Our optimized conditions for promoting the oxidative cyclization of substrates **6** and **12** (Scheme III) are derived from a related transformation initially reported by Yamamura[17] and later modified by Inoue.[18,19] We have found that the optimal protocol for the cyclization of **6** is oxidation with 10 equiv of thallium(III) nitrate trihydrate (TTN) (excess TTN is necessary to ensure complete reaction) in 5:1 THF/methanol at 1 mM concentration with 3 equiv of pyridine/equiv of TTN to serve as an acid scavenger. Increasing the ratio of THF to methanol results in incomplete reaction, while increasing the ratio of methanol to THF results in a lower yield. The reduction of the resulting para-quinol **13** is accomplished in situ by the addition of excess $CrCl_2$.[20] We have found these conditions to be superior to the zinc/acetic acid reduction described by Yamamura[19] as they avoid the isolation of the unstable intermediate para-quinol methyl ether. Under the conditions described above, the cyclic product **14** is isolated in 42% overall yield from the cyclization precursor **6**.

Model peptide **12** was cyclized and subsequently reduced under analogous conditions except that 1:1 CH_2Cl_2/methanol was employed as the solvent. When these conditions were employed, the macrocyclic diphenyl ether **16** was obtained in 48% overall yield. One notable difference between the two macrocyclizations is the displacement of bromine by methoxide in the formation of para-quinol **15**.[21] Presumably, this substitution occurs in the cyclization of **12** and *not* in the cyclization of **6** due to a more sterically crowded environment at the para position of the intermediate leading to **15**. *These observations thus dictate the order of assemblage of the macrobicyclic diether* **19**.

In order to evaluate the oxidative coupling strategy to provide the C, D, E bicyclic phenyl ether vancomycin synthon, the monocyclic diphenyl ether **14** was treated with trifluoroacetic acid to remove the Boc protecting group, and the resulting amine was coupled to tripeptide **11** with diisopropylcarbodiimide and hydroxybenzotriazole to provide the hexapeptide **17** in 72-78% overall yield (Scheme III).[16] The allyl group was then removed as described previously in 92-93% yield to provide hexapeptide **18**. The optimal conditions for the cyclization of **18** were found to be 5 equiv of TTN in 30:1 methylene chloride/methanol at 1 mM concentration (4 h, -23 °C). After in situ reduction of the resulting para-quinol ether with excess $CrCl_2$, the dicyclic compound **19** was obtained in 40% overall yield.

These studies clearly demonstrate the feasibility of pursuing a total synthesis of vancomycin and related antibiotics via biomimetic oxidative phenolic coupling.

Acknowledgment. Support has been provided by the National Institutes of Health, Eli Lilly, and Merck. The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities. J.A.E. and K.M.D. acknowledge support as NSF Predoctoral Fellows.

Supplementary Material Available: Spectral data for all compounds and detailed experimental procedures for the oxidative macrocyclizations as well as for the syntheses of **2-6**, **17**, and **18** (15 pages). Ordering information is given on any current masthead page.

(16) A diastereomeric compound, 7%, was also produced in this coupling reaction.

(17) Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481-4484.

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(21) In the oxidation of an analogue of **6** containing the Cbz protecting group rather than the Boc protecting group, approximately 5-10% of the methoxy-substituted derivative of **14** was also observed. In the limited number of systems that we have studied, increasing the ratio of THF to methanol and addition of pyridine increases the ratio of the bromo- to the methoxy-substituted cyclic products.

Aristolochene Biosynthesis and Enzymatic Cyclization of Farnesyl Pyrophosphate

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Received July 21, 1989

Aristolochene (**1**) is a bicyclic sesquiterpene belonging to the eremophilane group of hydrocarbons. The (-) enantiomer of **1** was first isolated in 1970 by Govindachari et al. from the plant *Aristolochia indica*.[1] It is also reported to occur in *Bixa orellana* leaf oil and in the defensive secretions of *Syntermes* soldier termites.[2,3] The (+) enantiomer **1** was recently isolated in our laboratory from the mycelial extracts of the fungus *Aspergillus terreus*.[4] The (+) enantiomer is also the probable biosynthetic precursor of PR toxin produced by *Penicillium roquefortii*.[5] Recently, Hohn and co-workers have isolated aristolochene synthase from *P. roquefortii*[6] and purified the enzyme to homogeneity.[7]

