Optically Active Arsenic Macrocycles. Stereospecific Syntheses of Enantiomers and Diastereomers of 14-Membered *trans*-As_2S_2 Chelating Macrocycles Containing Resolved Asymmetric Tertiary Arsine Donors

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Abstract: The first optically active macrocycles containing arsenic, (*R*,*R*)- and (*S*,*S*)-**1**, have been synthesized by template dimerizations of the enantiomers of deprotonated (±)-(2-mercaptoethyl)[2-(methoxymethyl)phenyl]methylarsine, (±)-**3**, on palladium(II) with boron tribromide. The optically pure enantiomers of the asymmetric bidentate were obtained from unusual μ-thiolato-*S*-bridged palladium(II) diastereomers containing ortho-metalated (*R*)-dimethyl(1-(2-naphthyl)ethyl)amine. Thus, treatment of an equilibrium mixture of optically pure palladium(II) complexes *cis*,*trans*-(*S*,*S*)-**8** in chloroform with boron tribromide gave, after displacement from the metal, a 66% yield of the air-stable 14-membered *trans*-As_2S_2 macrocycle (*R*,*R*)-(2-$CH_2C_6H_4As^*MeCH_2CH_2S)_2$, (*R*,*R*)-**1**, $[\alpha]_D$ −180° (CH_2Cl_2), together with a 13% yield of seven-membered (*R*)-(2-$CH_2C_6H_4As^*MeCH_2CH_2S$), (*R*)-**2**, $[\alpha]_D$ −32.5° (CH_2Cl_2). Use of optically inactive (*R**,*S**)-**8** as starting material, which exists in chloroform as an equilibrium mixture of four identifiable diastereomers, gave the corresponding racemic *trans*-As_2S_2 macrocycle (*R**,*R**)-**1**, diastereometrically pure, in 50% yield, along with 38% of (±)-**2**. Racemic (*R**,*R**)-**1** was subsequently converted into less soluble *meso*-(*R**,*S**)-**1** in a quantitative, and diastereospecific, crystallization-induced asymmetric disequilibration of the two diastereomers in chloroform in the presence of hydrochloric acid. Both diastereomers of the new *trans*-As_2S_2 macrocycle powerfully sequester "soft" metals. The energy of the stereochemically homogeneous palladium(II) chelate of (*R**,*R**)-**1**, however, is lower than the energies of the almost degenerate pair of diastereomeric cations produced by (*R**,*S**)-**1**, thus providing a rationale for the sole formation of the former in the original template dimerization of deprotonated (±)-AsSH.

Tertiary arsine-*As* and tertiary phosphine-*P* are two of the most important "soft" donor centers in coordination chemistry. Nevertheless, the number of well-defined macrocyclic chelating agents containing two or more arsenic or phosphorus donors is few compared to the bewildering range of compounds known with "hard" ether-*O* and amine-*N* donors.[1] Certainly, no optically active macrocycles containing resolved tertiary arsenic or phosphorus stereocenters have been reported hitherto. Such molecules should be potentially powerful and stereospecific chelating agents for synthetically important second-row and third-row transition metals. Apart from metal ion specificities that might be exhibited by the macrocycles, the availability of stable and stereochemically defined metal chelates is important to the study of discrimination between enantiomers and other related phenomena that bear on the development of metal-based auxiliaries for asymmetric synthesis.

There are two basic strategies open to the synthesis of cyclic poly(tertiary arsines and phosphines). Both are intended to minimize competitive linear polymerizations that are prone to occur between terminal donor and acceptor sites of reacting precursor molecules. One strategy involves the use of a metal ion to hold the reacting groups in orientations correct for selective multistep reactions. This is the so-called metal–template approach.[2] Thus, in the excellent work carried out to date, nickel(II) and palladium(II) have been employed as template ions for cyclizations leading to a variety of chelating tertiary phosphine-containing macrocycles.[3-6] The second approach uses the dilution principle to facilitate desirable couplings. Many new types of macrocyclic tertiary arsines and phosphines have been synthesized by this technique.[7] The most recent work describes syntheses of 14-membered rings containing *cis*- and *trans*-P_2S_2 donor atom sets.[8] A number of macrocyclic poly(tertiary arsines) and related compounds have also been prepared with use of high reagent dilutions, including a 16-membered *trans*-As_2S_2 macrocycle (in 2% yield).[9] With the notable exception of unusually high *R**,*S** diastereoselection in alkylations of 1,2-$C_6H_4(ELiPh)_2$ (where E = As or P),[10] however, the cyclizations reported hitherto are essentially nonstereoselective with complex mixtures of diastereomers resulting from synthesis of compounds containing two or more chiral centers at phosphorus (E_{inv} = ca. 30 kcal mol^{-1}) or at arsenic (E_{inv} > 40 kcal mol^{-1}).[11]

In this paper we report stereospecific syntheses of each of the two diastereomers of the important new type of chelating *trans*-As_2S_2 macrocycle **1**. The synthetic strategy emerged from our investigations of resolutions of chiral arsenic and phosphorus bidentates with asymmetric palladium(II) resolving agents.[12] Furthermore, with use of appropriate optically active palladium(II) precursor complexes we have synthesized the corresponding enantiomers of **1**, the first examples of optically active macrocyclic tertiary arsines. Aspects of optical resolution, protection, and the stereocontrol of dimerization of heavily functionalized tertiary arsine precursor molecules by palladium(II) are discussed.

Results and Discussion

Synthetic Strategy. It was anticipated that the reaction depicted in Scheme I would proceed with appropriate choice of M and X. Provided M gave intermediates of stabilities sufficient for reactions of coordinated precursors, yields were expected to be high with

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(12) Roberts, N. K.; Wild, S. B. *J. Am. Chem. Soc.* **1979**, *101*, 6254. Martin, J. W. L.; Palmer, J. A. L.; Wild, S. B. *Inorg. Chem.* **1984**, *23*, 2664 and references therein.

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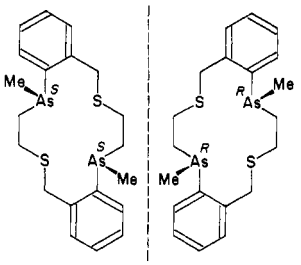
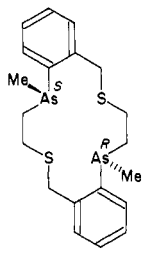
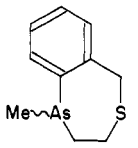


(R^*,R^*)-1



(R^*,S^*)-1

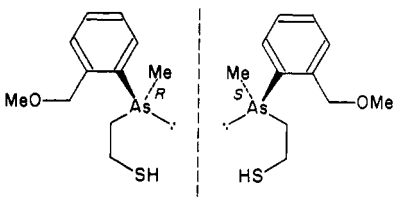
intermediates of trans geometries producing diastereomeric complexes of the desired *trans*-As_2S_2 macrocycle **1**, whereas cis geometries would lead to **2** (Scheme II). The ultimate requirement of displacing the macrocycles from M was also considered: excessive stabilities of product complexes were unwanted.



(±)-2

Studies of model compounds in our laboratory[13,14] showed the square-planar complexes of the type $[M(AsS)_2]$ containing deprotonated asymmetric 2-mercaptoethyl-substituted tertiary arsines are labile for M = Ni(II), Pd(II), or Pt(II), with up to four diastereomers of the complexes being present in solutions under ambient conditions. The kinetic stabilities of the complexes increase in the order Ni < Pd < Pt. Palladium(II) was chosen as the template ion M in this work. A final requirement was that leaving group X be generated from a protecting group under conditions that labile precursor complexes could tolerate. A suitable choice for the protecting group was OMe: benzyl methyl ethers are converted in high yield into benzyl bromides by boron tribromide.[15]

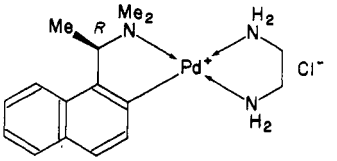
Synthesis and Resolution of (±)-(2-Mercaptoethyl)[2-(methoxymethyl)phenyl]methylarsine ((±)-3. Asymmetric bidentate (±)-**3** was prepared in five high yielding steps from 2-bromobenzyl methyl ether as shown in Scheme III. Tertiary arsine (±)-**3** is an air-sensitive colorless oil, bp 118–120 °C (0.05 mmHg). This chiral ligand was resolved by the fractional crystallization of a pair of unusual μ-thiolato-*S* diastereomers, each of which contained two ortho-metalated (*R*)-[(dimethyl(1-(2-naphthyl)ethyl)-aminato-C^2,N]palladium(II) resolving units per bridging deprotonated thiolato-*S* ligand (Scheme IV). The initial mixture of diastereomers was prepared from 2 equiv of resolving agent (R,R)-**4**·CH_2Cl_2[13] and 1 equiv each of (±)-**3** and of triethylamine. The isolated yield of the mixture was 95%. The structures proposed for the diastereomers are based upon an X-ray crystal structure determination of the less soluble diastereomer isolated



(±)-3

in the resolution of model ligand (±)-$MePhAsCH_2CH_2SH$.[13] The solubilities, optical rotations, and ^1H NMR spectra (apart from the absence of the CH_2OMe resonances in the model compound) of the less soluble diastereomers in each case were almost identical; the S_{As},S_S,R,R[17] stereochemistry has accordingly been proposed for crystalline **5**. It is noteworthy that the reaction produced only 2 of the 16 possible diasteromers (including isomers due to palladium stereocenters). We have remarked previously on the regiospecificity of coordination of donors of asymmetrical and unsymmetrical bidentates to this particular resolving cation: the softest of the two donors invariably takes up a position trans to the NMe_2 group in the complexes.[12,13,16] In the model compound, the five-membered ring containing the asymmetric tertiary arsine-*As* and the μ-thiolato-*S* stereocenters of *S* absolute configuration adopts a δ conformation that is apparently dictated by the preference of the As–phenyl group for an equatorial position in the puckered ring. The orthogonal relationship between the square planes containing the palladium atoms allows repulsive forces between the ortho-metalated naphthyl rings to be minimized.[13] The structure proposed for the more soluble diastereomer retains the structural features of the fully characterized less soluble diastereomer.

