These data delineate part structure a.



Only 12 ¹³C 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, RCT⁸ (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 13membered 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

(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 mm², while those of NaCl varied from 3.45 to 3.55 min, and the areas from 135.0 to 140.7 mm². (10) Schmitz, F. J.; Hollenbeak, K. H.; Campbell, D. C. J. Org. Chem. 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 ¹H-¹H correlation of 1 and 2, ¹³C-¹³C 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.

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

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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] sig-matropic 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

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Scheme I



Scheme II^a





9: X = CI (<u>3S, 4S)</u> 11: X = H (<u>3S, 4S)</u> 10: X = CI (<u>3R, 4R)</u> 12: X = H (<u>3R, 4R</u>)

^aReagents: (i) (EtO₂C)₂CHR, NaH, THF, 25 °C; (ii) Cl₃CCOCl, Zn(Cu), THF, 0 °C; (iii) Al(Hg), THF-MeOH-H₂O or Zn(Cu), THF-H₂O.

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 (3S,4S)or (3R,4R)- 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

Arylsulfanyllactone	Method ^a	Product(s)	Yield ^b (Ratio) ^c
	A		87% (α / β = 1 : 2)
	A		85% (E / Z = 1.3 : 1)
	A		55% ($\alpha / \beta = 4.5 : 1$)
	Me B) 85%
	o B		94% (trans / cis = 10 : 1

^a Method A: freshly distilled *n*-Bu₃SnH (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*-Bu₃SnOTf (1.2-1.5 equiv), and the mixture stirred at 40-50 °C for 15-30 min. ^bYields 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 BF₃·Et₂O or AlCl₃ 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

⁽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, 1 H NMR, 13 C NMR, mass spectral) and microanalytical and/or high resolution mass data.

⁽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 EtAlCl₂ 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, CDCl₃) 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.

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Supplementary Material Available: Characterization data (IR, ¹H NMR, ¹³C 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.

Regiocontrol in the Intermolecular Cobalt-Catalyzed Olefin-Acetylene Cycloaddition

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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



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

Scheme I





Since its introduction, the reaction (referred to as the Pauson⁴ 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 ultrasound⁷ 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

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