The proposed mechanism for the formation of aristolochene from farnesyl pyrophosphate (FPP) (2), the universal precursor of sesquiterpenes,[10] is shown in Scheme I. Cell-free extracts of *A. terreus* prepared from mycelia harvested between 45 and 60 h after inoculation showed terpenoid cyclase activity.[11] Preparative incubation of [1-^{3}H]FPP (**2a**)[12] with crude cell-free extracts produced radioactive hydrocarbon **1a**,[13] which was found to cochromatograph with synthetic (±)-aristolochene[14] on TLC (SiO_2, $AgNO_3$-SiO_2) as well as by radio-GC analysis (FFAP). Dilution with carrier (±)-aristolochene and oxidation with MCPBA followed by hydrolysis with $HClO_4$ gave the corresponding diol **3a**, which was recrystallized to constant activity, thereby confirming

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(6) Hohn, T. M.; Plattner, R. D. *Arch. Biochem. Biophys.* **1989**, *272*, 137.

(7) The epimeric sesquiterpene, (+)-5-epiaristolochene, has been demonstrated to be an intermediate[8a] in the biosynthesis of the phytoalexins capsidiol and debneyol.[8a] It has recently been shown that treatment of tissue cultures of *Nicotiana tabacum* with various elicitors results in appearance of a cyclase capable of converting FPP to a sesquiterpene hydrocarbon identified as (+)-5-epiaristolochene.[9]

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(13) The mycelia from 500 mL of 45-h culture were used to prepare the cell-free extract[11] in 190 mL of buffer (10 mM Tris, 5 mM $MgCl_2 \cdot 6H_2O$, 5 mM β-mercaptoethanol, and 15% v/v glycerol adjusted to pH 7.8 with 6 N HCl). [1-^{3}H]FPP (8.8×10^5 dpm, 7 mmol) was incubated with 2 mL of crude extract at 30 °C for 2 h, and the resulting radioactive hydrocarbon (4.0×10^4 dpm) was extracted into pentane, passed through a small SiO_2 column, and concentrated by Vigreux distillation.

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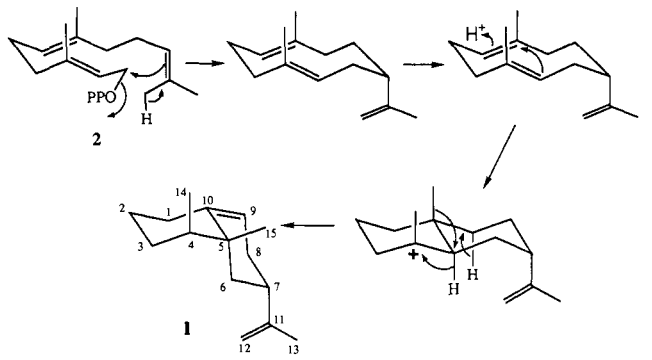
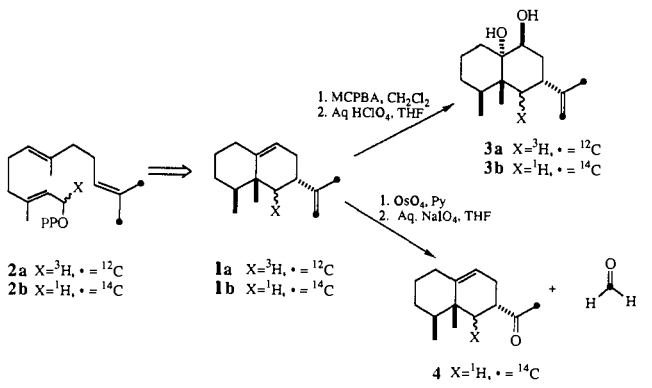
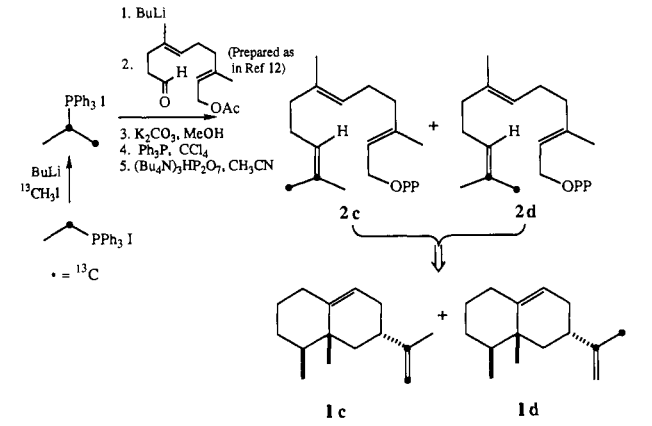
Scheme I



Scheme II



Scheme III



the structure of the enzymatic cyclization product. When an analogous incubation was carried out using [12,13-^{14}C]FPP (**2b**),[12] selective oxidation (OsO_4 followed by $NaIO_4$) of the derived aristolochene (**1b**) gave the methyl ketone **4** (semicarbazone, 6.61 × 10^4 dpm/mmol), which retained one-half the ^{14}C label present in the corresponding diol **3b** (1.28 × 10^5 dpm/mmol), as expected (Scheme II).

