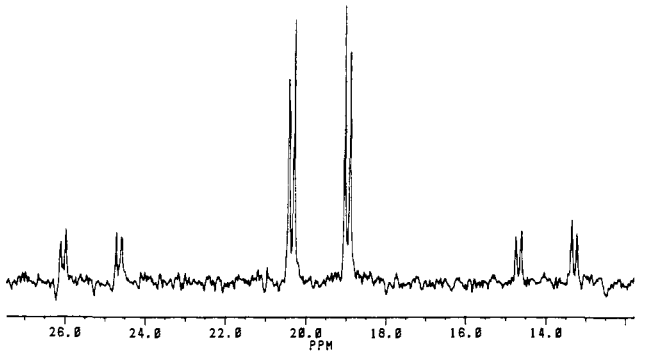
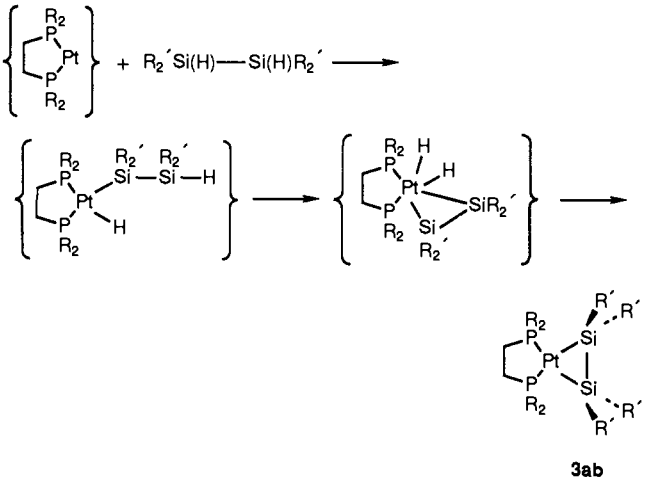


Figure 1. $^{29}Si[^1H]$ NMR spectrum for **3a**.

Scheme I. Proposed Mechanism for the Formation of **3ab**

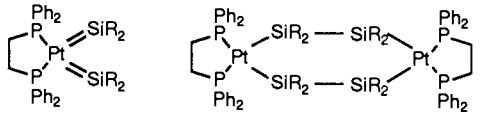


3ab

The NMR, IR, and mass spectra of **3ab**[10] are consistent with their formulation as platinum–disilene complexes. In the fast atom bombardment MS of **3ab**, the highest mass (100%) peaks are those due to the parent ions, **3ab**$^+$. The IR spectra showed no indication of Si–H or Pt–H stretching frequencies, in the 1700–2500 cm^{-1} region. The $^{29}Si\{^1H\}$ NMR spectra, displayed for **3a** in Figure 1, show the expected pattern of a doublet of doublets from coupling to two different ^{31}P nuclei, along with satellites arising from coupling to ^{195}Pt. The ^{29}Si chemical shift values, 19.60 ppm for **3a** and −7.84 ppm for **3b**, are intermediate between those for typical disilenes (45–90 ppm) and those for other disilicon three-membered ring compounds (~ −60 ppm).[1e] The ^{31}P NMR spectra are singlets with satellites due to ^{195}Pt and ^{29}Si, the latter corroborating the values obtained from the ^{29}Si NMR spectrum.

We attribute the larger of the $^2J_{P,Si}$ values, 138 Hz for **3a** and 148 Hz for **3b**, to trans coupling between silicon and phosphorus. The $^1J_{Pt,P}$ coupling constants, 1344 Hz for **3a** and 1545 Hz for **3b**, are much smaller than those for **1ab** or for Pt–olefin complexes (ca. 3500 Hz).[11] This indicates that in **3ab** the Pt–P bond is made less covalent by a ligand of relatively high trans influence.[12] Silyl groups have been shown to reduce Pt–P coupling constants in trans bonds markedly.[13]

The proposed structure for **3ab** corresponds to the synergistic bonding of the Dewar–Chatt–Duncanson model, commonly used to describe bonding from alkenes to transition metals. Two other structures which might be considered for **3ab** are the bis-silylene structure **5** and the dimeric structure **6**. Although an oxygen-



5 **6**

bridged bis-silylene complex of iron has recently been synthesized,[14] this structure seems unlikely in the absence of stabilization by bases and is inconsistent with the observation of an $iPr_2SiSiiPr_2^+$ fragment in the mass spectrum of **3a**. Structure **6** can be ruled out because no long-range spin couplings, $^2J_{Pt,Si}$ or $^3J_{P,Si}$, were observed.