The separation of the almost equimolar mixture of (S_{As},S_S,R,R)-**5** and (R_{As},R_S,R,R)-**5** was achieved by fractional crystallization. Two recrystallizations from acetone–dichloromethane–ethanol solvent mixture afforded an 88% yield of pure less soluble (S_{As},S_S,R,R)-**5**, $[\alpha]_D$ −322° (CH_2Cl_2). Diastereomer (R_{As},R_S,R,R)-**5** would not crystallize from the highly enriched mother liquor containing it under any of the conditions tried. Optically active (*R*)-**3** was liberated from (S_{As},S_S,R,R)-**5** in two steps (Scheme V).[19] Aqueous 1,2-ethanediamine displaced the terminal palladium resolving unit with formation of (S_{As},R)-**6** and (*R*)-**7**;



(*R*)-7

the latter was reconverted into resolving agent (R,R)-**4** with hydrochloric acid.[16] Diastereomer (S_{As},R)-**6** did not crystallize, although it was shown to be pure by elemental analysis and by

(13) Leung, P.-H.; McLaughlin, G. M.; Martin, J. W. L.; Wild, S. B. *Inorg. Chem.* **1986**, *25*, 3392.

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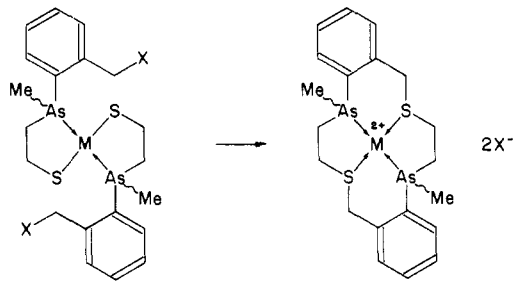
(17) The nomenclature adopted here is based upon recent Chemical Abstracts Service Index practice[18] with non-carbon stereocenters specified in cases where more than one type of stereocenter is present. Enantiomers have simplified descriptors. Full sterochemical descriptions are given in the Experimental Section. Absolute chiralities are expressed in terms of the Cahn–Ingold–Prelog (CIP) sequence rules.[18,20]

(18) Blackwood, J. E.; Giles, P. M., Jr. *J. Chem. Inf. Comput. Sci.* **1975**, *15*, 67–72. *Chemical Abstracts, Index Guide to Volume 76*; Chemical Abstracts Service: Columbus, OH, 1972. *Chemical Abstracts, Ninth Collective Index, Index Guide to Volume 76–85*; Chemical Abstracts Service: Columbus, OH, 1977; paragraph 203. Also see: Cahn, R. S.; Dermer, O. C. *Introduction to Chemical Nomenclature*, 5th ed.; Butterworths: London, 1979; pp 140–150.

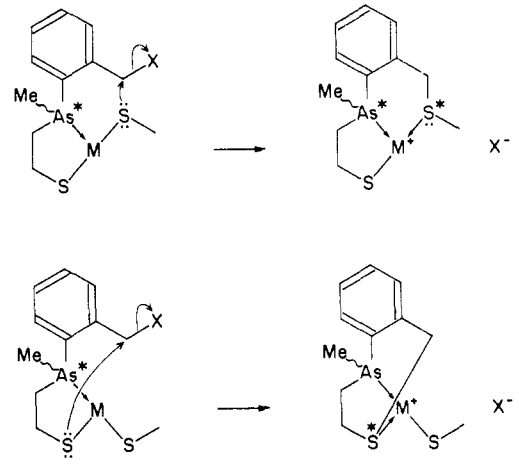
(19) The replacement of a lone pair by a heavy metal changes the priority of that ligand (or phantom ligand) from 4 to 1; since this is an odd change (4–1 = 3), the CIP descriptor must be reversed when the ligand is displaced from the metal and vice-versa.[20]

(20) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

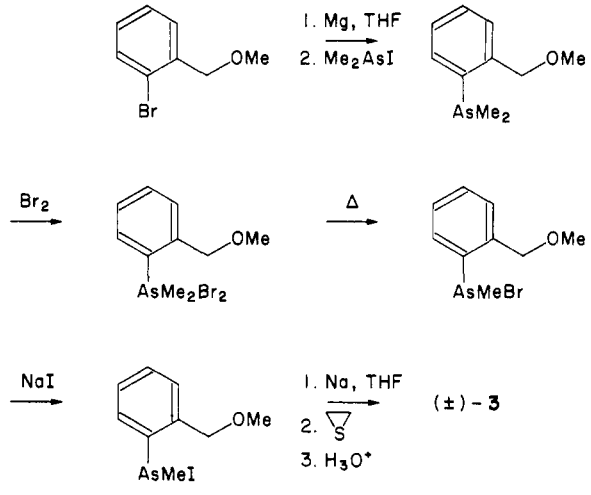
Scheme I



Scheme II

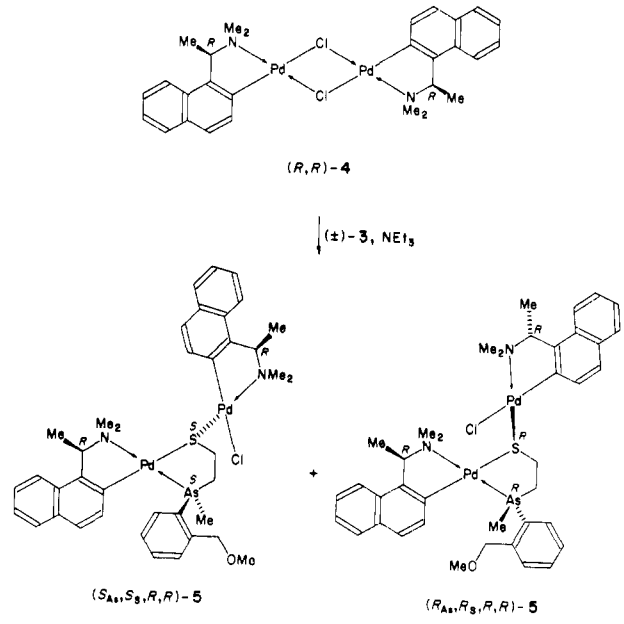


Scheme III

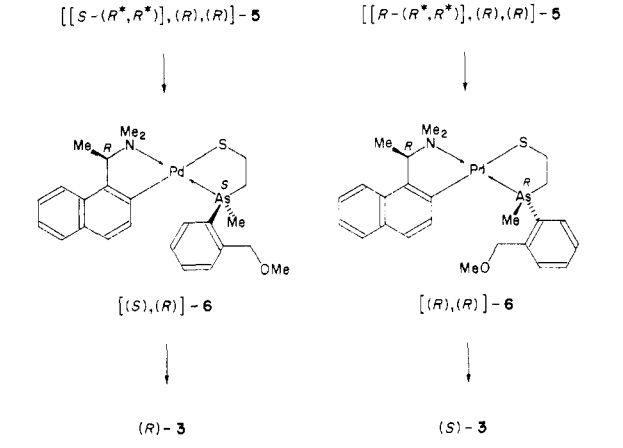


^{1}H NMR spectroscopy. Treatment of (S_{As},*R*)-**6** with cyanide liberated the resolved tertiary arsine (*R*)-**3**: bp 120–121 °C (0.05 mmHg); $[\alpha]_{546}$ +7.8° (CH_2Cl_2) ($[\alpha]_D$ + 1.1° (CH_2Cl_2)). Stereospecific displacement from the metal was confirmed by the quantitative repreparation of (S_{As},S_S,*R*,*R*)-**5** from liberated (*R*)-**3** and (*R*,*R*)-**4**·CH_2Cl_2 in $CDCl_3$: the ^{1}H NMR spectrum of the sample (prepared in situ) indicated diastereomer (S_{As},S_S,*R*,*R*)-**5** only. In a further test of optical purity, labile [Pd(AsS)$_2$] was prepared from (*R*)-**3** of $[\alpha]_{546}$ +7.8° (CH_2Cl_2) with care being taken to avoid separation of diastereomers. Proton NMR signals of the thermodynamically stable *R**,*S** diastereomers[14] of the complex (see below) were absent from the spectrum (Figure 3). Partially resolved (*S*)-**3** of $[\alpha]_{546}$ −3.6° (CH_2Cl_2) was recovered from the diastereomeric complexes remaining in the mother liquor after removal of (S_{As},S_S,*R*,*R*)-**5**. The impure ligand was brought to optical purity by conversion into crystalline (R_{As},R_S,*S*,*S*)-**5**, $[\alpha]_D$ +322° (CH_2Cl_2), with use of (*S*,*S*)-**4**·CH_2Cl_2. Optically pure (*S*)-**3** of $[\alpha]_{546}$ −7.8° (CH_2Cl_2) was displaced from the pure diastereomer as described already for its enantiomer; it gave (R_{As},R_S,*R*,*R*)-**5** exclusively upon reaction with (*R*,*R*)-**4**·CH_2Cl_2.

