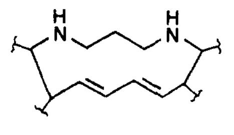
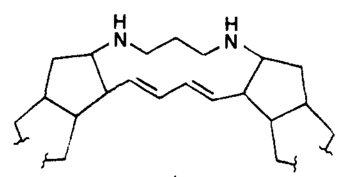
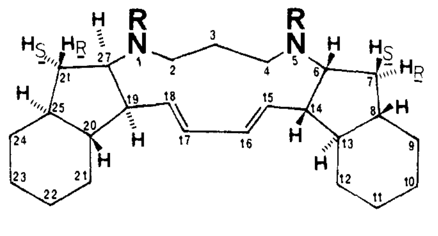
These data delineate part structure **a**.



a



b



1 R = H

2 R = H_2^+ Cl$^-$

3 R = Ac

Only 12 ^{13}C NMR signals are observed: ten (δ 136.02–30.79) represent two carbons each; a triplet at δ 27.04 integrates for one, a triplet at δ 24.60 for four carbons.[5] Papuamine (**1**) therefore is a pentacyclic diamine symmetrical about a line through the central methylene (δ 27.04) and bisecting the C-16,17 bond (C_2 symmetry axis). COSY, RCT[8] (Tables I and II, Supplementary Material), and 2D INADEQUATE (Table III, Supplementary Material) experiments allowed expansion to part structure **b**, which is compatible with **1** or a cage structure, where C-10 is bonded to C-23 or C-22 and C-11 to C-22 or C-23. Observed coupling between C-10,11 (or C-22,23) methylenes eliminates the cage structure. A 2D NOE experiment (Table IV, Supplementary Material) allowed stereochemical assignments, and heteronuclear correlation data (Table V, Supplementary Material) confirmed the structure. Figure 1 summarizes the essential data from Tables I–V (Supplementary Material).

Evidence that the natural compound is a dihydrochloride derives from treatment of **2** with triethylamine in methanol, yielding crystalline triethylammonium chloride, and by quantitative high performance ion chromatography.[9]

A Dreiding model of papuamine (**2**) reveals a flexible 13-membered ring, which allows many spatial arrangements of the two trans hydrindanes. This unique alkaloid bears no biogenetic resemblance to other known *Haliclona* metabolites, polymeric alkylpyridines,[10] irregular sesquiterpenes,[11] or a complex polycyclic alkaloid.[12]

Acknowledgment. We thank Dr. Don Gerhart for help with the field collection; Professor P. Bergquist for identification of the sponge; Helen Karuso for antifungal assays; the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln for mass measurements; Dr. Robin Kinnel for helpful discussions; the Department of Environment and Conservation, Government of Papua New Guinea for permission to collect the sponge; the staff of the Motopore Island Research Station of the University of Papua New Guinea for assistance with field work; the Dionex Corporation for the loan of an HPIC instrument; the National Science Foundation; and the University of Hawaii Sea Grant College Program under Institutional Grant NA81AA-D-0070 from NOAA, Office of Sea Grant, U.S. Department of Commerce for financial support.

Supplementary Material Available: Tables I–V of ^{1}H–^{1}H correlation of **1** and **2**, ^{13}C–^{13}C connectivity of **1**, NOE of **2**, and ^{1}H–^{13}C correlation of **1** (4 pages). Ordering information is given on any current masthead page.

(8) RCT = relay coherence transfer: Bax, A; Drobny, G. *J. Magn. Reson.* **1985**, *61*, 306–320.

(9) Carried out with a Dionex AS4A column, eluted with 2.0 mM Na_2CO_3/0.75 mM $NaHCO_3$, 12.5 mM H_2SO_4 suppressor, conductivity detection. Papuamine dihydrochloride (**2**) prepared from **1** (440 ppm) was compared with NaCl (993 ppm). In three runs the retention times of **2** varied from 3.25 to 3.45 min, the area from 54.6 to 57.6 mm^2, while those of NaCl varied from 3.45 to 3.55 min, and the areas from 135.0 to 140.7 mm^2.