Unambiguous evidence for the distribution of isotopic label in the cyclization product was obtained by incubation of 5.75 μmol of a mixture of [11,12-$^{13}C_2$]- and [11,13-$^{13}C_2$]FPP (**2c,d**), prepared as shown in Scheme III and containing [12,13-^{14}C]FPP as internal standard, with crude aristolochene synthase at 30 °C for 3 h, yielding 370 nmol of aristolochene. After addition of carrier aristolochene (8 mg) to the crude pentane extract, the labeled aristolochene (**1c,d**) was purified by SiO_2 column chromatography (pentane) followed by $AgNO_3$–SiO_2 preparative TLC (solvent: 70% hexane, 30% benzene) and then analyzed by 100.61-MHz ^{13}C NMR. The peak corresponding to C-11 (δ 150.64 ppm) appeared as a pair of doublets flanking the natural abundance singlet (J (^{13}C–^{13}C) = 72 and 42 Hz), while the resonances corresponding to C-12 (δ 108.27 ppm, J = 72 Hz) and C-13 (δ 20.84 ppm, J = 42 Hz) each appeared as enhanced doublets.

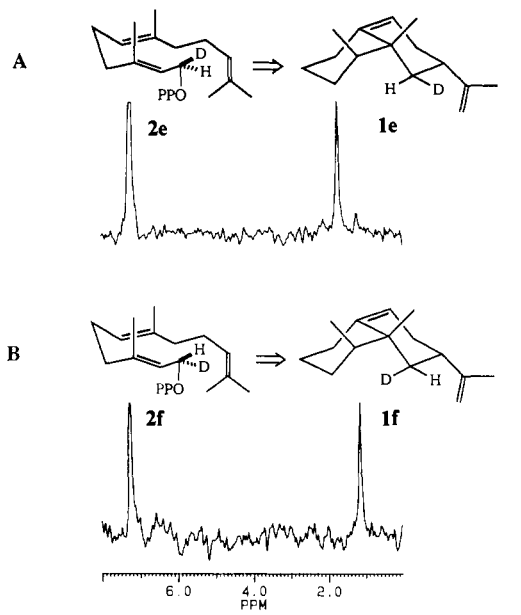


Figure 1. Deuterium NMR spectra (61.4 MHz) of aristolochene **1e** (300 nmol) and **1f** (480 nmol) derived from (A) (1*R*)-[1-^{2}H]FPP (**2e**) and (B) (1*S*)-[1-^{2}H]FPP (**2f**). Shifts are relative to natural abundance $CDCl_3$ at δ 7.24.

In order to establish the stereochemistry of the initial cyclization at C-1 of FPP, we required unambiguous assignments of the ^{1}H NMR chemical shifts of the geminal protons at C-6 of **1**. On the basis of ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCORR spectroscopy, the signal at δ 1.76 ppm (dt, J = 13.6, 4.0 Hz, geminal coupling to H-6_{ax}, vicinal coupling to H-7_{ax} and "*W*" coupling to H-8_{eq}) was assigned to the 6-equatorial proton and the signal at δ 1.17 (t, J = 13 Hz, geminal coupling to H-6_{eq}, vicinal coupling to H-7_{ax}) was assigned to H-6_{ax}. These assignments were supported by the results of difference NOE spectroscopy. Thus, irradiation at 1.76 ppm led to enhancement of the proton resonances at 2.25 (H-7, 3.8%), 1.17 (H-6_{ax}, 15%), 0.96 (H-15, 2.5%), and 0.83 ppm (H-14, 3.5%) whereas irradiation at 0.83 ppm resulted in enhancement of the peaks at 1.76 (H-6_{eq}, 2%) and 0.96 ppm (H-15, 1.5%). Furthermore, irradiation of the signal at 0.96 ppm gave rise to enhancements at 2.25 (H-7, 3.0%), 1.76 (H-6_{eq}, 1.2%), and 0.83 ppm (H-14, 1.7%). The observed NOEs were consistent with the conformation of aristolochene calculated by using the MacroModel molecular modeling program and an MM2 force field.