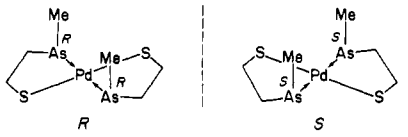
Scheme IV



Scheme V

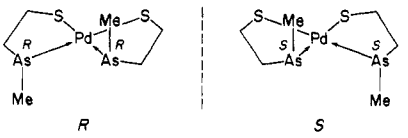


Palladium(II)-Mediated Dimerization of (+)-(*R*)-3: Synthesis of Optically Active *trans*-As_2S_2 Macrocycle (+)-(*R*,*R*)-1. Protected template (*S*,*S*)-**8** was prepared from (*R*)-**3** and tetrachloropalladate(II) in the presence of base (the aromatic substituents on the arsenic atoms have been omitted from the structural formulae for clarity). The optical purity of the complex was demonstrated by the absence of *R**,*S** diastereomers in the ^{1}H NMR spectrum of a 0.05 M solution of complex in $CDCl_3$ at 20 °C. The identification of the cis and trans isomers of (*S*,*S*)-**8** was based upon a knowledge of the relative chemical shifts of resonances due to geometrical isomers in similar complexes containing an analogous asymmetrical tertiary phosphine in which $^2J_{PP'}$ values were diagnostic of coordination geometries.[14] The methoxy groups in (*S*,*S*)-**8** protect the electrophilic benzylic carbon centers from attack by the highly nucleophilic thiolato-*S* donors. It was anticipated that deprotection would induce the desired intramolecular cyclizations with formation of 14-membered or 7-membered rings depending upon the coordination geometries of the intermediates (Scheme II). Thus, treatment of the equilibrium cis:trans = 1:3 mixture of (*S*,*S*)-**8** in chloroform with boron tribromide (4.5 equiv)[15] gave, after 2 h at 25 °C and a further 16 h at 40 °C, intermediate complexes that yielded 79% cyclized material upon decomposition with aqueous cyanide solution: 66% of the desired optically active macrocycle (*R*,*R*)-**1**, $[\alpha]_D$ −180° (CH_2Cl_2), and 13% of seven-membered (*R*)-**2**, $[\alpha]_D$ −32.5° (CH_2Cl_2). Both products are air-stable crystalline solids. The enantiomorphic heterocycles (*S*,*S*)-**1** and (*S*)-**2** were prepared under identical conditions from (*R*,*R*)-**8** and boron tribromide.



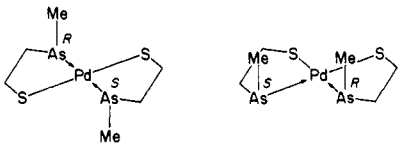
R S

trans-(R*,R*)-8



R S

cis-(R*,R*)-8



trans-(R*,S*)-8 cis-(R*,S*)-8

A propitious choice of reagents and reaction conditions was indicated by the high yields of cyclized products.

Palladium(II)-Mediated Dimerization of (±)-3: Diastereospecific Synthesis of the Racemic *trans*-As_2S_2 Macrocycle (±)-(*R,*R**)-1.** The complex (±)-**8** was prepared in high yield from tetrachloropalladate(II) and (±)-**3** in the presence of base. The complex crystallized as deep-orange prisms that were subsequently found by X-ray crystallography[21] to contain molecules of the meso-trans diastereomer *trans*-(*R**,*S**)-**8** only. The crystalline product dissolved in $CDCl_3$ at −78 °C without loss of identity, as demonstrated by the presence of a singlet As*Me* resonance in the ^1H NMR spectrum of a sample at that temperature. When the temperature of the solution was raised, however, rearrangement with intermolecular ligand exchange (ligand redistribution) occurred with formation of an equilibrium mixture of the four possible square-planar diastereomers (Figure 3). A 0.05 M solution of the complex in $CDCl_3$ at 20 °C contained the following mixture of diastereomers: *cis*-(*R**,*R**)-**8** (15%), *trans*-(*R**,*R**)1-**8** (42%), *cis*-(*R**,*S**)-**8** (5%), and *trans*-(*R**,*S**)-**8** (38%). The diastereomers were identified as described previously for complexes of the model ligand.[14] The position of the equilibrium was dependent upon the solvent employed, but regardless of the medium chosen, solid *trans*-(*R**,*S**)-**8** was isolated from the solutions always in second-order asymmetric transformations.[22] Trans diastereomers of the complex predominated in all solvents investigated with significant racemic-meso diastereoselection being found between the cis diastereomers. Thus, coordination of the nonequivalent donors of the asymmetric bidentates (in-plane electronic discrimination) is diastereoselective in favor of trans isomers (cis:trans = 1:4 in $CDCl_3$ at 20 °C) with out-of-plane electronic or steric discrimination being evident in cis diastereomers only (racemic:meso = 3:1 in $CDCl_3$ at 20 °C) due to the proximity of the interacting asymmetric stereocenters in the latter complexes.

Deprotection of the equilibrium mixture of protected [Pd$(AsS)_2$] diastereomers with 4.5 equiv of boron tribromide, under optimized conditions (2 h at 25 °C, 16 h at 40 °C), led to a mixture of intermediate complexes from which the crystalline racemic *trans*-As_2S_2 macrocycle (*R**,*R**)-**1** was displaced in 50% yield, along with 38% of (±)-**2**. The yield of 14-membered product was not improved by changing the conditions, although larger quantities of the 7-membered heterocycle were sometimes isolated. The meso *trans*-As_2S_2 macrocycle (*R**,*S**)-**1** was not produced in any of the runs performed, despite the presence of the appropriate protected diastereomer *trans*-(*R**,*S**)-**8** in the reaction mixtures at equilibrium. It was shown in later work that palladium(II) bromide complexes of (*R**,*S**)-**1** were not transformed into the corresponding (*R**,*R**)-**1** complexes by heating at 40 °C for 18 h in chloroform. Thus, (*R**,*S**)-**1** would have been isolated if it had been a kinetic product. Provided square-planar coordination geometries prevail in the intermediates, only *trans*-(*R*,*R**)-[Pd$(AsS)_2$] species lead to (*R**,*R**)-**1**; others lead to (±)-**2**. With this in mind, the equilibrium concentrations of the *protected* precursors were expected to give (*R**,*R**)-**1**:(±)-**2** = 42:58, rather than the 50:38 ratio observed. In the absence of detailed kinetic studies it is inappropriate to speculate on the mechanism of the stereospecific template synthesis of (*R**,*R**)-**1**. The reason for the diastereospecificity of the cyclization emerged eventually from a study of the relative energies of the square-planar palladium(II) chelates of (*R**,*R**)-**1** and of (*R**,*S**)-**1**.

