with newer bottles of dicobalt octacarbonyl.

(10) Sternberg, H. W.; Greenfield, H.; Friedel, R. A.; Wotiz, J.; Markby, R.; Wender, I. *J. Am. Chem. Soc.* **1954**, *76*, 1457.
(11) Dickson, R. S.; Fraser, P. J. *Adv. Organomet. Chem.* **1974**, *12*, 323.

The IR spectra of the unpurified complexes were consistent with reported data.[11] The presence of characteristic bands at 2090, 2050 and 2025 cm^{-1} in the IR spectra of alkyne dicobalt hexacarbonyls has been reported.[10] The absence of a 1859 cm^{-1} band corresponding to both the acetylenic group and bridging carbonyls was also noted.[10] Further purification by passing the crude products through a plug of silica gel using hexane as the eluting solvent did not change the IR spectra of the complexes.

(Phenylacetylene)hexacarbonyldicobalt (1):[10] IR (cm^{-1}) 2090, 2054, 2027, 1998.

(1-Hexyne)hexacarbonyldicobalt (2):[11] IR (cm^{-1}) 2954, 2926, 2087, 2047, 2012, 1998.

Preparation of 3-Methyl-3-butenyl Derivatives. 3-Methyl-3-butenyl-1-methanesulfonate (**45**) was prepared using the procedure described by Crossland and Servis.[12]

Preparation of *N*-(3-Methyl-3-butenyl)-*N*,*N*',*N*'-trimethylethylenediamine (9). A mixture of 2.5 g (15.2 mmol) of 3-methyl-3-butenyl-1-methanesulfonate (**45**) and 3.9 mL (30.4 mmol) of *N*,*N*,*N*'-trimethylethylenediamine was stirred with 10 mL of Et_2O under N_2 at rt for 5 d. The reaction mixture was washed once with a 10-mL portion of saturated aqueous $NaHCO_3$ solution and the aqueous layer washed three times with 5-mL portions of Et_2O. The organic extracts were combined and dried over Na_2SO_4, and the Et_2O was distilled off under N_2 at atmospheric pressure. Diamine **9** was obtained as a colorless distillate (1.4 g, 56%) at 55 °C under vacuum (0.15 mm Hg): 300-MHz ^1H NMR δ 1.73 (s, 3 H, CCH_3), 2.18, (d, d, J = 7.2, 5.5, 2 H, CCH_2CH_2N), 2.20 (s, 6 H, $N(CH_3)_2$), 2.25 (s, 3 H, NCH_3), 2.37–2.51 (m, 6 H, $CH_2NCH_2CH_2N$), 4.69 (bs, 1 H, olefin), 4.73 (bs, 1 H, olefin); 75-MHz ^{13}C NMR δ 22.8, 35.4, 42.7, 46.1, 55.8, 56.96, 57.7, 111.2, 144.8; IR (cm^{-1}) 3068, 2941, 1641, 1458; mass spectrum (GC, pentane) m/z (M^+ absent) 115 (for $C_6H_{15}N_2$, formed by loss of C_4H_7 = 55), 112 (100, for $C_7H_{14}N$, formed by loss of C_3H_8N = 58).

Preparation of 2-(Dimethylamino)ethyl 3-Methyl-3-butenyl Sulfide (11). A solution of 4.4 g (31.1 mmol) of 2-(dimethylamino)ethanethiol in 20 mL of THF was added to a suspension of 2.6 g (66.4 mmol) of NaH (prewashed with petroleum ether) in 60 mL of THF cooled to 0 °C and the resulting mixture stirred for 30 min. A solution of 3.4 g (20.7 mmol) of mesylate **45** in 20 mL of THF was then added to the reaction mixture, which was allowed to warm to rt. After 18 h, the mixture was washed twice with 50-mL portions of 10% aqueous NaOH solution, after which 25 mL of CH_2Cl_2 was added and the resulting solution washed with five 50-mL portions of distilled water. Drying over Na_2SO_4, concentration by rotary evaporation, and distillation under vacuum (0.25 mmHg) yielded thioamine **11** as a colorless distillate at 76 °C (2.8 g, 79% yield): 300-MHz ^1H NMR δ 1.73 (s, 3 H, CCH_3), 2.25 (s, 6 H, $N(CH_3)_2$), 2.29 (d, d, J = 7.7, 7.7, 2 H, CCH_2CH_2S), 2.49 (m, 2 H, SCH_2CH_2N), 2.63 (m, 4 H, $CH_2SCH_2CH_2N$), 4.73 (bs, 1 H, olefin), 4.77 (bs, 1 H, olefin); 75-MHz ^{13}C NMR δ 22.4, 30.2, 30.7, 38.1, 45.6, 59.7, 111.7, 144.6; IR (cm^{-1}) 3070, 2938, 1641, 1454; mass spectrum (EI) m/z 173 (M^+), 129, 106, 58 (100).

Synthesis of 2-(Ethylthio)ethyl 3-Methyl-3-butenyl Sulfide (13). The thioether was prepared from mesylate **45** via alkylation of the sodium salt of 2-mercaptoethanol, followed by formation of the corresponding thioester via Mitsunobu reaction[13] and reduction with LAH–$AlCl_3$ complex.[14]

The sodium salt of 2-mercaptoethanol was prepared by addition of 2.57 mL (37 mmol) of 2-mercaptoethanol into a suspension of 3.1 g (76 mmol) of NaH in 100 mL of THF at 0 °C and stirring for 30 min at 0 °C. A solution of 5.0 g mesylate **45** in 20 mL of THF and a catalytic amount of HMPA (~0.01 mL) was then added and the reaction stirred and allowed to warm to rt overnight. The mixture was then washed with two 100-mL portions of 10% aqueous NaOH solution, diluted with 75 mL of Et_2O, and washed several times with distilled water. The organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation to yield 2-[(3-methyl-3-butenyl)thio]ethanol (**46**) in 57% yield (2.5 g): 300-MHz ^1H NMR δ 1.73 (s, 3 H, CCH_3), 2.29 (t, J = 7.7, 2 H, CCH_2CH_2S), 2.63 (d, d, J = 7.1, 7.7, 2 H, CCH_2CH_2S), 2.74 (t, J = 6.0, 2 H, SCH_2CH_2O), 3.71 (t, J = 6.0, 2 H, SCH_2CH_2O), 4.73 (q, J = 1.1, 1 H, olefin), 4.78 (bs, 1 H, olefin); 75-MHz ^{13}C NMR δ 21.8, 29.7, 34.9, 37.6, 60.4, 111.3, 143.9; IR (cm^{-1}) 3412, 1439, 1187. Anal. Calcd for $C_7H_{14}SO$: C, 57.49; H, 9.65. Found: C, 57.25; H, 9.75.

The procedure of Volante[13] gave 2-[(3-methyl-3-butenyl)thio]ethylthioacetate (**47**) in 99% yield (1.4 g) from 1.0 g (6.9 mmol) of 2-[(3-methyl-3-butenyl)thio]ethanol (**46**): 300-MHz ^1H NMR δ 1.74 (s, 3 H, allylic CH_3), 2.31 (broad t, J = 7.7, 2 H, CCH_2CH_2S), 2.33 (s, 3 H, $C(O)CH_3$), 2.68 (d, d, J = 1.6, 8.2, 2 H, SCH_2CH_2S), 2.70 (d, d, J = 2.2, 8.2, 2 H, SCH_2CH_2S), 3.07 (t, J = 7.7, 2 H, CCH_2CH_2S), 4.74 (d, d, J = 1.1, 1.1, 1 H, olefin), 4.78 (bs, 1 H, olefin).

Reduction of the thioester to the thioether was accomplished using the procedure reported by Bublitz.[14] Sulfide **13** was obtained in 99% yield (0.46 g) from 0.50 g (2.5 mmol) of **47**: 300-MHz ^1H NMR δ 1.26 (t, J = 7.2, 3 H, SCH_2CH_3), 1.74 (s, 3 H, CCH_3), 2.30 (broad t, J = 7.5, 2 H, CCH_2CH_2S), 2.58 (q, J = 7.2, 2 H, SCH_2CH_3), 2.67 (d, d, J = 7.2, 8.1, 2 H, CCH_2CH_2S), 2.74 (s, 4 H, SCH_2CH_2S), 4.74 (bs, 1 H, olefin), 4.78 (bs, 1 H, olefin); 75-MHz ^{13}C NMR δ 14.9, 22.4, 26.2, 30.6, 32.0, 32.4, 38.1, 111.8, 144.4; IR (cm^{-1}) 2959, 1441; mass spectrum (EI) m/z 190 (M^+), 122, 89 (100). Anal. Calcd for $C_9H_{18}S_2$: C, 56.82; H, 9.54. Found: C, 56.80; H, 9.53.