(10) Schmitz, F. J.; Hollenbeak, K. H.; Campbell, D. C. *J. Org. Chem.* **1978**, *43*, 3916–3922.

(11) Capon, R. J.; Ghisalberti, E. L.; Jefferies, P. R. *Tetrahedron* **1982**, *38*, 1699–1703.

(12) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405.

Stereospecific Replacement of Sulfur from Chiral γ-Arylsulfanylbutyrolactones. Synthesis of Optically Pure Ring-Fused γ-Butyrolactones

Joseph P. Marino,* Edgardo Laborde, and Robert S. Paley

Department of Chemistry, The University of Michigan Ann Arbor, Michigan 48109

Received August 3, 1987

The transfer of chirality from sulfur to carbon has become a useful tool in asymmetric synthesis. Particularly notable in this area is the use of a chiral sulfinyl group to induce asymmetry in adjacent carbon centers.[1] Within this context, we have reported that γ-arylsulfanyl-γ-butyrolactones can be prepared in optically pure form and in useful yields by an enantiospecific [3,3] sigmatropic rearrangement of chiral vinyl sulfoxides with ketenes.[2,3] A distinctive feature of this new lactonization reaction is the transfer of chirality from sulfur to as many as three contiguous carbon centers.[2b]

In order to extend the synthetic utility of the sulfoxide-directed lactonization, we investigated the stereospecific replacement of the sulfur auxiliary from the newly created chiral γ-arylsulfanylbutyrolactones. Our first expectation was that an intramolecular substitution of the arylsulfanyl moiety by a carbon-based group would result in the formation of a ring-fused butyrolactone in optically active form. Such a strategy would be very valuable in the synthesis of naturally occurring sesquiterpene lactones. In this paper, we report that a variety of chiral ring-fused butyrolactones **4** can be prepared in a stereocontrolled fashion as outlined in Scheme I. Method A proceeds by homolytic cleavage of the γ-carbon–sulfur bond and subsequent intramolecular trapping of the resulting α-acyloxy radical.[4,5] Method B, on the other hand, formally involves an oxygen-assisted ionization of the arylsulfanyl group and a nucleophilic attack at the newly generated α-acyloxy carbocation. Method A is best suited for the synthesis of cis fused cyclopentabutyrolactones, whereas method B is the preferred route

(1) Reviews: (a) Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Part A, p 184. (b) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Part A, p 225. (c) Bravo, P.; Resnati, G. In *Perspectives in the Organic Chemistry of Sulfur*; Zwanenburg, B.; Klunder, A. J. H., Eds.; Elsevier: Amsterdam, 1987; p 89.

(2) (a) Marino, J. P.; Neisser, M. *J. Am. Chem. Soc.* **1981**, *103*, 7687. (b) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643. (c) Marino, J. P.; Fernández de la Pradilla, R. *Tetrahedron Lett.* **1985**, *26*, 5381. (d) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *Synthesis* **1987**, in press.

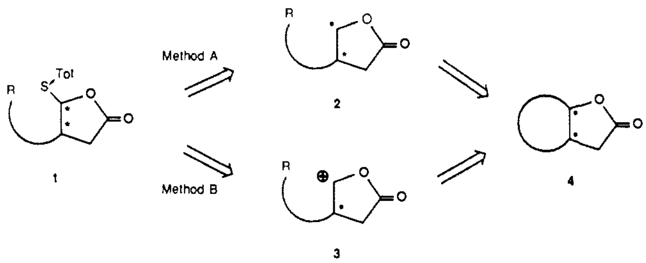
(3) For a review on chirality transfer via sigmatropic rearrangements, see: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: FL, 1984; Vol. 3, Part B, p 203.

(4) Review on radical cyclizations: (a) Giese, B. In *Organic Chemistry Series*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1986; Vol. 5, p 141. (b) Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2, p 121. (c) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.