Synthesis of the Meso *trans*-As_2S_2 Macrocycle (*R,*S**)-1.** Asymmetric arsenic stereocenters in tertiary arsines racemize in the presence of halo acids.[23] Thus, when a solution of (*R**,*R**)-**1** in $CDCl_3$ was exposed to $D_3O^+Cl^-$ it was transformed (over 24 h) into an almost equimolar mixture of the macrocyclic diastereomers (*R**,*R**)-**1** and (*R**,*S**)-**1**. The transformation was monitored by ^1H NMR spectroscopy. Moreover, when a solution of the rapidly equilibrating mixture of diastereomers was left for several weeks at 25 °C a *quantitative* crystallization occurred of all macrocyclic material as the less soluble and higher melting achiral meso diastereomer (*R**,*S**)-**1**:

$$(R^*,R^*)\text{-}\mathbf{1} \leftrightarrow (R^*,S^*)\text{-}\mathbf{1}\downarrow$$

We have previously observed a quantitative transformation between the *R**,*S** and *R**,*R** diastereomers of 1,2-C_6H_4(AsMePh)$_2$ under similar conditions.[24]

Square-Planar Palladium(II) Derivatives of 14-Membered *trans*-As_2S_2 Macrocycles: Relative Stabilities of Diastereomeric Complex Cations. Salts of the type [Pd(*trans*-As_2S_2)]$(ClO_4)_2$, **9**, were prepared from acetonitrile solutions of [Pd$(MeCN)_4$]$(ClO_4)_2$ and the various forms of the *trans*-As_2S_2 ligand. In each case ^1H NMR spectroscopy was used to ensure that the recrystallized products were representative of total products. The perchlorate salts behaved as di-univalent electrolytes in acetonitrile and in dimethyl sulfoxide but as uni-univalent electrolytes in acetone. It is pertinent to remark that although the syntheses of the perchlorate salts proceeded smoothly for both diastereomers of the ligand, (*R**,*R**)-**1** only (and its enantiomers) reacted as expected with tetrachloropalladate(II) or tetrabromopalladate(II) in methanol. The coordination of the macrocyclic ligands to the palladium was stereospecific with respect to the arsenic stereocenters as demonstrated by the recovery of the respective ligand diastereomers (or enantiomers) from the complexes after decomposition with cyanide. The six square-planar diastereomers possible for the palladium(II) cations are depicted in Figures 1 and 2. Apart from the pairs of chiral arsenic-*As* stereocenters in each of the diastereomers there are pairs of chiral sulfur-*S* stereocenters. *Terminal* thioether-*S* stereocenters in palladium(II) complexes have inversion barriers of 50–70 kJ mol^{-1}; thus, diastereomerism due to chirality of terminal thioether-*S* stereocenters in palladium(II) complexes is not usually observed by ^1H NMR spectroscopy at temperatures above 60 °C.[25] The inversion barriers of sulfur-*S* stereocenters in macrocyclic complexes, however, will also be affected by conformational barriers within the interlocking chelate rings. Ligand (*R**,*R**)-**1** produced a unique perchlorate salt of C_2 symmetry as demonstrated by the single sharp AsMe resonance at δ 2.24 in the ^1H NMR spectrum of a sample of the complex in dimethyl sulfoxide-d_6. (The C_1 diastereomer has nonequivalent As*Me* groups.) The palladium(II) derivative of (*R**,*R**)-**1** was subsequently found by X-ray crystallography to contain the $R^*_{As},R^*_{As},S^*_S,S^*_S$ cation (Figure 1).[21] Complex ($R^*_{As},R^*_{As},S^*_S,S^*_S$)-**9** was recovered unchanged from a dimethyl

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(25) Abel, E. W.; Bhargava, S. K.; Orrell, K. G. *Prog. Inorg. Chem.* **1984**, *32*, 1. The thioether-*S* inversion barrier is dependent upon the nature and size of the chelate ring and upon trans substituents.

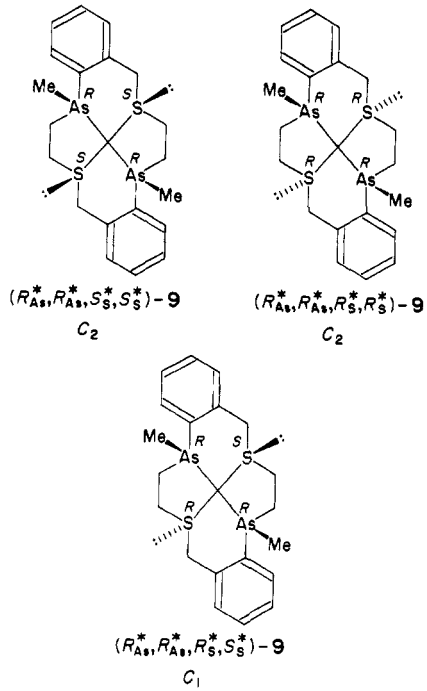

Figure 1. Square-planar palladium(II) diastereomers of (R^*,R^*)-**1** (**9**). One enantiomer only of each diastereomer is depicted.

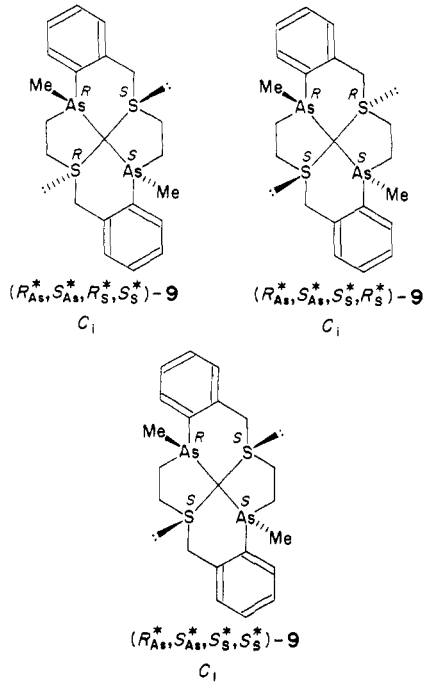

Figure 2. Square-planar palladium(II) diastereomers of (R^*,S^*)-**1** (**9**). One enantiomer only of the C_i diastereomer is depicted.

sulfoxide solution in which it had been heated for 5 min at 150 °C. Indeed, the ^{1}H NMR spectrum of the complex in dimethyl sulfoxide-d_6 showed no change over the range 20–150 °C. Interestingly, the structure in which the substituents (or lone pairs) on the four asymmetric donor stereocenters of the coordinated macrocycle in the complex take up axial positions on the same side of the square-plane was found in the platinum(II) chelate of a 14-membered racemic *trans*-P_2S_2 macrocycle,[9] in the rhodium(I) derivative of the macrocyclic tetrathioether 1,4,8,11-tetrathiacyclodecane (and in its 6,6,13,13-tetramethyl analogue),[26] and in the nickel(II) derivative of 1,4,8,11-tetramethyl-1,4,8,11-

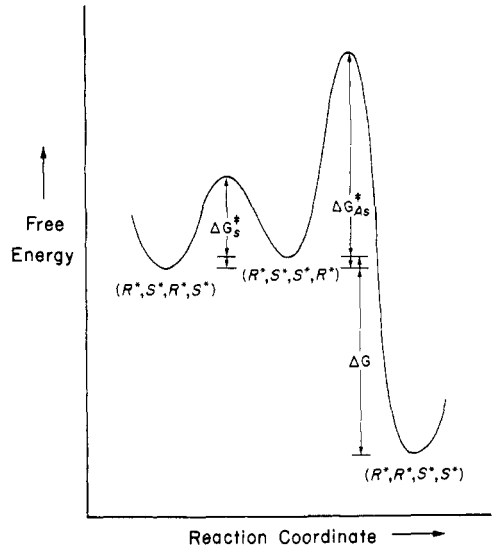

Figure 3. Energy profile for the macrocyclic square-planar palladium(II) complexes (**9**).

tetraazacyclotetradecane.[27] In (R^*_{As},R^*_{As},S^*_S,S^*_S)-**9**, the palladium atom is situated out of the plane of the donor atoms; this allows the palladium atom to assume normal distances to the arsenic atoms (2.39 Å) and to the sulfur atoms (2.31 Å).[21]

Ligand (R^*,S^*)-**1**, on the other hand, was nonstereoselective with respect to the coordination of the prochiral thioether-*S* donors, giving, upon reaction with $[Pd(MeCN)_4](ClO_4)_2$, an equimolar mixture of centrosymmetrical (R^*_{As},S^*_{As},R^*_S,S^*_S)-**9** and (R^*_{As},S^*_{As},S^*_S,R^*_S)-**9** (Figure 2). The mixture of complexes crystallizes as a *conglomerate* (separate crystals of each of the two diasteromers) or as a *compound* (each crystal contains both diastereomeric cations). It was therefore impossible to differentiate on the basis of ^{1}H NMR data between nonstereoselective synthesis of the centrosymmetric R^*_{As},S^*_{As},R^*_S,S^*_S and R^*_{As},S^*_{As},S^*_S,R^*_S diastereomers, each exhibiting a single As*Me* resonance, and the stereospecific synthesis of the asymmetric R^*_{As},S^*_{As},S^*_S,S^*_S diastereomer, which contains nonequivalent As*Me* groups. Subsequent crystal structure determinations, however, confirmed the nondiastereoselective synthesis and the existence of the two crystalline modifications of the compound. The Pd–As and the Pd–S bonds in the centrosymmetrical palladium(II) diastereomers of (R^*,S^*)-**1**, (R^*_{As},S^*_{As},R^*_S,S^*_S)-**9**, and (R^*_{As},S^*_{As},S^*_S,R^*_S)-**9** are shorter (Pd–As = 2.36, Pd–S = 2.27 Å) than those in the (R^*,R^*)-**1** derivative, (R^*_{As},R^*_{As},S^*_S,S^*_S)-**9** (Pd–As = 2.39, Pb–S = 2.31 Å), the latter being normal for the types of atoms involved. Full details of the structures of the three diastereomeric salts will be reported elsewhere.[21]