Synthesis of *N*-(3-Methyl-3-butenyl)-*N*,*N*',*N*'-trimethyl-1,3-diaminopropane (15). Prepared following the procedure used for the synthesis of amine **9** using 2.7 g (16.3 mmol) of 3-methyl-3-butenyl-1-methanesulfonate (**45**) and 4.78 mL (32.61 mmol) of *N*,*N*,*N*'-trimethyl-1,3-propanediamine in 5 mL of Et_2O stirred at rt for 6 d. The product was obtained as a clear, colorless distillate at 46 °C under 0.10 mmHg (1.1 g, 36% yield): 300-MHz ^1H NMR δ 1.63 (d, d, d, J = 7.1, 7.7, 7.7, 2 H, $N\text{-}CH_2CH_2CH_2N$), 1.71 (s, 3 H, CCH_3), 2.17 (partly obscured, broad, d, d, J = 7.1, 7.7, 2 H, CCH_2CH_2N), 2.20 (s, 6 H, $N(CH_3)_2$), 2.22 (s, 3 H, NCH_3), 2.26 (d, d, J = 7.7, 8.2, 2 H, CCH_2CH_2N), 2.36 (d, d, J = 7.7, 7.7, 2 H, $NCH_2CH_2CH_2N$), 2.46 (d, d, J = 7.7, 8.2, 2 H, $NCH_2CH_2CH_2N$), 4.68 (bs, 1 H, olefin), 4.72 (bs, 1 H, olefin); 75-MHz ^{13}C NMR δ 22.3, 25.3, 35.1, 41.9, 45.2, 55.6, 56.0, 57.8, 110.7, 144.3; IR (cm^{-1}) 2935, 1631, 1450; mass spectrum (EI) m/z 184 (M^+), 129, 112, 58 (100).

Synthesis of 3-(Dimethylamino)propyl 3-Methyl-3-butenyl Sulfide (17). This substrate was prepared via nucleophilic displacement of mesylate **45** with the sodium salt of 3-mercaptopropanol, mesylation of the resulting alkoxy thioether, and displacement of the mesylate with dimethylamine.

The procedure described for alcohol **46** was used to prepare 3-[(3-methyl-3-butenyl)thio]-1-propanol (**48**) in 64% yield (3.1 g) from 3.6 g (40 mmol) of 3-mercaptopropanol, 3.4 g (85 mmol) of NaH, and 5.0 g (31 mmol) of 3-methyl-3-butenyl-1-methanesulfonate (**45**) in 200 mL of THF: 300-MHz ^1H NMR δ 1.59 (t, J = 5.5, 1 H, –OH), 1.74 (s, 3 H, CCH_3), 1.86 (t, t, J = 7.1, 6.0, 2 H, $SCH_2CH_2CH_2O$), 2.30 (d, d, J = 8.2, 7.7, 2 H, CCH_2CH_2S), 2.65 (m, 4 H, $CH_2SCH_2CH_2CH_2O$), 3.77 (d, t, J = 6.0, 5.5, 2 H, CH_2O), 4.74 (bs, 1 H, olefin), 4.78 (bs, 1 H, olefin).

Mesylation of **48** using the procedure of Crossland and Servis[12] produced 3-[(3-methyl-3-butenyl)thio]-1-propyl-1-methanesulfonate (**49**) in 98% yield.

A solution of 3.5 g of mesylate **49** in 5 mL of Et_2O was cooled to –78 °C in a 20-mL resealable tube under the fume hood, after which dimethylamine was added to the reaction vessel until it was approximately three-fourths full, after which the tube was capped lightly. The tube was then removed from the dry ice bath and allowed to slowly warm to rt. After a few min, the tube was capped tightly and the reaction mixture was stirred overnight at rt, after which the reaction vessel was again cooled to –78 °C in the fume hood, the cap removed, and the reaction allowed to warm to rt. The mixture was washed three times with 15 mL aliquots of saturated aqueous $NaHCO_3$ solution and the solvent distilled off. Amine **17** was obtained as a clear, colorless distillate at 63 °C under 0.10 mmHg (1.5 g, 59% yield): 300-MHz ^1H NMR δ 1.72 (s, 3 H, CCH_3), 1.74 (t, t, J = 7.1, 7.7, 2 H, $SCH_2CH_2CH_2N$), 2.21 (s, 6 H, $N(CH_3)_2$), 2.28 (broad d, d, J = 7.1, 8.2, 2 H, CCH_2CH_2S), 2.33 (d, d, J = 7.1, 7.7, 2 H, $SCH_2CH_2CH_2N$), 2.55 (d, d, J = 7.1, 7.7, 2 H, $SCH_2CH_2CH_2N$), 2.62 (d, d, J = 7.7, 8.2, 2 H, CCH_2CH_2S), 4.72 (bs, 1 H, olefin), 4.76 (bs, 1 H, olefin); 75-MHz ^{13}C NMR δ 21.9, 27.4, 29.7, 30.1, 37.6, 45.2, 58.5, 111.1, 144.2; IR (cm^{-1}) 3061, 2960, 1631, 1450; mass spectrum (EI) m/z

(12) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(13) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.
(14) Bublitz, D. E. *J. Org. Chem.* **1967**, *32*, 1630.

172 (M - 1$^+$), 154, 142, 118, 58 (100). Anal. Calcd for $C_{10}H_{21}SN$: C, 64.11; H, 11.30. Found: C, 63.92; H, 11.19.

Synthesis of 3-(Ethylthio)propyl 3-Methyl-3-butenyl Sulfide (19). A mixture of 2.2 mL (29 mmol) of ethanethiol and 1.4 g (35 mmol) of NaH in 100 mL of THF was stirred at 0 °C for 30 min after which a solution of 4.6 g (20 mmol) of 3-[(3-methyl-3-butenyl)thio]propyl-1-methanesulfonate (**49**) in 10 mL of THF was added and the mixture allowed to warm to rt. After 1 day, the mixture was washed twice with 75-mL portions of 10% aqueous NaOH solution and diluted with 50 mL of Et_2O and the organic layer washed five times with 75 mL of distilled water. Drying over Na_2SO_4, concentration by rotary evaporation, and distillation under vacuum (116 °C, 1.0 mmHg) gave **19** in 61% yield (2.4 g): 300-MHz ^{1}H NMR δ 1.28 (t, J = 7.7, 3 H, SCH_2CH_3), 1.78 (s, 3 H, CCH_3), 1.86 (d, t, J = 7.1, 6.6, 2 H, $SCH_2CH_2CH_2S$), 2.29 (t, J = 7.7, 2 H, CCH_2CH_2S), 2.54 (q, J = 7.7, 2 H, SCH_2CH_3), 2.63 (m, 6 H, $CH_2SCH_2CH_2CH_2S$), 4.73 (bs, 1 H, olefin), 4.78 (bs, 1 H, olefin); 75-MHz ^{13}C NMR δ 15.0, 22.4, 26.1, 29.5, 30.5, 30.7, 31.2, 38.1, 111.7, 144.7; IR (cm^{-1}) 2967, 2922, 1641, 1446; mass spectrum (EI) m/z 204 (M$^+$), 175, 149, 135, 107, 89, 69. Anal. Calcd for $C_{10}H_{20}S_2$: C, 58.77; H, 9.86. Found: C, 58.18; H, 9.92.