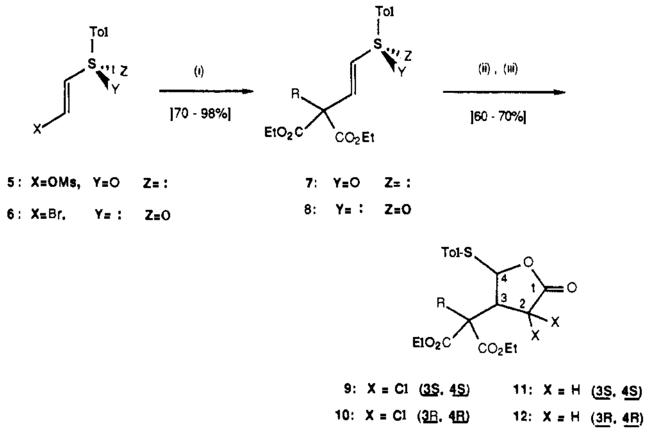
(5) For an analogous cyclization involving α-acylamino radicals, see: (a) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430. (b) Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1982**, *23*, 4765.

0002-7863/88/1510-0966$01.50/0

Scheme I



Scheme II[a]



[a]Reagents: (i) $(EtO_2C)_2CHR$, NaH, THF, 25 °C; (ii) Cl_3CCOCl, Zn(Cu), THF, 0 °C; (iii) Al(Hg), THF-MeOH-H_2O or Zn(Cu), THF-H_2O.

to cis fused cyclohexabutyrolactones or trans fused cycloheptabutyrolactones.

The starting γ-arylsulfanylbutyrolactones were prepared in optically pure form as illustrated in Scheme II. The (*E*)-β-malonylvinyl sulfoxides **7** and **8**, obtained by addition–elimination of a diethyl malonate derivative onto the chiral sulfoxides **5** and **6**, respectively,[6] were treated with dichloroketene to afford the corresponding γ-*p*-tolylsulfanyl-α,α-dichlorobutyrolactones **9** and **10**. Selective removal of the chlorine atoms with zinc–copper couple or aluminum amalgam then provided the desired (3*S*,4*S*)- or (3*R*,4*R*)-γ-*p*-tolylsulfanyl-γ-butyrolactones **11** and **12**, respectively, in good overall yield. The R group in these compounds was chosen so as to bear an aromatic ring or double or triple bond that would act as the radical trap or the nucleophile in the subsequent cyclization reaction (Scheme II).

Treatment of γ-*p*-tolylsulfanylbutyrolactones **11a–c** with tri-*n*-butyltin hydride and a catalytic amount of AIBN in toluene (Table I, entries 1–3) resulted in the isolation of the five- and six-membered ring-fused butyrolactones **13–15** in good to excellent yields.[7]

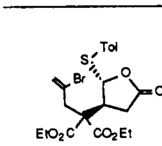
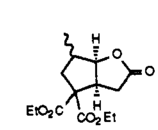
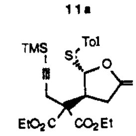
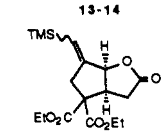
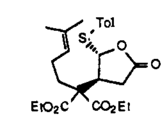
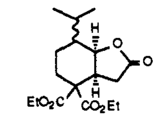
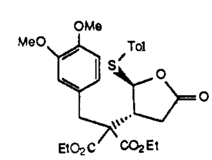
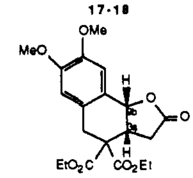
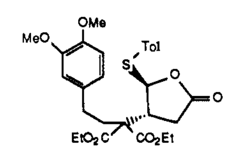
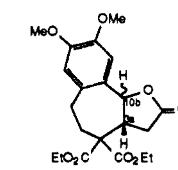
Several aspects of the results presented in Table I are noteworthy. In particular, lactone **11a** possessing a bromovinyl appendage provided a 1:2 ratio of epimeric 2-oxabicyclo[3.3.0]octan-3-ones **13** and **14**, respectively, in an 87% combined yield. It should be noted that two different radicals could have been generated from a system like **11a**: a vinyl radical or an α-acyloxy radical. The products obtained, however, suggest that the reaction proceeded exclusively via the oxygen-stabilized radical to give a tertiary bromide, from which the bromine atom was finally displaced by excess tin hydride.