The isolation of three of the six possible diastereomeric salts provided a rare opportunity to determine the relative stabilities of the diastereomeric cations present. The centrosymmetrical R^*_{As},S^*_{As},R^*_S,S^*_S and R^*_{As},S^*_{As},S^*_S,R^*_S diastereomers of **9** are related by inversions of the thioether-*S* stereocenters: either directly, by a concerted double inversion, or indirectly, by separate inversions through the asymmetric R^*_{As},S^*_{As},S^*_S,S^*_S diastereomer, which is an intermediate. Heating of the mixture of centrosymmetrical diastereomers in dimethyl sulfoxide-d_6 to ca. 70 °C caused a broadening of the ^{1}H NMR resonances (which was reversed upon cooling of the sample), but the data were of insufficient quality for conclusions to be drawn. The ^{1}H NMR spectrum of dissymmetric (R^*_{As},R^*_{As},S^*_S,S^*_S)-**9** under similar conditions, however, was unaltered; indeed, a solution of the complex in dimethyl sulfoxide-d_6 was heated at 150 °C for 30 min without change. We were therefore surprised to find that the equimolar mixture of (R^*_{As},S^*_{As},R^*_S,S^*_S)-**9** and (R^*_{As},S^*_{As},S^*_S,R^*_S)-**9** in dimethyl sulfoxide underwent a quantitative conversion into (R^*_{As},R^*_{As},S^*_S,S^*_S)-**9** upon brief heating at 150

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°C [$t_{1/2}$(isomerization) = ca. 2 min]. The transformation was irreversible and involved unprecedented inversions of coordinated tertiary arsine-*As* stereocenters in halide-free salts. Although no proven, it is unlikely that the heating caused complete dissociation of the macrocyclic ligand from the metal ion. The only other example known to us of similar behavior concerns the epimerization of inner tertiary arsine-*As* stereocenters in a kinetically stable cobalt(III) *chloride* complex of a linear tetra(tertiary arsine) when the salt was boiled in acetonitrile.[28] The mechanism suggested for the inversion of the arsenic stereocenters in the cobalt complex involved rearrangements of intermediate five-coordinate pseudoarsonium ion pairs. A similar mechanism has been proposed for the racemization of organoarsonium halides.[29] A further dramatic observation was the failure of optically pure (R_{As},R_{As},S_S,S_S)-**9** to racemize under the conditions that the equimolar mixture of (R^*_{As},S^*_{As},R^*_S,S^*_S)-**9** and (R^*_{As},S^*_{As},S^*_S,R^*_S)-**9** was transformed into racemic (R^*_{As},R^*_{As},S^*_S,S^*_S)-**9**. Indeed, the half-life for racemization of a solution of (R_{As},R_{As},S_S,S_S)-**9** in dimethyl sulfoxide was ca. 8 h at 150 °C. Since the barriers to inversion of the tertiary arsine-*As* stereocenters in the square-planar diastereomers of (R^*,R^*)-**1** and of (R^*,S^*)-**1** must be similar in the absence of conformational effects, the slow mutarotation of the optically active complex indicates a predominance of conformational over vicinal effects in the macrocyclic complexes. (It is recognized, however, that it is a matter of convenience to apply a conformational–vicinal factorization to the analysis of complicated systems involving four asymmetric donor stereocenters and associated asymmetric and interlocking chelate rings.[30]) The data presented here, taken in conjunction with those obtained on related compounds involving similar linear ligands, are consistent with intramolecular inversions of the coordinated thioether-*S* and tertiary arsine-*As* stereocenters in the complexes. An approximate free energy profile for the diastereomers of **9** is given in Figure 3. Free energy of activation $\Delta G_S^{\ddagger}$ corresponds to the vicinal and associated conformational factors associated with the thioether-*S* inversions and $\Delta G_{As}^{\ddagger}$ to the corresponding factors concerning tertiary arsine-*As* inversions in the interlocking five- and six-membered rings of the macrocyclic complex cations. The R^*_{As},S^*_{As},S^*_S,S^*_S cation may be an intermediate in the transformation between the R^*_{As},S^*_{As},R^*_S,S^*_S and the R^*_{As},S^*_{As},S^*_S,R^*_S cations, although the energy profile describes a concerted transformation. It is significant that the R^*_{As},R^*_{As},S^*_S,S^*_S cation is the most stable of the three isolated and that this diastereomer is the sole product of the palladium(II)-mediated dimerization of deprotonated (±)-**3**. A large difference in free energy (ΔG) between the (R^*,R^*)-As and the (R^*,S^*)-As sets of complexes was indicated by the slow mutarotation of (R_{As},R_{As},S_S,S_S)-**9** [$t_{1/2}$ = ca. 8 h], since (R^*_{As},S^*_{As},R^*_S,S^*_S)-**9** and (R^*_{As},S^*_{As},S^*_S,R^*_S)-**9** are intermediates in the racemization ($\Delta G^{\ddagger} = \Delta G + \Delta G_{As}^{\ddagger}$). The driving force for the transformation is presumably the relaxation of strain within the macrocyclic complex; for example, the Pd–As and the Pd–S bonds in the (R^*,S^*)-As diastereomers are compressed (see above).

The present results impinge, in a general sense, on the understanding of the macrocyclic ligand–cation interaction. Widely studied systems involving unsymmetrical crown-4 ethers and related compounds also produce complexes containing four asymmetric donor stereocenters and associated chiral chelate rings. The stereoselectivities of coordination of these molecules to metal ions have not been studied in detail, however, although the data are crucial to the understanding of the stabilities of the complexes involved. The availability, for the first time, of the pure diastereomers and enantiomers of a chelating *trans*-As_2S_2 macrocycle has presented the first opportunity to probe in detail the subtle relationship that exists between a macrocyclic ligand and the metal ion it chelates.

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Experimental Section

Preparations were performed under a positive pressure of argon. ^{1}H NMR spectra were obtained on Bruker CXP 200 and Jeolco FX 200 spectrometers; chemical shifts are reported as δ values relative to internal tetramethylsilane. Optical rotations were measured on the specified solutions in 1 dm cells at 20 °C with a Perkin-Elmer Model 241 polarimeter. Molar conductivities were measured with aWissenschaftlich-Technische Werkstätten D8120 Weilheim conductivity bridge for 10^{-3} M solutions of the complexes at 20 °C. Elemental analyses were performed by staff within the Research School of Chemistry.

Synthesis of Precursor Bidentate (±)-(2-Mercaptoethyl)[2-(methoxymethyl)phenyl]methylarsine ((±)-3): Dimethyl[2-(methoxymethyl)-phenyl]arsine. A cold (0 °C) solution of the Grignard reagent derived from 1-bromo[2-(methoxymethyl)]benzene (150 g, 0.75 mol)[31] and magnesium (19 g, 0.78-g equiv), in absolute THF (310 mL), was treated over 1 h with iododimethylarsine (169 g, 0.73 mol) in the same solvent (200 mL). After the addition, the reaction mixture was boiled for 30 min, and then the THF was removed by distillation. Diethyl ether (400 mL) was added to the residue, which was then treated with hydrochloric acid (500 mL, 2 M). The organic layer was separated, combined with two 200-mL diethyl ether extracts of the aqueous phase, and dried ($MgSO_4$). Distillation afforded the pure arsine (148 g, 88%) as a colorless oil: bp 70–72 °C (0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 6 H, AsMe), 3.39 (s, 3 H, OMe), 4.63 (s, 2 H, CH_2), 7.25–7.57 (m, 4 H, aromatics).

Anal. Calcd for $C_{10}H_{15}AsO$: C, 53.1; H, 6.7. Found: C, 53.1; H, 6.9.

Dibromodimethyl[2-(methoxymethyl)phenyl]arsenic(V). A solution of bromine (90 g, 0.56 mol) in dichloromethane (150 mL) was added cautiously to a stirred solution of the tertiary arsine (120 g, 0.53 mol) in the same solvent (600 mL) at 0 °C. Concentration of the reaction mixture, followed by removal of the solvent under aspirator vacuum, afforded the colorless crystalline product (191 g, 93%) after washing with cold acetone and subsequent drying in a vacuum: mp 155–156 °C dec. ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 6 H, AsMe), 3.62 (s, 3 H, OMe), 4.81 (s, 2 H, CH_2), 7.30–8.29 (m, 4 H, aromatics).

Anal. Calcd for $C_{10}H_{15}AsBr_2O$: C, 31.1; H, 3.9. Found: C, 31.0; H, 3.9.