Both (1*R*)- and (1*S*)-[1-^{2}H]FPP (**2e** and **2f**)[15a] were separately incubated with crude aristolochene synthase from *A. terreus*, and the purified product from each incubation was analyzed by 61.42-MHz ^{2}H NMR spectroscopy. Aristolochene (**1e**) obtained from (1*R*)-[1-^{2}H]FPP exhibited a single peak at δ 1.76 ppm corresponding to H-6_{eq} (H-6_{re}) (Figure 1) and that (**1f**) from (1*S*)-[1-^{2}H]FPP showed a single peak at δ 1.17 ppm corresponding to H-6_{ax} (H-6_{si}) of aristolochene. These results clearly indicate that the cyclization of FPP to aristolochene is proceeding with *inversion of configuration* at C-1 of FPP, consistent with the mechanism illustrated in Scheme I. Similar results have been obtained for the enzymatic formation of pentalenene, involving initial cyclization of FPP through an 11-membered-ring, rather than a 10-membered-ring, intermediate.[15a] By contrast, cyclization of FPP to 6-membered-ring products requires initial isomerization to the tertiary allylic isomer nerolidyl pyrophosphate and has been shown to result in net *retention of configuration* at C-1 of the allylic pyrophosphate substrate.[15b,16,17]

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Square-Planar Complexes of Platinum(II) That Luminesce in Fluid Solution

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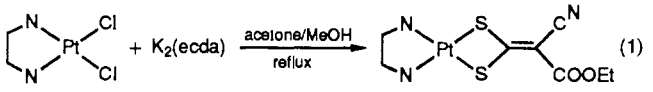
Very few mononuclear complexes of square-planar geometry luminesce in fluid solution,[1,2] principally because efficient radiationless decay occurs via collisions with solvent in the open coordination sites. Of the few d^8 complexes that do emit in fluid solution, only the cyclometalated species $Pt(thpy)_2$ (thpy = 2-(2-pyridyl)thiophenide) possesses an emitting state showing metal involvement.[3] Other luminescent Pt(II) complexes either are not mononuclear[4a] or emit only as solids at low temperature.[4b-e] In this paper we describe two new Pt(II) complexes that exhibit strong solution luminescence, show solvatochromic behavior, and undergo electron-transfer quenching with both donors and acceptors. These complexes are members of a larger class of solution luminescent dithiolate diimine d^8 systems.[5]

The complexes Pt(N⌒N)(ecda), where ecda = ethyl 2-cyano-3,3-dimercaptoacrylate and N⌒N = 4,4′-dimethyl-2,2′-bipyridine (**1**), and 4,7-diphenyl-1,10-phenanthroline (**2**) were prepared via eq 1 from $Pt(N⌒N)Cl_2$ and K_2(ecda). The complexes were



(1)

recrystallized from either CH_2Cl_2 or acetone, yielding analytically pure samples. Through characterization by electronic absorption, infrared, and ^1H NMR spectroscopies and field desorption mass spectrometry, the complexes were determined to be mononuclear square-planar systems.[6] Complex **1** exists in two forms depending on its solvent of crystallization—**1a** from CH_2Cl_2 is yellow and **1b** from acetone is red—but in all solution measurements, **1a** and **1b** are identical and show the same parent ion peak at m/e 566. Both **1** and **2** possess significantly greater solubility than the other Pt(II) diimine dithiolate complexes, which permitted their complete characterization including photochemical behavior.

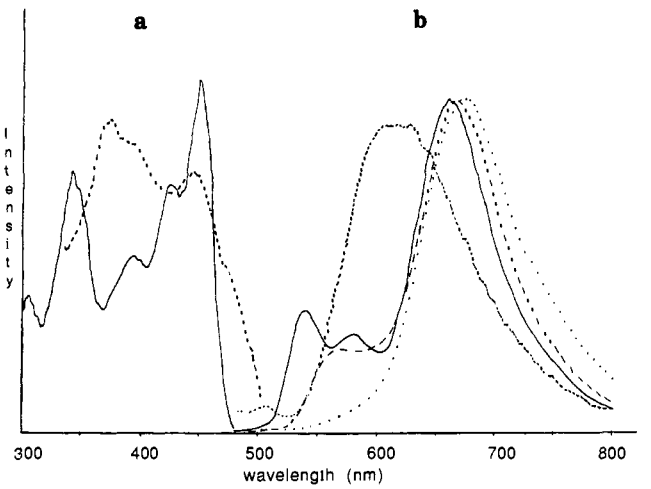


Figure 1. (a) Excitation spectra of Pt(dpphen)(ecad), **2** at 77 K in $DMF/CH_2Cl_2/MeOH$ collected at 540 nm (—) and 640 nm (---). (b) Emission spectra at 80 K (—), 140 K (---), 165 K (···), and 210 K (-·-).