Preparation of 3-Butenyl Derivatives. All substrates were prepared from the mesylate of 3-buten-1-ol (**50**), which was prepared in high yield using the procedure of Crossland and Servis.[12]

Synthesis of *N*-(3-Butenyl)-*N*,*N*′,*N*′-trimethyl-1,3-diaminopropane (21). Prepared as described for the synthesis of amine **9** from 0.88 g (5.9 mmol) of 3-butenyl-1-methanesulfonate (**50**) and 1.0 mL (7.1 mmol) of *N*,*N*,*N*′-trimethyl-1,3-propanediamine in 5 mL of Et_2O stirred at rt for 3 d (1.1 g, quantitative): 300-MHz ^{1}H NMR δ 1.64 (d, d, d, d, J = 5.5, 7.1, 7.7, 7.7, 2 H, $NCH_2CH_2CH_2N$), 2.21 (obscured m, 2 H, CCH_2CH_2N), 2.21 (s, 6 H, $N(CH_3)_2$), 2.22 (s, 3 H, NCH_3), 2.27 (d, d, J = 7.7, 7.7, 2 H, $NCH_2CH_2CH_2N$), 2.37 (d, d, J = 7.1, 7.7, 2 H, $NCH_2CH_2CH_2N$), 2.41 (d, d, J = 6.6, 7.7, 2 H, CCH_2CH_2N), 4.99 (d, d, d, d, J = 1.1, 1.1, 3.2, 9.9, 1 H, olefin), 5.05 (d, d, d, d, J = 1.6, 1.6, 3.2, 17.0, 1 H, olefin), 5.79 (d, d, d, d, J = 6.6, 7.1, 9.9, 17.0, 1 H, vinyl); 75 MHz ^{13}C NMR δ 25.3, 31.4, 41.9, 45.3, 55.5, 56.9, 57.8, 115.5, 136.9; IR (cm^{-1}) 2934, 1452; mass spectrum (EI) m/z 170 (M + 1$^+$), 129, 125, 110, 58 (100).

Synthesis of 3-Butenyl 3-(Dimethylamino)propyl Sulfide (24). This substrate was obtained after displacement of 3-butenyl-1-methanesulfonate (**50**) with the sodium salt of 3-mercaptopropanol followed by formation of the corresponding mesylate and reaction with dimethylamine.

The procedure described for alcohol **46** was used to prepare 3-(3-butenylthio)propan-1-ol (**51**) in 99% yield (2.0 g) from 1.4 g (15.7 mmol) of mercaptopropanol, 1.3 g (31.5 mmol) of sodium hydride, and 2.1 g of mesylate **50** (13.7 mmol) in 150 mL of THF stirred at rt for 7 h: 300-MHz ^{1}H NMR δ 1.85 (d, d, d, d, J = 6.0, 6.0, 7.1, 7.1, 2 H, $SCH_2CH_2CH_2O$), 2.34 (broad d, d, d, J = 6.6, 7.7, 7.7, CCH_2CH_2S), 2.59 (t, J = 7.7, CCH_2CH_2S), 2.65 (t, J = 7.1, 2 H, $SCH_2CH_2CH_2O$), 3.76 (t, J = 6.0, 2 H, $SCH_2CH_2CH_2O$), 5.03 (d, d, d, d, J = 1.6, 1.6, 2.2, 9.9, 1 H, olefin), 5.08 (d, d, d, d, J = 1.6, 1.6, 2.2, 17.0, 1 H, olefin), 5.82 (d, d, d, d, J = 6.6, 6.6, 9.9, 17.0, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 28.6, 31.3, 31.7, 33.6, 61.7, 116.0, 136.9; IR (cm^{-1}) 3406, 2982, 1714.

Mesylation of **51** using the procedure of Crossland and Servis[12] gave 3-[(3-butenyl)thio]propyl-1-methanesulfonate (**52**) in 95% yield.

The procedure described for the preparation of amine **17** from mesylate **49** was employed using 1.2 g (5.4 mmol) of mesylate **52** and ~10 mL of dimethylamine in 2 mL of ether stirred at rt overnight which yielded thioamine **24** as a colorless distillate at 54 °C under 0.10 mmHg (0.19 g, 21% yield): 300-MHz ^{1}H NMR δ 1.75 (d, d, d, d, J = 7.1, 7.1, 7.7, 7.7, 2 H, $SCH_2CH_2CH_2N$), 2.23 (s, 6 H, $N(CH_3)_2$), 2.31 (partly obscured, d, d, d, J = 1.6, 1.6, 6.6, 6.6, 2 H, CCH_2CH_2-S), 2.36 (partly obscured, d, d, J = 7.1, 7.7, 2 H, $SCH_2CH_2CH_2N$), 2.57 (d, d, d, J = 6.6, 7.7, 4 H, SCH_2), 5.02 (d, d, d, d, J = 1.6, 1.6, 1.6, 9.9, 1 H, olefin), 5.07 (d, d, d, d, J = 1.6, 1.6, 1.6, 17.0, 1 H, olefin), 5.82 (d, d, d, d, J = 6.6, 6.6, 9.9, 17.0, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 27.5, 29.9, 31.4, 33.8, 45.3, 58.6, 115.9, 137.1; IR (cm^{-1}) 2962, 1188; mass spectrum (EI) m/e 173 (M$^+$), 128, 118, 105, 58 (100).

Synthesis of 3-Butenyl 3-(Ethylthio)propyl Sulfide (27). A 0.87-mL (12 mmol) portion of ethanethiol, 0.42 g (10 mmol) of NaH, 1.3 g (5.8 mmol) of 3-(3-butenylthio)-1-methanesulfonate (**52**), and a catalytic amount of HMPA (~0.01 mL) in 110 mL of THF was stirred at rt overnight using the procedure described for sulfide **19**. Distillation of the crude product under vacuum (0.10 mmHg) gave sulfide **27** in 31% yield (0.34 g) as a colorless distillate at 80 °C: 300-MHz ^{1}H NMR δ 1.24 (t, J = 7.1, 3 H, SCH_2CH_3), 1.86 (d, d, d, d, J = 7.1, 7.1, 7.1, 7.7, 2 H, $SCH_2CH_2CH_2S$), 2.34 (d, d, d, d, d, J = 1.1, 1.6, 1.6, 7.1, 8.8, 2 H, CCH_2CH_2S), 2.51 (q, J = 7.1, 2 H, SCH_2CH_3), 2.58 (d, d, J = 7.1, 7.7, 2 H, $SCH_2CH_2CH_2S$), 2.62 (d, d, J = 7.1, 7.1, 2 H, $SCH_2CH_2CH_2S$), 2.65 (d, d, J = 7.1, 8.8, 2 H, CCH_2CH_2S), 5.03 (d, d, d, d, J = 1.1, 1.1, 1.6, 9.9, 1 H, olefin), 5.08 (d, d, d, d, J = 1.6, 1.6, 1.6, 17.0, 1 H, olefin), 5.83 (d, d, d, d, J = 6.6, 6.6, 9.9, 17.0, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 14.4, 25.6, 29.0, 30.2, 30.7, 31.2, 33.6, 36.5, 36.6, 115.8, 136.8; IR (cm^{-1}) 2962, 1436; mass spectrum (EI) m/z 190 (M$^+$), 179, 161, 135 (100).

Preparation of 4-Pentenyl Derivatives. The substrates described below were derived from 4-pentenyl-1-methanesulfonate (**53**), which was prepared quantitatively using known procedures.[12]

Synthesis of *N*′-(4-Pentenyl)-*N*,*N*′,*N*′-trimethyl-1,3-diaminopropane (32). The protocol given for amine **9** was applied using 1.1 g (6.6 mmol) of 4-pentenyl-1-methanesulfonate (**53**) and 1.2 mL of *N*,*N*,*N*′-trimethyl-1,3-propanediamine in 1 mL of Et_2O stirred for 7 d at rt to give amine **32** in 76% yield (0.92 g) after solvent removal: 300-MHz ^{1}H NMR δ 1.54 (d, d, d, d, J = 7.1, 7.1, 7.7, 7.7, 2 H, $NCH_2CH_2CH_2N$), 1.62 (d, d, d, d, J = 7.1, 7.1, 7.7, 8.2, 2 H, $CCH_2CH_2CH_2N$), 2.04 (d, d, d, d, d, J = 1.1, 1.1, 6.6, 7.2, 8.2, 2 H, $CCH_2CH_2CH_2N$), 2.20 (s, 6 H, $N(CH_3)_2$), 2.26 (d, d, J = 7.1, 7.7, 2 H, $CCH_2CH_2CH_2N$), 2.31 (partly obscured, d, d, d, J = 5.5, 7.7, 7.7, 2 H, $NCH_2CH_2CH_2N$), 2.34 (partly obscured, d, d, d, J = 5.5, 7.1, 7.1, 2 H, $NCH_2CH_2CH_2N$), 4.93 (d, d, d, d, J = 1.1, 1.1, 1.6, 9.9, 1 H, olefin), 5.00 (d, d, d, d, J = 1.6, 1.6, 1.6, 17.0, 1 H, olefin), 5.81 (d, d, d, d, J = 6.6, 6.6, 9.9, 17.0, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 25.4, 26.3, 31.4, 42.1, 45.3, 55.7, 57.1, 57.8, 114.5, 138.8; IR (cm^{-1}) 2932, 1627, 1452; mass spectrum (EI) m/z 184 (M$^+$), 139, 124, 110, 58 (100).