Bromo(methyl)[2-(methoxymethyl)phenyl]arsine. The dibromoarsenic(V) compound (110 g, 0.28 mol) was heated at 160 °C under reduced pressure (water aspirator). When bromomethane evolution had ceased (after ca. 2 h), the residual oil was distilled. The pure compound was obtained as a pale-yellow oil (80 g, 96.5%); bp 95–98 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H, AsMe), 3.36 (s, 3 H, OMe), 4.55 (s, 2 H, CH_2), 7.05–8.20 (m, 4 H, aromatics).

Anal. Calcd for $C_9H_{12}AsBrO$: C, 37.2; H, 4.2. Found: C, 37.4; H, 4.1.

Iodo(methyl)[2-(methoxymethyl)phenyl]arsine. Metathesis of the bromoarsine (58 g, 0.2 mol) by treatment with a solution of NaI (50 g, 0.33 mol) in acetone (600 mL) afforded the iodoarsine, which was isolated as a golden-yellow oil (62 g, 92%): bp 108–110 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3 H, AsMe), 3.41 (s, 3 H, OMe), 4.60 (s, 2 H, CH_2), 7.10–8.15 (m, 4 H, aromatics).

Anal. Calcd for $C_9H_{12}AsIO$: C, 32.0; H, 3.5. Found: C, 32.2; H, 3.5.

(±)-(2-Mercaptoethyl)[2-(methoxymethyl)phenyl]methylarsine ((±)-3). A solution of the iodoarsine (85 g, 0.25 mol) in THF (600 mL) was stirred in contact with sodium (12 g, 0.52 mol) for 5 h at 20 °C; the sodium arsenide solution was then treated with ethylene sulfide (15.1 g, 0.25 mol). The reaction mixture was stirred for 30 min before removing the solvent by distillation. A solution of NH_4Cl (11 g) in water (400 mL) was added to the residue that remained, and dichloromethane (3 × 100 mL) was used to extract the product from the aqueous phase. Distillation of the organic extracts afforded (±)-**3** as a foul smelling colorless oil (55.4 g, 81%): bp 118–120 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3 H, AsMe), 1.53 (t, $^3J_{HH}$ = 7.6 Hz, 1 H, SH), 1.92–2.07 (m, 2 H, $AsCH_2$), 2.53–2.69 (m, 2 H, SCH_2), 3.40 (s, 3 H, OMe), 4.57, 4.66 (ABq, $^2J_{HH}$ = 11.2 Hz, 2 H, CH_2), 7.29–7.55 (m, 4 H, aromatics).

Anal. Calcd for $C_{11}H_{17}AsOS$: C, 48.5; H, 6.3. Found: C, 48.4; H, 6.5.

Resolving agent di-μ-chlorobis[(*R*)-dimethyl(1-(2-naphthyl)ethyl)-aminato-C^2,N)]dipalladium(II) dichloromethane solvate, (*R*,*R*)-4·CH_2Cl_2, was prepared and isolated as previously described.[13]

Resolution of (±)-3: Synthesis of Diastereomers and Isolation of (S_{As},S_S,*R*,*R*)-5. A mixture of (±)-**3** (8.1 g, 30.0 mmol), triethylamine (4.2 mL, 30.1 mmol), and (*R*,*R*)-**4**·CH_2Cl_2 (22.8 g, 30.0 mmol) in dichloromethane (400 mL) was stirred until all of the resolving agent had

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dissolved. The yellow solution was then washed with water (to remove $[Et_3NH]Cl$) and dried ($MgSO_4$). The solution of diastereomers was concentrated (to ca. 150 mL), diluted with a mixture of acetone (150 mL) and ethanol (70 mL), and once again concentrated (to ca. 150 mL) on the steam bath. Beautiful yellow crystals of (S_{As},S_S,*R*,*R*)-**5** of ca. 90% purity separated upon cooling of the concentrated solution to room temperature; these were filtered-off, washed with a mixture of dichloromethane–acetone–ethanol (2:2:1), and dried: $[\alpha]_D$ −280.7° (*c* 1.0, CH_2Cl_2). The crude product was recrystallized from 150 mL of a 3:2:1 mixture of dichloromethane, acetone, and ethanol. Pure (S_{As},S_S,*R*,*R*)-**5** was thus isolated as yellow needles (12 g, 88%): mp 205–206 °C; $[\alpha]_D$ −322.2° (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.86 (d, 3 H, $^3J_{HH}$ = 6.1 Hz, CH*Me*), 1.94 (d, $^3J_{HH}$ = 6.1 Hz, 3 H, CH*Me*), 2.30 (s, 3 H, AsMe), 2.40–3.18 (m, 4 H, CH_2CH_2), 2.83 (s, 3 H, NMe), 2.87 (s, 3 H, NMe), 3.24 (s, 3 H, NMe), 3.36 (s, 3 H, NMe), 3.41 (s, 3 H, OMe), 4.20–4.38 (m, 2 H, C*H*Me), 4.39, 5.31 (ABq, $^2J_{HH}$ = 11.2 Hz, 2 H, CH_2), 6.85–8.12 (m, 16 H, aromatics).

Anal. Calcd for $C_{39}H_{48}N_2AsClOPd_2S$: C, 51.1; H, 5.3; N, 3.1. Found: C, 50.8; H, 5.4; N, 2.9.

[*SP*-4,3-[(*S*),(*R*)]]-[Dimethyl(1-(2-naphthyl)ethyl)aminato-*C*^{2},*N*][(methyl(2-(methoxymethyl)phenyl)arsino)ethanethiolato-*As*,*S*]palladium(II) ((*S*$_{As}$,*R*)-6). A solution of (S_{As},S_S,*R*,*R*)-**5** (12.0 g, 15.1 mmol) was stirred for 1 h in contact with a solution of 1,2-ethanediamine (10 mL, 149.6 mmol) in water (100 mL). The organic layer was then separated and dried ($MgSO_4$). Removal of solvent afforded a yellow glass (8.2 g, 94%; $[\alpha]_D$ −301° (*c* 1.0, CH_2Cl_2)) that could not be induced to crystallize: ^1H NMR ($CDCl_3$) δ 1.85 (d, 3 H, $^3J_{HH}$ = 6.6 Hz, CH*Me*), 1.93 (s, 3 H, AsMe), 2.48–2.87 (m, 4 H, CH_2CH_2), 2.88 (s, 3 H, NMe), 2.96 (s, 3 H, NMe), 3.34 (s, 3 H, OMe), 4.37 (q, 1 H, $^3J_{HH}$ = 6.4 Hz, C*H*Me), 4.57, 5.24 (ABq, $^2J_{HH}$ = 11.7 Hz, 2 H, CH_2), 6.90–7.81 (m, 10 H, aromatics).

Anal. Calcd for $C_{25}H_{32}NAsClOPdS$: C, 52.2; H, 5.6; N, 2.4. Found: C, 52.0; H, 5.4; N, 2.3.

The aqueous layer contained (*R*)-**7**, which was converted into (*R*,*R*)-**4** by treatment with concentrated hydrochloric acid.[16]

(*R*)-(2-Mercaptoethyl)[2-(methoxymethyl)phenyl]methylarsine ((*R*)-3). Diastereomer (S_{As},*R*)-**6** (7.54 g, 13.1 mmol) was decomposed by reacting a solution of it in dichloromethane (200 mL) with an excess of sodium cyanide (4.0 g, 81.6 mmol) in water (200 mL) over 12 h. The colorless organic layer, after repeated washing with water, dilute H_2SO_4 (2 M), and water again, was subsequently dried over $MgSO_4$ and then distilled, affording (*R*)-**3** as a colorless oil (2.46 g, 69%): bp 120–121 °C (0.05 mmHg); $[\alpha]_D$ +1.1° (*c* 26.3, CH_2Cl_2); $[\alpha]_{365}$ +7.8° (*c* 26.3, CH_2Cl_2); ^1H NMR ($CDCl_3$) identical with that of corresponding racemic material.

Anal. Calcd for $C_{11}H_{17}AsOS$: C, 48.5; H, 6.3. Found: C, 48.6; H, 6.4.

The optical purity of (*R*)-**3** was established by the quantitative repreparation of (S_{As},S_S,*R*,*R*)-**5** from it and (*R*,*R*)-**4**·CH_2Cl_2. Furthermore, ^1H NMR spectroscopy indicated the absence of thermodynamically stable *R**,*S** diastereomers in solutions of labile bis(bidentate)-palladium(II) derivatives of deprotonated (*R*)-**3** (see below).

(*S*)-(2-Mercaptoethyl)[2-(methoxymethyl)phenyl]methylarsine ((*S*)-3). The mother liquor from the isolation of (S_{As},S_S,*R*,*R*)-**5** was treated with 1,2-ethanediamine, and with potassium cyanide, as described above. The recovered ligand had, after distillation, $[\alpha]_{365}$ −3.6° (*c* 10.0, CH_2Cl_2). It was reacted with the calculated quantity of (*S*,*S*)-**4**·CH_2Cl_2 to give, after the usual crystallizations, (S_{As},S_S,*R*,*R*)-**5** ($[\alpha]_D$ +322° (*c* 1.0, CH_2Cl_2)) with a melting point and ^1H NMR data identical with those of its enantiomer. Displaced (*S*)-**3** had $[\alpha]_D$ −1.2° (*c* 10.0, CH_2Cl_2), $[\alpha]_{365}$ −7.9° (*c* 10.0, CH_2Cl_2).