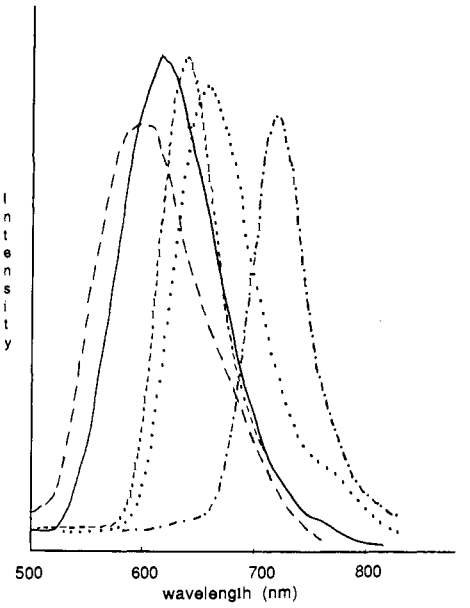


Figure 2. Emission spectra of **1** in CH_2Cl_2 (---) and in the solid state: yellow form at 298 K (—) and 77 K (---); red form at 298 K (···) and 77 K (-·-).

Solutions of **1** and **2** exhibit an intense absorption in the 400–500-nm region ($\epsilon \sim 14000$–15000) which shifts to higher energy with increasing solvent polarity. For **1** the absorption maximum changes from 450 nm in $CHCl_3$ to 418 nm in DMSO, while for **2** the change is from 468 to 438 nm. Titration of CH_2Cl_2 solutions of the complexes with DMF also leads to a gradual shift of the absorption maxima to higher energy. Both complexes exhibit similar electrochemical behavior, undergoing two reversible reductions and an irreversible oxidation in DMF. The values of $E_{1/2}^{red(1)}$, $E_{1/2}^{red(2)}$ and E_p^{ox} are −1.28, −1.77, and 0.83 V for **1** and −1.12, −1.68, and 0.75 V for **2** relative to Fc^+/Fc at 0.40 V (determined by using a glassy carbon electrode and a Ag wire quasi-reference).

Both complexes show the extraordinary property of luminescing in fluid solution at room temperature. The emissions are broad and asymmetric as shown in Figures 1 and 2. For complex **2** the emission in $CH_2Cl_2/DMF/MeOH$ (1:1:1 v/v/v) shifts to lower energy upon cooling to a glass with emergence of two higher energy bands below 90 K (Figure 1). The excitation spectra of **1** and

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(2) Ballardini, R.; Gandolfi, M. T.; Balzani, V.; Kohnke, F. H.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 692.
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(5) In these Pt(N⌒N)(S⌒S) complexes, the diimine ligands include 2,2′-bipyridine (bpy), 1,10-phenanthroline (phen), 4,4′-dimethyl-2,2′-bipyridine (dmpby), 4,4′-diphenyl-2,2′-bipyridine (dpbpy), and 4,7-diphenyl-1,10-phenanthroline (dpphen) while the dithiolates are maleonitriledithiolate (mnt), 2,2-dicyano-1,1-ethylenedithiolate (i-mnt), and ethyl 2-cyano-3,3-dimercaptoacrylate (ecda). See: (a) Zuleta, J. A.; Burberry, M.; Eisenberg, R. 8th International Symposium on the Photochemistry and Photophysics of Coordination Compounds, Santa Barbara, Aug 13–17, 1989. (b) Zuleta, J. A.; Burberry, M.; Eisenberg, R. *Coord. Chem. Rev.* In press.
(6) ^1H NMR (CH_2Cl_2) for **1**: δ 8.31 (d, 1 H), 8.21 (d, 1 H), 7.92 (s, 2 H), 7.34 (d, 2 H), 4.22 (q, 5.5 Hz, 2 H), 2.59 (s, 6 H), 1.33 (t, 5.5 Hz, 3 H). IR spectra (KBr) show peaks due to coordinated diimine by comparison to $Pt(N⌒N)Cl_2$ and to ecda at 2203, 1449, and 1153 cm^{-1} for **1** and 2201, 1451, and 1158 cm^{-1} for **2**. Field desorption mass spectrometry gives parent peaks at m/e of 566 for **1** and 714 for **2**.

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