Synthesis of 3-(Dimethylamino)propyl 4-Pentenyl Sulfide (35). The amino thioether was obtained from 4-pentenyl-1-methanesulfonate (**53**) via nucleophilic displacement with the sodium salt of mercaptopropanol followed by mesylation[12] and substitution with dimethylamine.

Reaction of 2.8 g (30 mmol) of 3-mercaptopropanol, 1.5 g of NaH (62 mmol), and 4.1 g (25 mmol) of mesylate **53** in 120 mL of THF with 0.01 mL of HMPA overnight at rt, as described above for alcohol **46**, gave 3-(4-pentenylthio)-1-propanol (**54**) in 99% yield (4.0 g): 300-MHz ^{1}H NMR δ 1.67 (d, d, d, d, J = 7.1, 7.1, 7.7, 7.7, 2 H, $CCH_2CH_2CH_2S$), 1.83 (d, d, d, d, J = 6.0, 6.0, 7.1, 7.1, 2 H, $SCH_2CH_2CH_2O$), 2.14 (broad, d, d, d, J = 6.0, 7.1, 7.7, 2 H, $CCH_2CH_2CH_2S$), 2.52 (t, J = 7.1, 2 H, SCH_2), 2.62 (t, J = 7.1, 2 H, SCH_2), 3.75 (t, J = 6.0, 2 H, $SCH_2CH_2CH_2O$), 4.97 (d, d, d, d, J = 1.1, 1.1, 1.6, 10.4, 1 H, olefin), 5.02 (d, d, d, d, J = 1.6, 1.6, 1.6, 17.0, 1 H, olefin), 5.77 (d, d, d, d, J = 7.1, 7.1, 10.4, 17.0, 1 H, vinyl-H).

Mesylation of thio alcohol **54** to give 3-[(4-pentenylthio)-propyl]-1-methanesulfonate (**55**) was performed using known procedures.[12]

Dimethylamine was stirred with 2.2 g (9.2 mmol) of thioether mesylate **55** in 1 mL of Et_2O for 5 d using the procedure given for amine **17**. Sulfide **35** was obtained in 55% yield (0.95 g) after vacuum distillation (0.10 mmHg) at 69 °C: 300-MHz ^{1}H NMR δ 1.67 (partly obscured, quintet, J = 7.1, 2 H, $SCH_2CH_2CH_2N$), 1.73 (partly obscured, t, t, J = 7.1, 7.7, 2 H, $CCH_2CH_2CH_2S$), 2.14 (d, d, d, d, d, J = 1.6, 1.6, 6.6, 7.7, 7.7, 2 H, $CCH_2CH_2CH_2S$), 2.21 (s, 6 H, $N(CH_3)_2$), 2.33 (t, J = 7.1, 2 H, $SCH_2CH_2CH_2N$), 2.51 (d, d, J = 7.1, 7.1, 2 H, $SCH_2CH_2CH_2N$), 2.52 (d, d, J = 7.1, 7.1, 2 H, $CCH_2CH_2CH_2S$), 4.97 (d, d, d, d, J = 1.6, 1.6, 2.2, 10.4, 1 H, olefin), 5.02 (d, d, d, d, J = 1.6, 1.6, 2.2, 17.0, 1 H, olefin), 5.78 (d, d, d, d, J = 6.6, 6.6, 10.4, 17.0, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 27.4, 28.5, 29.6, 31.2, 32.5, 45.2, 58.5, 115.1, 137.9; IR (cm^{-1}) 2962, 1452; mass spectrum (EI) m/z 187 (M$^+$), 118, 101, 58 (100).

Synthesis of 3-(Ethylthio)propyl 4-Pentenyl Sulfide (38). A mixture of 0.72 g of sodium hydride (18 mmol), 1.5 mL of ethanethiol (20 mmol), and 2.4 g (10 mmol) of mesylate **55** in 100 mL of THF was stirred at rt for 10 h with ~0.10 mL of HMPA, using the method described for sulfide **19**. Distillation under vacuum (0.20 mmHg) gave sulfide **38** as a light yellow distillate

at 118 °C (1.2 g, 57%): 300-MHz ^{1}H NMR δ 1.25 (t, J = 7.7, 3 H, SCH_2CH_3), 1.66 (d, d, d, d, J = 7.1, 7.1, 7.7, 7.7, 2 H, $CCH_2CH_2CH_2S$), 1.84 (d, d, d, d, J = 7.1, 7.1, 7.1, 7.1, 2 H, $SCH_2CH_2CH_2S$), 2.14 (d, d, d, d, d, J = 1.1, 1.6, 6.6, 7.1, 7.1, 2 H, $CCH_2CH_2CH_2S$), 2.50 (t, J = 7.1, 2 H, $SCH_2CH_2CH_2S$), 2.51 (partly obscured, t, J = 7.1, 2 H, $SCH_2CH_2CH_2S$), 2.59 (t, J = 7.1, 2 H, $CCH_2CH_2CH_2S$), (partly obscured, q, J = 7.7, 2 H, SCH_2CH_3), 4.96 (d, d, d, d, J = 1.1, 1.1, 1.6, 13.2, 1 H, olefin), 5.02 (d, d, d, d, J = 1.6, 1.6, 1.6, 17.0, 1 H, olefin), 5.75 (d, d, d, d, J = 6.6, 6.6, 13.2, 17.0, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 14.4, 25.6, 28.4, 29.1, 30.1, 30.6, 31.1, 32.4, 115.1, 137.8; IR (cm^{-1}) 2961, 1627, 1441; mass spectrum (EI) m/z 204 (M$^+$), 175, 135, 107 (100). Anal. Calcd for $C_{10}H_{20}S_2$: C, 58.77; H, 9.86. Found: C, 58.92; H, 9.90.

Pauson–Khand Reactions. The Pauson–Khand reactions were run by characteristically warming a mixture of the olefinic substrate and a 2-fold excess of the corresponding alkyne dicobalt hexacarbonyl complex in toluene at 90–95 °C under an atmosphere of N_2. One equiv of the (alkyne)hexacarbonyldicobalt complex was added to the reaction mixture every 24 h until the reaction was brought to completion. The progress of the reactions was monitored by TLC using mixtures of 10% NH_4OH in MeOH and $CHCl_3$ for the amine reactions and mixtures of hexane and EtOAc for reactions with all other substrates. Upon completion, the mixture was cooled to ambient temperature, and the products were obtained by the employment of one of the workup procedures described below.

Procedure A (Acid–Base Workup). The reaction mixture was cooled to rt, diluted with ether, and washed with 10% aqueous HCl solution (6 × 10 mL). The resulting aqueous layer was washed twice with ether and then neutralized with a 10% aqueous NaOH solution. Extraction with EtOAc (4 × 50 mL), drying over Na_2SO_4, and solvent evaporation gave the crude reaction mixture.

Procedure B (Amine Oxide Extraction Workup).[3c,6] The reaction mixtures were diluted with hexane and passed through a plug of silica gel using hexane as the eluting solvent until the eluent was colorless (maroon cobalt complexes were washed from the plug column). The products were eluted from the plug using a mixture of hexane and EtOAc, followed by concentration by rotary evaporation. The resulting black-brown mixture was diluted with CH_2Cl_2 and stirred with an excess of *N*-methylmorpholine *N*-oxide (NMMO) or trimethylamine *N*-oxide (TMAO) for 20 min or until a color change was noted. The mixture was then transferred into a separatory funnel and washed twice with distilled water or brine, after which the organic layer was dried over Na_2SO_4 and the solvent evaporated to obtain the crude products.

Procedure C (Silica Gel Plug Column). The reaction mixtures were diluted with hexane and passed through a plug of silica gel using hexane as the eluting solvent until the eluent was colorless (maroon cobalt complexes were washed from the plug column). The crude products were then eluted from the plug of silica gel using a mixture of one part 10% ammonia in methanol to three parts chloroform and concentrated by rotary evaporation.