Soluble Diastereomer (R_{As},R_S,*R*,*R*)-5. This complex was prepared from (*S*)-**3** (1.0 g, 3.7 mmol) and (*R*,*R*)-**4**·CH_2Cl_2 (2.8 g, 3.7 mmol) in the usual way. It was obtained as a yellow glass (3.2 g, 95%) that resisted all attempted crystallizations: $[\alpha]_D$ −37.5° (*c* 10.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.71 (d, 3 H, $^3J_{HH}$ = 6.1 Hz, CH*Me*), 2.05 (d, $^3J_{HH}$ = 6.1 Hz, 3 H, CH*Me*), 2.06 (s, 3 H, AsMe), 2.38–3.30 (m, 4 H, CH_2CH_2), 2.74 (s, 3 H, NMe), 2.84 (s, 3 H, NMe), 3.25 (s, 3 H, NMe), 3.48 (s, 3 H, OMe), 3.49 (s, 3 H, NMe), 4.21–4.38 (m, 2 H, C*H*Me), 4.36, 5.24 (ABq, $^2J_{HH}$ = 11.2 Hz, 2 H, CH_2), 6.80–8.10 (m, 16 H, aromatics).

Anal. Calcd for $C_{39}H_{48}N_2AsClOPd_2S$: C, 51.1; H, 5.3; N, 3.1. Found: C, 51.5; H, 5.4; N, 3.0.

Template Macrocycle Syntheses: [*SP*-4,1-(*S*),(*S*)]-Bis[(methyl(2-(methoxymethyl)phenyl)arsino)ethanethiolato-*As*,*S*]palladium(II) ((*S*,*S*)-8). A solution of $Li_2[PdCl_4]$ (from 0.75 g of $PdCl_2$, 4.2 mmol and 0.75 g of LiCl) in methanol (50 mL) was added slowly to a mixture of (*R*)-**3** (2.25 g, 8.3 mmol) in methanol (50 mL)–aqueous sodium hydroxide (5 mL, 2 M, 1.2 equiv). After ca. 30 min the solvent was evaporated off, the orange residue was dissolved in dichloromethane, and the solution was washed several times with water. Removal of the solvent left a yellow glass (2.1 g, 86%) that could not be crystallized from any of the solvents tried: $[\alpha]_D$ −110° (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.10 (s, 1.8 H, AsMe (cis)), 1.86 (s, 4.2 H, AsMe (trans)), 2.40–2.84 (m, 8 H, CH_2CH_2), 3.42 (s, 4.2 H, OMe (trans)), 3.50 (s, 1.8 H, OMe (cis)), 4.64, 4.76 (ABq, $^2J_{HH}$ = 11.0 Hz, 1.2 H, CH_2(cis)), 4.72, 5.05 (ABq, $^2J_{HH}$ = 11.7 Hz, 2.8 H, CH_2(trans)), 6.90–7.80 (m, 8 H, aromatics).

Anal. Calcd for $C_{22}H_{32}As_2O_2PdS_2$: C, 40.7; H, 5.0. Found: C, 40.4; H, 4.8.

[*R*-(9*R,18*R**)]-5,7,8,9,14,16,17,18-Octahydro-9,18-dimethyldibenzo[*e*,*l*][1,8,4,11]dithiadiarsacyclotetradecin ((*R*,*R*)-1).**[32] Precursor complex (*S*,*S*)-**8** (2.65 g, 4.1 mmol) was dissolved in chloroform (50 mL), and the solution was treated with boron tribromide (4.6 g, 18.5 mmol, 4.5 equiv). The reaction mixture was then stirred for 2 h at 25 °C and for another 16 h at 40 °C. At this stage, the mixture was cooled to room temperature, treated with aqueous sodium hydroxide (100 mL, 1 M) and potassium cyanide (5 g) in water (25 mL). The colorless organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to dryness. The oil that remained was chromatographed on silica gel (Merk Si-60, size B) at 30 psi with dichloromethane–*n*-hexane (1:3 v/v) as eluent, giving two fractions.

Fraction 1 (retention volume 225 mL), **(2*R*)-2-methyl-2-arsa-5-thiabicyclo[5,4,0]nona-1(7),8,10-triene ((*R*)-2),** as colorless needles (0.25 g, 13%): mp 80–82 °C; $[\alpha]_D$ −32.5° (*c* 10.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3 H, AsMe), 2.01–3.29 (m, 4 H, CH_2CH_2), 3.70, 4.15 (ABq, $^2J_{HH}$ = 14.5 Hz, 2 H, CH_2), 7.10–7.32 (m, 4 H, aromatics); M_r 239 ± 10 (found), 240 (calcd).

Anal. Calcd for $C_{10}H_{13}AsS$: C, 50.0; H, 5.5. Found: C, 50.3; H, 5.6.

Fraction 2 (retention volume 435 mL), (*R*,*R*)-**1**, as colorless needles (1.3 g, 66%): mp 132–133 °C; $[\alpha]_D$ −180° (*c* 5.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.08, (s, 6 H, AsMe), 1.73–2.55 (m, 8 H, CH_2CH_2), 3.56, 4.41 (ABq, $^2J_{HH}$ = 13.7 Hz, 4 H, CH_2), 7.03–7.27 (m, 8 H, aromatics); M_r 486 ± 20 (found), 480 (calcd).

Anal. Calcd for $C_{20}H_{26}As_2S_2$: C, 50.0; H, 5.5. Found: C, 50.2; H, 5.6.

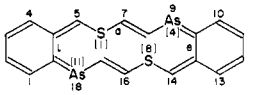
The *S* enantiomers of both compounds were prepared from optically pure (*R*,*R*)-**8** under similar conditions: (*S*,*S*)-**1** had mp 132–133 °C and $[\alpha]_D$ −181° (*c* 1.0, CH_2Cl_2); (*S*)-**2** had mp 80–82 °C and $[\alpha]_D$ −32.5° (*c* 1.0, CH_2Cl_2).

[*SP*-4,1-(*R),(*S**)]-Bis[(methyl(2-(methoxymethyl)phenyl)arsino)ethanethiolato-*As*,*S*]palladium(II) ((*R**,*S**)-8).** A mixture of (±)-**3** (7.24 g, 26.6 mmol) in methanol (50 mL), and aqueous sodium hydroxide (14 mL, 2 M, 1.1 equiv) was treated with $Li_2[PdCl_4]$ (from 2.34 g of $PdCl_2$ (13.2 mmol) and 2.0 g of LiCl) in methanol (100 mL). After ca. 30 min, the yellow precipitate was collected, washed with water and with ethanol, and dried. The crude product was purified by crystallization from hot dichloromethane–ethanol (1:1) mixture. The compound was isolated as large orange prisms (6.5 g, 83%): mp 183–185 °C; ^1H NMR ($CDCl_3$, −78 °C) δ 1.80 (s, 6 H, AsMe), 2.39–2.91 (m, 8 H, CH_2CH_2), 3.43 (s, 6 H, OMe), 4.69, 5.09 (ABq, $^2J_{HH}$ = 11.7 Hz, 4 H, CH_2), 6.89–7.78 (m, 8 H, aromatics); ^1H NMR ($CDCl_3$, 25 °C) δ 1.10 (s, 0.9 H, AsMe-*cis*-[(*R**),(*R**)]), 1.64 (s, 0.3 H, AsMe-*cis*-[(*R**),(*S**)]), 1.85 (s, 2.52 H, AsMe-*trans*-[(*R**),(*R**)]), 1.86 (s, 2.28 H, AsMe-*trans*-[(*R**),(*S**)]), 2.35–3.00 (m, 8 H, CH_2CH_2), 3.40 (s, 0.9 H, OMe-*cis*-[(*R**),(*R**)]), 3.42 (s, 2.52 H, OMe-*trans*-[(*R**),(*R**)]), 3.47 (s, 2.28 H, OMe-*trans*-[(*R**),(*S**)]), 3.50 (s, 0.9 H, OMe-*cis*-[(*R**),(*R**)]), 4.64, 4.76 (ABq, $^2J_{HH}$ = 11.0 Hz, 1.2 H, CH_2-*cis*-[(*R**),(*R**)]), 4.72, 5.05 (ABq, $^2J_{HH}$ = 11.7 Hz, 1.88 H, CH_2-*trans*-[(*R**),(*R**)]), 4.72, 5.11 (ABq, $^2J_{HH}$ = 11.7 Hz, 1.32 H, CH_2-*trans*-[(*R**),(*S**)]), 6.90–7.80 (m, 8 H, aromatics).