The cyclization of γ-arylsulfanylbutyrolactone **11b**, bearing a trimethylsilyl-substituted triple bond, gave an 85% yield of vinylsilanes **15** and **16**.[5] The structures of these regioisomers were confirmed by protodesilylation with iodine in refluxing aqueous

(6) The preparation of the chiral β-substituted vinyl sulfoxides **5–8** will be described in full in due course.

(7) All new compounds gave satisfactory spectroscopic (IR, ^1H NMR, ^{13}C NMR, mass spectral) and microanalytical and/or high resolution mass data.

Table I. Cyclization of γ-Arylsulfanylbutyrolactones

Arylsulfanyllactone	Method[a]	Product(s)	Yield[b] (Ratio)[c]
 **11a**	A	 **13-14**	87% (α/β = 1 : 2)
 **11b**	A	 **15-16**	85% (E/Z = 1.3 : 1)
 **11c**	A	 **17-18**	55% (α/β = 4.5 : 1)
 **12a**	B	 **19**	85%
 **12b**	B	 **20-21**	94% (trans/cis = 10 : 1)

[a]Method A: freshly distilled *n*-Bu_3SnH (1.1–1.5 equiv) was added dropwise to a solution of arylsulfanyllactone and AIBN (0.1 equiv. in toluene (5 mL/mmol), and the mixture was refluxed for 12–24 h. Method B: to a solution of arylsulfanyllactone in toluene (20 mL/mmol) was added dropwise a 0.05 M solution of *n*-Bu_3SnOTf (1.2–1.5 equiv), and the mixture stirred at 40–50 °C for 15–30 min. [b]Yields refer to isolated products after chromatographic purification. [c]Ratios refer to isomeric products and are based on 360-MHz ^1H NMR analysis of the reaction mixtures.

benzene,[8] followed by ozonolysis of the resulting single alkene to give the corresponding keto lactone.[9]

In an attempt to delineate the effect of ring size on the outcome of this radical cyclization, lactone **11c** was treated with tributyltin hydride. The epimeric 2-oxabicyclo[3.4.0]nonan-3-ones **17** and **18** were isolated from this reaction in a 4.5:1 ratio, respectively, and in a 55% combined yield. The lower yield of cyclized products has been attributed to the less favored cyclization of the 6-heptenyl radical generated from **11c**. The thermodynamically more stable cis ring juncture in compounds **17** and **18** is supported by the spectroscopic data.

To carry forward the ionic mechanism of the cyclization, we treated γ-arylsulfanylbutyrolactones **12a,b** (Table I) with various Lewis acids; whereas the initial attempts with $BF_3 \cdot Et_2O$ or $AlCl_3$ were unsuccessful,[10] the reaction of γ-arylsulfanylbutyrolactone **12a** with tri-*n*-butyltin triflate in toluene provided a *single* isomer of the tricyclic product **19** in an 85% isolated yield.[11,12] The cis

(8) Utimoto, K.; Kitai, M.; Nozaki, H. *Tetrahedron Lett.* **1975**, *33*, 2825. Direct ozonolysis of the vinylsilanes produced a complex mixture of products (cf. Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* **1978**, *100*, 294).

(9) The optical purity of the keto lactone (>99%) was determined with the use of a chiral shift reagent, Eu(hfc)$_3$.

(10) In addition, oxidation of the tolylsulfanyl group in **12a** with 2 equiv of mCPBA and reaction of the resulting sulfone with $EtAlCl_2$ did not afford the desired cyclized product. For a similar successful transformation, see: Trost, B. M.; Ghadiri, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7260.

(11) For a stereospecific displacement of a phenylsulfanyl group with tributyltin triflate, see: Keck, G. E.; Enholm, E. J.; Kachensky, D. F. *Tetrahedron Lett.* **1984**, 1867.