Synthesis of 2-Phenyl-5-[2-[[2-(dimethylamino)ethyl]methylamino]ethyl]-5-methyl-2-cyclopentenone (10). A mixture of 170 mg (1.0 mmol) of *N,N,N′,N′*-(3-methyl-3-butenyl)trimethylethylenediamine (**9**) and 582 mg (1.5 mmol) of cobalt complex **1** was stirred at 93 °C for 1 week, with the addition of 388 mg (1.0 mmol) of complex **1** every 24 h. Workup procedure C was then performed, which gave a black mixture containing cobalt residues. Application of procedure B (TMAO) gave the product as a yellow oil in 10% yield (28 mg). (Note: Comparable yields of products were obtained with workup procedure A): 500-MHz ^{1}H NMR δ 1.19 (s, 3 H, CCH_3), 1.70 (d, d, d, J = 13.3, 10.1, 4.6, 1 H, $CCHCH_2N$), 1.85 (d, d, d, J = 13.3, 10.1, 6.0, $CCHHCH_2N$), 2.20 (s, 3 H, NCH_3), 2.27 (d, d, J = 10.1, 4.6, 1 H, CCH_2CHHN), 2.30 (d, d, J = 10.1, 6.0, 1 H, CCH_2CHHN), 2.35 (m, 2 H, NCH_2CH_2N), 2.42 (m, 2 H, NCH_2CH_2N), 2.49 (d, d, J = 19.7, 3.2, 1 H, 4-*H*), 2.76 (d, d, J = 19.7, 3.2, 1 H, 4-H), 7.31–7.42 (m, 3 H, aromatic), 7.71–7.74 (m, 2 H, aromatic), 7.74 (obscured, t, J = 3.2, 1 H, vinyl-H); IR (cm^{-1}) 2922, 2850, 1690 (CO), 1486; mass spectrum (EI) m/z 300.6 (M$^+$), 242, 199, 171, 115, 58.

Synthesis of 2-Phenyl-5-[2-[[2-(dimethylamino)ethyl]thio]ethyl]-5-methyl-2-cyclopentenone (12). A solution of 86 mg (0.5 mmol) of 2-(dimethylamino)ethyl 3-methyl-3-butenyl sulfide (**11**) and 776 mg (2 mmol) of (phenylacetylene)hexacarbonyldicobalt (**1**) in 5 mL of toluene was heated to 92 °C for 2 d, after which procedure C was employed, followed by procedure B (TMAO) to give a dark yellow oil. Flash chromatography with a 5% solution of (10% NH_4OH–MeOH) in $CHCl_3$ gave the enone product **12** in 36% yield (54 mg): 500-MHz ^{1}H NMR δ 1.21 (s, 3 H, CCH_3), 1.82 (d, d, d, J = 13.2, 11.9, 4.6, 1 H, $CCHHCH_2S$), 1.92 (d, d, d, J = 13.7, 11.9, 5.5, 1 H, $CCHHCH_2S$), 2.35 (s, 6 H, $N(CH_3)_2$), 2.42 (d, d, J = 11.9, 5.5, 1 H, CCH_2CHHS), 2.49 (partly obscured, d, d, J = 19.7, 2.8, 1 H, 4-H), 2.50 (obscured, d, d, J = 11.9, 4.6, 1 H, CCH_2CHHS), 2.60–2.69 (m, 4 H, SCH_2CH_2N), 2.73 (d, d, J = 19.7, 2.8, 1 H, 4-*H*), 7.32–7.41 (m, 3 H, aromatic), 7.71 (broad d, J = 7.3, 2 H, aromatic), 7.76 (d, J = 2.8, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 23.9, 27.5, 30.7, 37.9, 40.2, 43.7, 47.7, 58.0, 127.2, 128.5, 128.6, 128.6, 128.7, 156.6, 231.3; IR (cm^{-1}) 3053, 2957, 1690 (CO), 1487; mass spectrum (EI) m/z 303 (M$^+$), 132 (100), 58.

Synthesis of 2-Phenyl-5-[2-[[2-(ethylthio)ethyl]thio]ethyl]-5-methyl-2-cyclopentenone (14). A mixture of 0.10 g (0.62 mmol) of 2-(ethylthio)ethyl 3-methyl-3-butenyl sulfide (**13**) and 0.48 g (1.2 mmol) of (phenylacetylene)hexacarbonyldicobalt (**1**) in 6.2 mL of toluene was stirred at 90 °C for 28 h, after which workup procedure B was performed (products were eluted using 1:1 EtOAc–hexane), with the products being stirred *overnight* with NMMO in CH_2Cl_2. Flash chromatography using 1:5 EtOAc/hexane as the eluting solvent gave enone **14** in 30% yield (59 mg): 300-MHz ^{1}H NMR δ 1.19 (s, 3 H, CCH_3), 1.24 (t, J = 7.2, 3 H, SCH_2CH_3), 1.80 (d, d, d, J = 13.7, 11.5, 4.9, 1 H, $CCHHCH_2S$), 1.90 (d, d, d, J = 13.7, 11.5, 5.5, 1 H, $CCHHCH_2S$), 2.40 (d, d, d, J = 16.5, 12.6, 5.5, 1 H, CCH_2CHHS), 2.46 (d, d, J = 19.8, 2.7, 1 H, 4-*H*), 2.48 (d, d, d, J = 16.5, 12.6, 4.9, 1 H, CCH_2CHHS), 2.55 (q, J = 7.2, 2 H, SCH_2CH_3), 2.69 (s, 4 H, SCH_2CH_2S), 2.70 (d, d, J = 19.8, 2.7, 1 H, 4-H), 7.36 (m, 3 H, aromatic), 7.70 (m, 2 H, aromatic), 7.75 (t, J = 2.7, vinyl-H); 75-MHz ^{13}C NMR δ 14.5, 23.7, 25.8, 27.1, 31.5, 32.0, 38.2, 40.4, 47.7, 127.2, 128.6, 128.8, 131.8, 141.8, 156.2, 211.0; IR (cm^{-1}) 2989, 2961, 1683 (CO), 1432; mass spectrum (EI) m/z 320 (M$^+$), 172 (100), 89. Anal. Calcd for $C_{18}H_{24}S_2O$: C, 67.47; H, 7.56. Found: C, 67.82; H, 7.11.

Synthesis of 2-Phenyl-5-[2-[[3-(dimethylamino)propyl]methylamino]ethyl]-5-methyl-2-cyclopentenone (16). A mixture of 0.10 g (0.54 mmol) of *N*-(3-methyl-3-butenyl-*N,N′*-*N′*-trimethyl-1,3-diaminopropane (**15**) and 0.42 g of cobalt complex **1** (1.1 mmol) was stirred in 5 mL of toluene at 90 °C for 2.5 d, after which workup procedure A gave enone **16** in 46% yield (79 mg): 500-MHz ^{1}H NMR δ 1.55 (s, 3 H, CCH_3), 1.94 (t, t, J = 7.8, 7.3, 2 H, $NCH_2CH_2CH_2N$), 2.04 (d, d, d, J = 13.3, 10.1, 5.0, 1 H, $CCHHCH_2N$), 2.22 (d, d, d, J = 13.3, 10.1, 6.0, 1 H, $CCHHCH_2N$), 2.53 (s, 3 H, NCH_3), 2.54 (s, 3 H, NCH_3), 2.56 (s, 3 H, NCH_3), 2.58–2.70 (m, 6 H, $CH_2NCH_2CH_2CH_2N$), 2.83 (d, d, J = 19.7, 2.8, 1 H, 4-H), 3.13 (d, d, J = 19.7, 2.8, 1 H, 4-H), 7.67–7.77 (m, 4 H, aromatic), 8.08 (obscured, m, 1 H, aromatic), 8.10 (obscured, t, J = 2.8, vinyl-H); 75-MHz ^{13}C NMR δ 24.3, 25.1, 35.2, 40.2, 41.8, 45.2, 46.7, 53.2, 55.6, 57.7, 127.2, 128.4, 128.5, 132.1, 141.8, 155.7, 211.4; IR (cm^{-1}) 2955, 2810, 1683 (CO), 1437; mass spectrum (EI) m/z 314 (M$^+$), 143, 58 (100).