Anal. Calcd for $C_{22}H_{32}As_2O_2PdS_2$: C, 40.7; H, 5.0. Found: C, 41.0; H, 5.0.

(*R,*R**)-1 and (±)-2.** With use of (*R**,*S**)-**8** as precursor, and with similar conditions to those used for the synthesis and purification of the optically active compounds, the *racemic* 7- and 14-membered-ring compounds were prepared. Macrocycle (*R**,*R**)-**1** was obtained as white plates in 50% yield: mp 127–129 °C.

(32) The systematic name of this compound is consistent with current Chemical Abstracts practice,[33] with the following structure as the parent ring system:



(33) *Chemical Abstracts Tenth Collective Index Guide*; Chemical Abstracts Service: Columbus, OH, 1977–1981; Vol. 86–95, Appendix IX. *Chemical Abstracts Ring Systems Handbook*; Chemical Abstracts Service: Columbus, OH, 1984; 1289RSF–1293RSF.

Anal. Calcd for $C_{20}H_{26}As_2S_2$: C, 50.0; H, 5.5. Found: C, 50.2; H, 5.6.

Seven-membered (±)-**2** was obtained as white needles in 38% yield: mp 75–76 °C.

Anal. Calcd for $C_{10}H_{13}AsS$: C, 50.0; H, 5.5. Found: C, 50.2; H, 5.6.

Both compounds had ^1H NMR spectra in $CDCl_3$ identical with those of the corresponding pure enantiomers.

Mineral Acid Catalyzed Asymmetric Transformations: Synthesis of (*R,*S**)-1.** A solution of (*R**,*R**)-**1** (2.5 g) in chloroform (100 mL) was treated with a mixture of methanol (5 mL) and hydrochloric acid (5 mL, 10 M). After two weeks, 2.2 g (88% yield) of pure (*R**,*S**)-**1** had separated from the mixture as long colorless needles: mp 197–198 °C; ^1H NMR ($CDCl_3$) δ 1.21 (s, 6 H, AsMe), 1.74–2.66 (m, 8 H, CH_2CH_2), 3.63, 4.53 (ABq, $^2J_{HH}$ = 13.7 Hz, 4 H, CH_2), 7.22–7.52 (m, 8 H, aromatics).

Anal. Calcd for $C_{20}H_{36}As_2S_2$: C, 50.0; H, 5.5. Found: C, 49.9; H, 5.4.

An additional 0.27 g (10.8%) of the compound was obtained upon concentration of the mother liquor.

Palladium(II) Complexes of the Macrocycles: [*SP*-4,1-[*R*-(9*R,18*R**,6*S**,15*S**)]]-[5,7,8,9,14,16,17,18-Octahydro-9,18-dimethyldibenzo[*e*,*l*][1,8,4,11]dithiadiarsacyclotetradecin-S^6,S^{15},As^9,As^{18}]palladium(II) Perchlorate ((*R*$_{As}$,*R*$_{As}$,*S*$_S$,*S*$_S$)-9).** Freshly prepared $[PdCl_2(MeCN)_2]$[34] (0.24 g, 0.92 mmol) was dissolved in acetonitritile (250 mL), and $AgClO_4$ (0.38 g, 1.99 equiv) was added to the solution (in the dark). After the mixture had been stirred for ca. 5 min, it was filtered (to remove AgCl), and the filtrate was treated with (*S*,*S*)-**1**, the latter being dissolved in a small quantity of acetonitrile. The reaction was allowed to proceed for ca. 1 h, whereupon the solvent was removed by evaporation and the residue was recrystallized from acetone. The pure complex crystallized as yellow needles (0.58 g, 71%): mp 265–267 °C; $[\alpha]_D$ −84° (*c* 5.0, Me_2SO-d_6); ^1H NMR (Me_2SO-d_6, 303 K) δ 2.24 (s, 6 H, AsMe), 1.93–4.18 (m, 8 H, CH_2CH_2), 4.35, 4.18 (ABq, $^2J_{HH}$ = 14.7 Hz, 4 H, CH_2), 7.26–7.55 (m, 8 H, aromatics); Λ_M 136 cm^2 Ω^{-1} mol^{-1} (Me_2CO) (1:1), 54 cm^2 Ω^{-1} mol^{-1} (Me_2SO) (1:2), 232 cm^2 Ω^{-1} mol^{-1} (MeCN) (1:2).

Anal. Calcd for $C_{20}H_{26}As_2Cl_2O_8PdS_2$: C, 30.6; H, 3.3. Found: C, 30.8; H, 3.4.

The following compounds were prepared similarly.

(*R$_{As}$,*R**$_{As}$,*S**$_S$,*S**$_S$)-[Pd(1)](ClO$_4$)$_2$ (from (*R**,*R**)-1)**: yellow needles from actone; mp 263–265 °C dec; 76% yield; ^1H NMR (Me_2SO-d_6) identical with that of pure enantiomer.

Anal. Calcd for $C_{20}H_{26}As_2Cl_2O_8PdS_2$: C, 30.6, H, 3.3. Found: C, 30.3; H, 3.6.

(*R$_{As}$,*S**$_{As}$,*R**$_S$,*S**$_S$)- and (*R**$_{As}$,*S**$_{As}$,*S**$_S$,*R**$_S$)-9 (from (*R**,*S*)-1)**: pale-yellow needles from acetonitrile-diethyl ether; mp 259–261 °C dec; ^1H NMR (Me_2SO-d_6, 25 °C) δ 1.36 (s, 6 H, AsMe) 2.26 (s, 6 H, AsMe), 2.58–4.49 (m, 16 H, CH_2CH_2), 4.06, 5.09 (ABq, $^2J_{HH}$ = 12.4 Hz, 4 H, CH_2), 4.64, 4.76 (ABq, $^2J_{HH}$ = 14.6 Hz, 4 H, CH_2), 7.52–7.85 (m, 16 H, aromatics); Λ_M 135 cm^2 Ω^{-1} mol^{-1} (Me_2CO), 54 cm^2 Ω^{-1} mol^{-1} (Me_2SO), 216 cm^2 Ω^{-1} mol^{-1} (MeCN).

Anal. Calcd for $C_{20}H_{26}As_2Cl_2O_8PdS_2$: C, 30.6; H, 3.3. Found: C, 30.4; H, 3.6.

(34) Hartley, F. R.; Murray, S. G.; McAuliffe, C. A. *Inorg. Chem.* **1979**, *18*, 1394.

Crown Thioether Chemistry: Structural and Conformational Studies of Tetrathia-12-crown-4, Pentathia-15-crown-5, and Hexathia-18-Crown-6. Implications for Ligand Design

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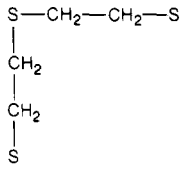
Abstract: Tetrathia-12-crown-4 (12S4) in the solid state adopts a square conformation with the sulfur atoms at the corners, to yield a structure derived from fusion at the terminal S atoms of two "bracket" units. This macrocycle crystallizes in the



monoclinic system, space group *Cc*, with *a* = 13.028 (7) Å, *b* = 12.884 (5) Å, *c* = 14.493 (7) Å, β = 108.18 (4)°, and *Z* = 8. Pentathia-15-crown-5 (15S5) assumes an irregular conformation generated from two bracket units by fusion at one S atom and connection of the remaining two terminal S atoms by a $-CH_2CH_2-$ linkage. This crown thioether also crystallizes in the monoclinic system, space group $P2_1/n$, with *a* = 16.444 (3) Å, *b* = 5.432 (1) Å, *c* = 18.255 (3) Å, β = 115.58 (1)°, and *Z* = 4. Hexathia-18-crown-6 (18S6) adopts a conformation produced by connection of two bracket units by two $-CH_2CH_2-$ linkages. It crystallizes in the orthorhombic system, space group *Fdd*2, with *a* = 20.466 (1) Å, *b* = 33.222 (3) Å, *c* = 5.213 (4) Å, and *Z* = 8. Analysis of these structures reveals a pronounced preference for gauche placement at C–S bonds. This preference causes the ubiquity of bracket units and contrasts with the antipathy to gauche placement of the C–O bonds in oxa-crown ethers. This marked difference derives from the difference in C–E bond lengths, which changes nonbonded 1,4-interactions in both C–C–E–C and E–C–C–E fragments.

Crown ethers, and more generally crown-like molecules of the form $(-CH_2-CH_2-E-)_x$, have seen extensive use as bioinorganic model systems, binucleating ligands, chelators for specific metal ions, and phase-transfer catalysts. For these purposes they have several advantages. They permit control of both the coordination environment (donor atoms) and, in principle, the stereochemistry at a metal ion. In addition, they are easily synthesized by routes that permit systematic variation of ring size as well as identity and placement of heteroatoms. On the other hand, they do have one disadvantage: their design remains an essentially empirical exercise. Despite the pioneering work of Dale on conformational

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