(12) More recently it has been discovered that the cyclization of tolylsulfanylbutyrolactones **12a,b** proceeds with triflic acid alone.

ring fusion of **19** was assigned on the basis of the strong (13%) NOE observed between the angular hydrogens H_{3a} (apparent q at δ 3.71, J = 10.1, 8.2, 9.6 Hz, $CDCl_3$) and H_{9b} (d at δ 5.82, J = 8.1 Hz). Treatment of **12b** with tributyltin triflate, on the other hand, produced a ca. 10:1 mixture of the trans and cis ring fused lactones **20** and **21**, respectively, in a 94% combined yield. The stereochemical assignment for these isomeric lactones was done on the basis of comparative ^1H NMR DNOE experiments.[13] Specifically, the observed NOE between the angular hydrogens H_{3a} and H_{10b} is 3% in the major isomer **20** and 17% in the minor isomer **21**, indicating a trans and a cis relationship, respectively.

The stereospecific intramolecular replacement of the sulfur atom from γ-arylsulfanylbutyrolactones via α-acyloxy radicals or α-acyloxy carbocations, then, broadens the range of application of the chiral sulfoxide-directed lactonization reaction. In addition, the present methodology provides a nontraditional entry into ring-fused lactones, for it allows the stereospecific construction of a carbocyclic ring onto a preformed lactone.

Acknowledgment. We thank Frank Parker for performing the NOE experiments and Professor John R. Wiseman for valuable comments. This work was supported by the National Institutes of Health (CA 22237) and the National Science Foundation Instrumentation Program.

Supplementary Material Available: Characterization data (IR, ^1H NMR, ^{13}C NMR, mass spectra, optical rotation, exact mass and/or element analysis) for lactones **13–21** (3 pages). Ordering information is given on any current masthead page.

(13) The coupling constant between the two bridgehead protons is essentially the same in both compounds (J = 9.5 Hz in the major isomer and 9.7 Hz in the minor isomer) and therefore was not diagnostic of the relative stereochemistry at the ring junction.

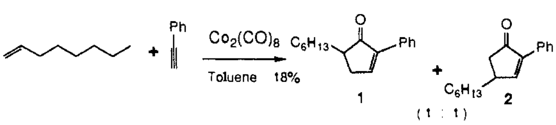
Regiocontrol in the Intermolecular Cobalt-Catalyzed Olefin–Acetylene Cycloaddition

Marie E. Krafft

Department of Chemistry, Florida State University Tallahassee, Florida 32306-3006

Received September 3, 1987

In 1973 Pauson showed that alkyne dicobalt octacarbonyl complexes react with olefins to give rise to cyclopentenones.[1,2] However, there are two major problems associated with the intermolecular cycloaddition. First, mixtures of regioisomeric cyclopentenones, i.e., **1** and **2**, are formed from unsymmetrically substituted olefins, although unsymmetrically substituted acetylenes prefer (due to steric interactions) an orientation which places the larger substituent in the α position of the cyclopentenone (eq 1). Second, the yields are consistently low when simple olefins

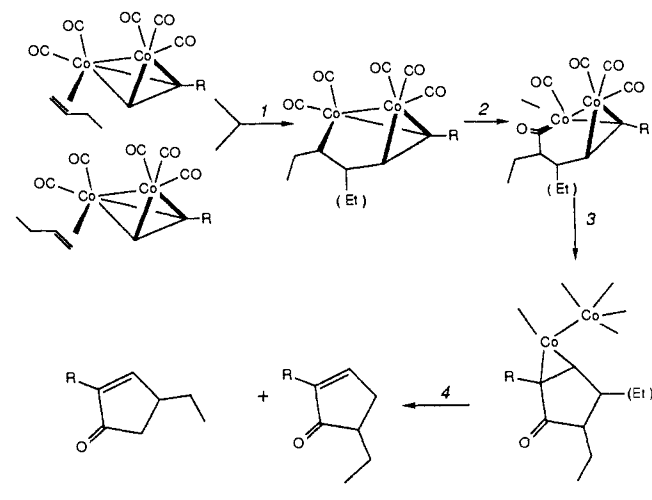


(1)