Synthesis of 2-Phenyl-5-[2-[[3-(dimethylamino)propyl]thio]ethyl]-5-methyl-2-cyclopentenone (18). To a solution of 0.10 g (0.58 mmol) of 3-(dimethylamino)propyl 3-methyl-3-butenyl sulfide (**17**) in 3.0 mL of toluene was added a solution of 0.45 g (1.2 mmol) of cobalt complex **1** in 2.8 mL of toluene, and the resulting mixture was stirred at 93 °C for 24 h. Workup procedure A yielded 86% (0.16 g) of enone **17**: 500-MHz ^{1}H NMR δ 1.99 (s, 3 H, CCH_3), 1.80 (d, d, d, J = 13.7, 11.4, 4.6, 1 H, $CCHHCH_2S$), 1.91 (d, d, d, J = 13.7, 11.4, 5.5, 1 H, $CCHHCH_2S$), 2.22 (obscured, t, J = 8.2, 2 H, $SCH_2CH_2CH_2N$), 2.24 (broad s, 6 H, NCH_3), 3.34 (obscured, d, d, J = 11.4, 5.5, 1 H, CCH_2CHHS), 2.37 (partly obscured, d, d, d, d, J = 8.2, 8.2, 7.3, 7.3, 2 H, $SCH_2CH_2CH_2N$), 2.46 (d, d, J = 11.4, 4.6, 1 H, CCH_2CHHS), 2.49 (obscured, d, d, J = 19.7, 2.8, 1 H, 4-*H*), 2.53 (t, J = 7.3, 2 H, $SCH_2CH_2CH_2N$), 2.72 (d, d, J = 19.6, 2.8, 1 H, 4-H), 7.30–7.40 (m, 3 H, aromatic), 7.70 (m, 2 H, aromatic), 7.75 (t, J = 2.8, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 23.6, 26.9, 27.0, 38.0, 40.2, 44.9, 47.6, 58.1, 127.1, 128.3, 128.4, 131.8, 141.6, 156.2, 211.0; IR (cm^{-1}) 2957, 1723, 1683 (CO), 1451; mass spectrum (EI) m/z 317 (M$^+$), 146, 118, 58 (100).

Synthesis of 2-Phenyl-5-[2-[[3-(ethylthio)propyl]thio]ethyl]-5-methyl-2-cyclopentenone (20). A solution of 204 mg (1 mmol) of 3-(ethylthio)propyl 3-methyl-3-butenyl sulfide (**19**)

and cobalt complex 1 in 5 mL of toluene was stirred at 90 °C. After 1 d, workup procedure B was performed to give a yellow oil which was chromatographed (1:4 EtOAc–hexane) to give enone **20** in 89% yield (298 mg): 300-MHz ^{1}H NMR δ 1.20 (s, 3 H, CCH_3), 1.24 (t, J = 7.1, 3 H, SCH_2CH_3), 1.80 (obscured, d, d, d, J = 13.2, 10.4, 5.5, 1 H, $CCHHCH_2S$), 1.83 (obscured, t, t, J = 7.7, 7.1, 2 H, $SCH_2CH_2CH_2S$), 1.90 (partly obscured, d, d, d, J = 13.2, 11.5, 5.0, 1 H, $CCHHCH_2S$), 2.35 (d, d, d, J = 12.6, 11.5, 5.5, 1 H, CCH_2CHHS), 2.45 (obscured, d, d, d, J = 12.6, 10.4, 5.0, 1 H, CCH_2CHHS), 2.50 (obscured, d, d, J = 19.8, 3.3, 1 H, 4-*H*), 2.51 (q, J = 7.1, 2 H, $S\text{-}CH_2CH_3$), 2.60 (d, d, J = 7.7, 7.1, 4 H, $CCH_2CH_2CH_2S$), 2.72 (d, d, J = 19.8, 3.3, 1 H, 4-H), 7.32–7.42 (m, 3 H, aromatic), 7.72 (d, d, J = 7.7, 2.2, 2 H, aromatic), 7.76 (t, J = 3.3, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 14.2, 23.7, 25.6, 26.9, 28.9, 30.1, 30.6, 48.0, 40.3, 47.7, 111.5, 127.1, 127.2, 128.5, 128.5, 131.8, 141.7, 156.1, 211.2; IR (cm^{-1}) 2955, 1687 (CO), 1443; mass spectrum (EI) m/z 334 (M$^+$), 199, 17 (100). Anal. Calcd for $C_{19}H_{26}S_2O$: C, 68.39; H, 7.83. Found: C, 68.39; H, 7.71.

Synthesis of 2-Phenyl-5-[2-[[3-(dimethylamino)propyl]methylamino]ethyl]-2-cyclopentenone (22) and 2-Phenyl-4-[2-[[3-(dimethylamino)propyl]methylamino]ethyl]-2-cyclopentenone (23). A solution of 50 mg (0.29 mmol) of *N*-(3-butenyl)-*N*,*N*′,*N*′-trimethyl-1,3-diaminopropane (**21**), 0.23 g of cobalt complex **1** (0.59 mmol), and 2.9 mL of toluene was stirred at 88 °C for 2 d, after which employment of workup procedure A yielded an intimate mixture of enones **22** and **23**. The product enones were present in ~2:1 ratio of **22** to **23** based on the relative integrations of the C-3 protons on the 500-MHz ^{1}H spectrum.

Synthesis of 2-Phenyl-5-[2-[[3-(dimethylamino)propyl]thio]ethyl]-2-cyclopentenone (25) and 2-Phenyl-4-[2-[[3-(dimethylamino)propyl]thio]ethyl]-2-cyclopentenone (26). A mixture of 50 mg (0.29 mmol) of 3-butenyl 3-(dimethylamino)propyl sulfide (**24**) and 220 mg of complex **1** (0.58 mmol) in 2.9 mL of toluene was stirred for 6 h at 86 °C. The solution was then subjected to workup protocol A, which gave an inseparable mixture of products **25** and **26** (the ratio of **25** to **26** was found to be ~15:1 based on 300-MHz ^{1}H NMR).

Synthesis of 2-Phenyl-5-[2-[[3-(ethylthio)propyl]thio]ethyl]-2-cyclopentenone (28) and 2-Phenyl-4-[2-[[3-(ethylthio)propyl]thio]ethyl]-2-cyclopentenone (29). A mixture containing 80 mg (0.42 mmol) of 3-butenyl 3-(ethylthio)propyl sulfide (**27**) and 330 mg of complex **1** in 4.2 mL of toluene was warmed to 87 °C and stirred for 1.5 h after which plug workup B (NMMO) was performed and the enones purified by flash chromatography using 1:3 EtOAc–hexane. The enones were obtained in ~9:1 ratio of **28** to **29** (60% isolated yield of both isomers). **2-Phenyl-5-[2-[[3-(ethylthio)propyl]thio]ethyl]-2-cyclopentenone (28)**: 500-MHz ^{1}H NMR δ 1.26 (t, J = 7.3, 3 H, SCH_2CH_3), 1.73 (d, d, d, d, J = 14.2, 8.7, 6.9, 5.5, 1 H, $CCHHCH_2S$), 1.87 (d, d, d, d, J = 7.3, 7.3, 6.9, 6.9, 2 H, $SCH_2CH_2CH_2S$), 2.18 (d, d, d, d, J = 14.2, 8.7, 7.3, 5.5, 1 H, $CCHHCH_2S$), 2.40 (d, d, d, J = 2.8, 2.8, 19.2, 1 H, 4-*CH*H), 2.54 (q, J = 7.3, 2 H, SCH_2CH_3), 2.63 (obscured, t, J = 7.3, 2 H, $SCH_2CH_2CH_2S$), 2.65 (obscured, d, d, J = 7.3, 6.9, 2 H, $SCH_2CH_2CH_2S$), 2.70 (obscured, d, d, d, J = 19.7, 8.7, 3.2, 1 H, CCH_2CHHS), 2.72 (obscured, d, d, d, J = 2.8, 2.8, 19.2, 1 H, 4-H), 2.73 (obscured, m, 1 H, 5-H), 2.94 (d, d, d, J = 19.7, 6.9, 3.2, 1 H, CCH_2CHHS), 7.31–7.41 (m, 3 H, aromatic), 7.70 (m, 2 H, aromatic), 7.78 (t, J = 2.8, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 14.5, 25.7, 29.1, 29.6, 30.3, 30.6, 31.2, 32.9, 45.4, 127.2, 127.4, 128.4, 128.5, 128.6, 131.8, 143.0, 157.2, 209.1; IR (cm^{-1}) 2961, 1728, 1684 (CO) 1437; mass spectrum (EI) m/z 320 (M$^+$), 135 (100), 58.

Synthesis of 2-Butyl-5-[2-[[3-(ethylthio)propyl]thio]ethyl]-2-cyclopentenone (30) and 2-Butyl-4-[2-[[3-(ethylthio)propyl]thio]ethyl]-2-cyclopentenone (31). A mixture of 50 mg (0.26 mmol) of bisthioether **27** and 160 mg (0.53 mmol) of cobalt complex **2** in 2.6 mL of toluene was stirred at 86 °C for 1.75 h, after which plug workup B (NMMO) and column chromatography (1:9 EtOAc–hexane) gave 63 mg (80% yield) of enone **30** and 4 mg of a mixture of both **30** and **31** (>40:1 ratio of **30** to **31**). **2-Butyl-5-[2-[[3-(ethylthio)propyl]thio]ethyl]-2-cyclopentenone (30)**: 500-MHz ^{1}H NMR δ 0.90 (t, J = 7.3, 3 H, $CCH_2CH_2CH_2CH_3$), 1.25 (t, J = 7.3, 3 H, SCH_2CH_3), 1.32 (t, q, J = 7.3, 7.3, 2 H, $CCH_2CH_2CH_2CH_3$), 1.45 (m, 2 H, $CCH_2CH_2CH_2CH_3$), 1.61 (d, d, d, d, J = 14.2, 8.7, 5.5, 5.0, 1 H, $CCHHCH_2S$), 1.86 (quintet, J = 7.3, 2 H, $SCH_2CH_2CH_2S$), 2.07 (d, d, d, d, J = 14.2, 9.2, 6.9, 5.0, 1 H, $CCHHCH_2S$), 2.16 (d, d, d, d, d, J = 7.3, 5.5, 1.8, 1.8, 1.4, 2 H, $CCH_2CH_2CH_2CH_3$), 2.22 (d, d, d, d, d, J = 18.3, 2.3, 1.8, 1.8, 1.4, 1 H, 4-H), 2.50 (d, d, d, d, J = 8.2, 6.9, 5.0, 2.3, 1 H, 5-H), 2.54 (q, J = 7.3, 2 H, SCH_2CH_3), 2.63 (m, 6 H, SCH_2), 2.77 (d, d, d, d, d, J = 18.3, 8.2, 6.4, 1.8, 1.8, 1 H, 4-*H*), 7.23 (d, d, t, J = 2.3, 1.8, 1.4, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 13.5, 14.5, 22.2, 24.3, 25.7, 29.1, 29.6, 29.7, 30.3, 30.6, 31.6, 33.2, 44.3, 146.1, 155.7, 211.4; IR (cm^{-1}) 2951, 1686 (CO), 1446; mass spectrum (EI) m/z 300 (M$^+$), 165, 135 (100). Anal. Calcd for $C_{16}H_{28}S_2O$: C, 63.97; H, 9.40. Found: C, 64.03; H, 9.42.

Synthesis of 2-Phenyl-5-[3-[[3-(dimethylamino)propyl]methylamino]propyl]-2-cyclopentenone (33) and 2-Phenyl-4-[3-[[3-(dimethylamino)propyl]methylamino]propyl]-2-cyclopentenone (34). A mixture of 0.27 mmol of *N*-(4-pentenyl)-*N*,*N*′,*N*′-trimethyl-1,3-diaminopropane (**32**, 50 mg) and 0.54 mmol (210 mg) of cobalt complex **1** in 2.7 mL of toluene was heated to 90 °C and stirred for 2 d. Enones **33** and **34** (48 mg, 56%) were obtained as an intimate mixture (~3:1 ratio of **33** to **34** by 500-MHz NMR) after employment of workup procedure A.

Synthesis of 2-Phenyl-5-[3-[[3-(dimethylamino)propyl]thio]propyl]-2-cyclopentenone (36) and 2-Phenyl-4-[3-[[3-(dimethylamino)propyl]thio]propyl]-2-cyclopentenone (37). A mixture of 50 mg (0.27 mmol) of 3-(dimethylamino)propyl 4-pentenyl sulfide and 210 mg (0.54 mmol) of phenylacetylene cobalt complex **1** in 2.7 mL of toluene at 85 °C was stirred for 3 d followed by employment of workup procedure A. Enones **36** and **37** were obtained (83% yield, 70 mg) as a chromatographically inseparable mixture (~4.5:1 ratio of **36** to **37** by 500-MHz NMR).

Synthesis of 2-Phenyl-5-[3-[[3-(ethylthio)propyl]thio]propyl]-2-cyclopentenone (39) and 2-Phenyl-4-[3-[[3-(ethylthio)propyl]thio]propyl]-2-cyclopentenone (40). Plug workup B (NMMO) was performed on a mixture of 50 mg (0.24 mmol) of 3-(ethylthio)propyl 4-pentenyl sulfide (**38**) and 190 mg (0.49 mmol) of cobalt complex **1** which was stirred in 2.4 mL of toluene at 85 °C for 1.5 d. The crude product (which contained **39** and **40** in a 2.4:1 ratio by integration of 500-MHz ^{1}H NMR resonances was purified by flash chromatography (1:9 EtOAc–hexane), which gave 37% (32 mg) of pure enone **39** and 11% (10 mg) of pure enone **40** (53% combined isolated yield). **2-Phenyl-5-[3-[[3-(ethylthio)propyl]thio]propyl]-2-cyclopentenone (39)**: 500-MHz ^{1}H NMR δ 1.27 (t, J = 7.7, 3 H, SCH_2CH_3), 1.56 (d, d, d, d, J = 12.6, 6.6, 5.5, 4.4, 1 H, $CCHCH_2CH_2S$), 1.70 (d, d, d, d, J = 7.7, 7.1, 6.6, 6.6, 2 H, $CCH_2CH_2CH_2S$), 1.85 (quintet, J = 7.1, 2 H, $SCH_2CH_2CH_2S$), 2.6 (d, d, d, d, J = 12.6, 7.1, 6.6, 4.4, 1 H, $CHHCH_2CH_2S$), 2.39 (d, d, d, J = 19.2, 2.7, 2.7, 1 H, 4-*H*), 2.53 (q, J = 7.7, 2 H, SCH_2CH_3), 2.55 (obscured, m, 1 H, 5-H), 2.56 (obscured, t, J = 7.1, 2 H, $SCH_2CH_2CH_2S$), 2.62 (d, d, J = 7.7, 6.6, 4 H, $CCH_2CH_2CH_2SCH_2$), 2.91 (d, d, d, J = 19.2, 6.6, 2.7, 1 H, 4-*H*), 7.29–7.42 (m, 3 H, aromatic), 7.71 (m, 2 H, aromatic), 7.79 (t, J = 2.7, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 14.5, 25.8, 27.2, 29.2, 30.4, 30.7, 30.9, 31.9, 33.1, 46.1, 127.2, 127.3, 128.6, 131.9, 143.1, 157.4, 209.4; IR (cm^{-1}) 2998, 1690 (CO); mass spectrum (EI) m/z 334 (M$^+$), 135 (100). **2-Phenyl-4-[3-[[3-(ethylthio)propyl]thio]propyl]-2-cyclopentenone (40)**: 500-MHz ^{1}H NMR δ 1.27 (t, J = 7.1, 3 H, SCH_2CH_3), 1.60 (d, d, d, J = 10.4, 9.9, 2.2, 1 H, $CCHHCH_2S$), 1.71 (obscured, d, d, d, d, d, J = 10.4, 9.9, 6.6, 2.7, 2.2, 1 H, 4-H), 1.73 (partly obscured, quintet, J = 7.7, 2 H, $CCH_2CH_2CH_2S$), 1.86 (broad quintet, J = 7.1, 2 H, $SCH_2CH_2CH_2S$), 2.25 (d, d, J = 18.7, 2.2, 1 H, 5-*H*), 2.52 (q, J = 7.1, 2 H, SCH_2CH_3), 2.57 (t, J = 7.1, 2 H, $SCH_2CH_2CH_2S$), 2.63 (d, d, J = 7.7, 7.1, 4 H, $CCH_2CH_2CH_2SCH_2$), 2.78 (d, d, J = 18.7, 6.6, 1 H, 5-*H*), 7.32–7.42 (m, 3 H, aromatic), 7.68 (m, 2 H, aromatic), 7.74 (d, J = 2.7, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 14.5, 22.3, 25.8, 27.4, 29.2, 30.9, 31.9, 33.9, 37.9, 42.5, 127.3, 128.6, 128.7, 143.2, 162.1, 207.1; IR (cm^{-1}) 2987, 1693 (CO); mass spectrum (EI) m/z 334 (M$^+$), 135 (100).