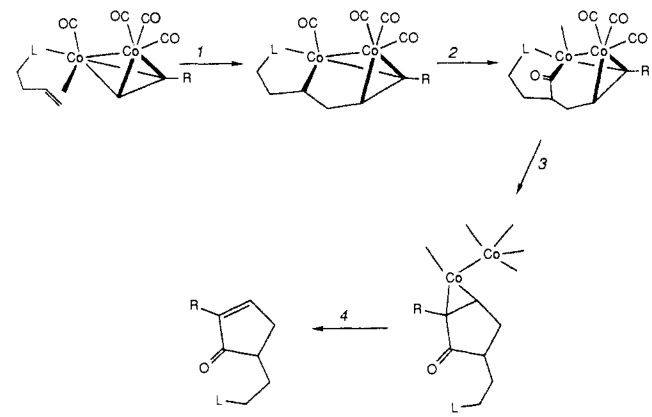
are used. We now report the first examples of the use of ligands to provide regiocontrol in the intermolecular olefin–acetylene cycloaddition and to contribute to a significant improvement in the overall yield.[3]

(1) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.
(2) Khand, I. U.; Pauson, P. L. *J. Chem. Res. M* **1977**, 168.
(3) Several examples of regiospecific cycloadditions have been reported: (a) Sampath, V.; Lund, E. C.; Knudsen, M. J.; Olmstead, M. M.; Schore, N. E. *J. Org. Chem.* **1987**, *52*, 3595. (b) Billington, D. C.; Pauson, P. L. *Organometallics* **1982**, *1*, 1560. (c) Bladon, P.; Khand, I. U.; Pauson, P. L. *J. Chem. Res. M* **1977**, 0153. (d) LaBelle, B. E.; Knudsen, M. J.; Olmstead, M. M.; Hope, H.; Yamuk, M. D.; Schore, N. E. *J. Org. Chem.* **1985**, *50*, 5215.

Scheme I



Scheme II



Since its introduction, the reaction (referred to as the Pauson[4] cyclization) has attracted much attention due to its synthetic utility;[5,6] however, use has been limited to the intramolecular modification due to the aforementioned problems. Recent studies employing the intramolecular version include the use of ultrasound[7] and silica gel as a medium for the cycloaddition.[8,9]

A mechanism has been proposed,[4,5] although experimental evidence is lacking. A potential solution to the regioisomer problem may, however, be envisioned by considering the proposed mechanism (Scheme I). Initially, the olefin must coordinate to

(4) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855.
(5) The Pauson cycloaddition has been utilized recently in the syntheses of Coriolin and Hirsutic acid: Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. Quadrone: Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483. Methylenomycin B: ref 3b. Deoxyprostaglandin: Newton, R. F.; Pauson, P. L.; Taylor, R. G. *J. Chem. Res. M* **1980**, 3501. For other applications to organic synthesis, see: Knudsen, M. J.; Schore, N. E. *J. Org. Chem.* **1984**, *49*, 5025. Billington, D. C.; Willison, D. *Tetrahedron Lett.* **1984**, *25*, 4041. Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. Schore, N. E.; Knudsen, M. J. *J. Org. Chem.* **1987**, *52*, 569. Magnus, P.; Becker, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 7495.
(6) L. A. Paquette *Recent Synthetic Developments in Polyquinane Chemistry*; Topics in Current Chemistry 119, Springer: Berlin, 1984. Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer: Berlin, 1987, and references cited therein. Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141.
(7) Caple, R.; Froen, D.; Kraeger, A. *Abstracts of Papers*, 193rd National Meeting of the American Chemical Society; Denver, CO, American Chemical Society: Washington DC, 1987, *ORGN 42*.
(8) Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Strychkov, Y. T.; Kyz'mina, L. G.; Mikaelian, G. S.; Caple, R.; Swanson, E. D. *Tetrahedron Lett.* **1986**, *27*, 1241. Simonian, S. O.; Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimov, I. I.; Caple, R.; Froen, D. E. *Tetrahedron Lett.* **1986**, *27*, 1245.
(9) For other related cobalt-mediated cycloadditions, see: Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539 and references cited therein; Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759. See, also: Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.

0002-7863/88/1510-0968$01.50/0