Synthesis of 2-Butyl-5-[3-[[3-(ethylthio)propyl]thio]propyl]-2-cyclopentenone (41) and 2-Butyl-4-[3-[[3-(ethylthio)propyl]thio]propyl]-2-cyclopentenone (42). A mixture of 50 mg (0.24 mmol) of bisthioether **38** and 151 mg (0.49 mmol) of complex **2** in 2.5 mL of toluene was stirred at 88 °C for 2 d, after which plug workup B (NMMO) was performed. Purification by flash chromatography (1:9 EtOAc–hexane) gave 15 mg of enone **41** and 14 mg of a mixture of **41** and **42** (44% isolated yield, 3:1

ratio of 41 to 42 by NMR). **2-Butyl-5-[3-[[3-(ethylthio)-propyl]thio]propyl]-2-cyclopentenone (41)**: 500-MHz ^{1}H NMR δ 0.89 (t, J = 7.3, 3 H, $CCH_2CH_2CH_2CH_3$), 1.24 (t, J = 7.3, 3 H, SCH_2CH_3), 1.31 (q, t, J = 7.3, 6.9, 2 H, $CCH_2CH_2CH_2CH_3$), 1.43 (m, 2 H, $CCH_2CH_2CH_2CH_3$), 1.63 (obscured, m, 1 H, $CCHHCH_2CH_2S$), 1.64 (partly obscured, t, t, J = 7.3, 6.9, 2 H, $CCH_2CH_2CH_2S$), 1.85 (quintet, J = 6.9, 2 H, $SCH_2CH_2CH_2S$), 1.87 (obscured, m, 1 H, $CCHHCH_2CH_2S$), 2.15 (d, d, d, d, d, J = 9.2, 7.3, 3.2, 1.8, 1.8, 2 H, $CCH_2CH_2CH_2CH_3$), 2.21 (d, d, d, d, d, J = 18.8, 3.2, 3.2, 2.3, 2.3, 1 H, 4-*H*), 2.53 (q, J = 7.3, 2 H, SCH_2CH_3), 2.54 (t, J = 7.3, 2 H, $CCH_2CH_2CH_2S$), 2.60 (t, J = 6.9, 2 H, $SCH_2CH_2CH_2S$), 2.62 (t, J = 6.9, 2 H, $SCH_2CH_2CH_2S$), 2.74 (d, d, d, d, J = 18.8, 9.2, 4.6, 2.3, 2.3, 2 H, 4-*H*), 7.23 (d, d, t, J = 3.2, 2.3, 1.8, 1 H, vinyl-H); 75-MHz ^{13}C NMR δ 13.5, 14.5, 22.2, 24.3, 25.7, 27.2, 29.2, 29.7, 30.3, 30.6, 30.8, 31.9, 33.3, 44.9, 146.1, 155.9, 211.8; IR (cm^{-1}) 2949, 1683 (CO), 1445; mass spectrum (EI) m/z 314 (M$^+$), 179 (100).

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Supplementary Material Available: Preparation of cobalt complexes 1 and 2, preparation of thioacetate 47, preparation and spectral data for sulfide 13, and NMR data for mesylates 45, 49, 50, 52, 53 and 55 (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Structures of Breynins A and B, Architecturally Complex, Orally Active Hypocholesterolemic Spiroketal Glycosides

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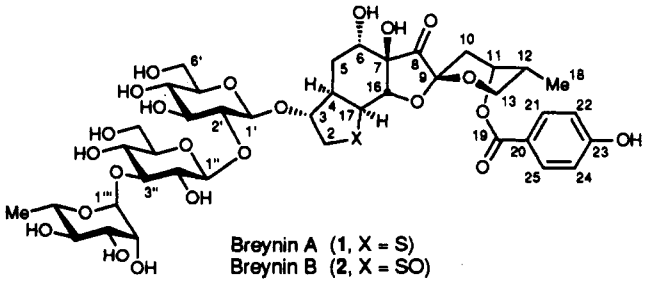
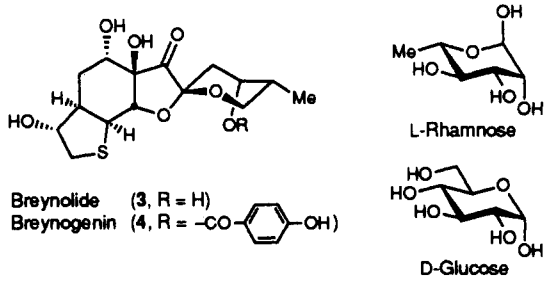
Breynin A and its oxy congener, breynin B, were reisolated from the woody portion of the Taiwanese shrub *Breynia officinalis* Hemsl and formulated as 1 and 2, respectively. An arsenal of NMR techniques including DEPT, heteronuclear chemical shift correlation, ^{1}H–^{1}H COSY, and inverse long-range ^{1}H–^{13}C experiments were employed. Of particular importance for the NMR study was the preparation of breynin A undecaacetate (11). The analysis independently generated structure 1, confirming the assignment for breynin A recently reported by Ohkuma et al. However, spectral data and direct oxidation of breynin A to B demonstrated that the latter is not the hemithioacetal 8 as suggested by Ohkuma, but rather the isomeric sulfoxide 2. Improved purification of the *Breynia* glycosides via droplet counter-current distribution and HPLC is also described.

In 1973, Hirata at Nagoya University, in collaboration with Sasaki at the Bristol-Myers Institute (Tokyo), reported the isolation of two sulfur-containing glycosides, breynins A and B (1 and 2), from the Taiwanese woody shrub *Breynia officinalis* Hemsl.[1] Initial screening demonstrated that both 1 and 2 are potent hypocholesterolemic agents,[2] reducing serum cholesterol in rats by 20–35% upon interperitoneal injection of 0.005–0.025 mg/kg/d. More recently, Trost discovered that the breynins are orally active, lowering rat serum cholesterol by 30–60% after ten daily doses of 10–20 mg/kg.[3]



Breynin A (1, X = S)
Breynin B (2, X = SO)

Exhaustive hydrolysis of breynin A afforded breynolide (3) along with D-glucose (2 equiv), L-rhamnose, and *p*-hydroxybenzoic acid.[1,4] The structure of 3 was secured via single-crystal X-ray analysis.[1,5] Also isolated was the parent aglycon breynogenin (4) which embodied the *p*-hydroxybenzoate unit.[4] Degradation and NMR studies employing the tri- and tetraacetate derivatives of 4 then demonstrated that the benzoate moiety was incorporated as a C(11) ester.[4] The critical connectivity of the saccharide units, however, remained unknown; only the C(7) tertiary hydroxyl was eliminated as a point of attachment via the observation of the hydroxyl proton as a singlet in the NMR spectrum of 1 in DMSO-d_6.



Breynolide (3, R = H)
Breynogenin (4, R = –CO–C$_6$H$_4$–OH)

L-Rhamnose

D-Glucose

Our interest in the breynins was initially stimulated by the structural similarity of breynolide (3) to phyllanthocin (5),[6] the aglycon methyl ester of the phyllanthoside anti-

(1) Sasaki, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, *14*, 2439.
(2) Koshiyama, H.; Hatori, M.; Ohkuma, H.; Fumihide, S.; Imanishi, H.; Ohbayashi, M.; Kawaguchi, H. *Chem. Pharm. Bull.* **1976**, *24*, 169.
(3) Trost, W. *IRCS Med. Sci.* **1986**, *14*, 905.
(4) Sakai, F.; Ohkuma, H.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *Chem. Pharm. Bull.* **1976**, *24*, 114.
(5) Sasaki, K.; Hirata, Y. *Acta Crystallogr.* **1974**, *B30*, 1347.
(6) Kupchan, S. M.; La Voie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199.

0022-3263/92/1957-5115$03.00/0