The formation of **3ab** may be rationalized via an oxidative addition–reductive elimination mechanism (Scheme I). First, the unsaturated Pt fragment, 1,2-bis(dialkyl/arylphosphino)-ethaneplatinum, generated from LiCl elimination or loss of ethylene, adds oxidatively to the two Si–H bonds to yield the six-coordinate Pt intermediate which then eliminates dihydrogen, forming **3ab**. These results show that disilenes can be stabilized as platinum complexes, even without sterically hindering substituents on silicon. We are now investigating the reaction chemistry of **3ab**, and, while initial attempts have been unsuccessful, efforts to obtain single crystals of **3ab** suitable for X-ray diffraction are continuing.

Acknowledgment. This work was supported by the Air Force Office of Scientific Research, Air Force Systems Command, USAF under contract No. F49620-86-C-0010 and the National Science Foundation, Grant No. CHE-8318810-02.

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(10) **3a**: MS (FAB) *m/e* 822 (M^+, 100% rel intensity), 751 (M^+ − Si*i*-Pr, 20%), 708 (M^+ − Si*i*-Pr_2, 38%), 594 (M^+, Si_2*i*-Pr_4, 70%); ^1H NMR (CD_2Cl_2), 25 °C, 200 MHz) 7.61 (m, 8 H, *o*-PhH), 7.43 (m, 12 H, *m*- and *p*-PhH), 2.14 (dt, $^2J_{PH}$ = 17.6 Hz, $^3J_{HH}$ = 6.3 Hz), 2.05 (dt, $^2J_{PH}$ = 17.6 Hz, $^3J_{HH}$ = 6.3 Hz), 1.55 (m, 4 H, *i*-PrH), 0.85 (d, $^3J_{HH}$ = 10.4 Hz, 24 H, *i*-PrH); $^{31}P\{^1H\}$ NMR (C_7D_8, 27 °C, 202.5 MHz) 56.21 ppm (s, $^1J_{Pt,P}$ = 1344 Hz, $^2J_{P(cis),Si}$ = 12.5 Hz, $^2J_{P(trans),Si}$ = 138 Hz); $^{29}Si\{^1H\}$ NMR (C_7D_8, 27 °C, 99.4 MHz, INEPT) 19.60 ppm (dd, $^1J_{Pt,Si}$ = 1128 Hz, $^2J_{P(cis),Si}$ = 12.5 Hz, $^2J_{P(trans),Si}$ = 138 Hz). Anal. Calcd for $C_{38}H_{52}P_2Si_2Pt$: C, 55.52; H, 6.38. Found: C, 55.69; H, 6.36. **3b**: MS (FAB) *m/e* 982 (M^+, 100% rel intensity), 906 (M^+ − Ph, 77%), 877 (M^+ − SiPh, 46%), 800 (M^+ − $SiPh_2$, 52%); ^1H NMR (CD_2Cl_2, 25 °C, 200 MHz) 7.42 (m, 8 H, *o*-PhH), 7.1 (m, 12 H, *m*- and *p*-PhH), 2.3 (m, 4 H, PCH_2CH_2P), 1.7–1.4 (m, 44 H, CyH); $^{31}P\{^1H\}$ NMR (C_7D_8, 25 °C, 202.5 MHz) 73.47 ppm (s, $^1J_{Pt,P}$ = 1545 Hz, $^2J_{P(cis),Si}$ = 13.5 Hz, $^2J_{P(trans),Si}$ = 148 Hz); $^{29}Si\{^1H\}$ NMR (C_7D_8, 30 °C, 99.4 MHz, INEPT) −7.84 ppm (dd, $^2J_{P(cis),Si}$ = 13.5 Hz, $^2J_{P(trans),Si}$ = 148 Hz, $^1J_{Pt,Si}$ = 1125 Hz). Anal. Calcd for $C_{50}H_{68}P_2PtSi_2$: C, 61.1; H, 6.93. Found: C, 58.7; H, 6.94.

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The Total Synthesis of (−)-Cryptosporin†

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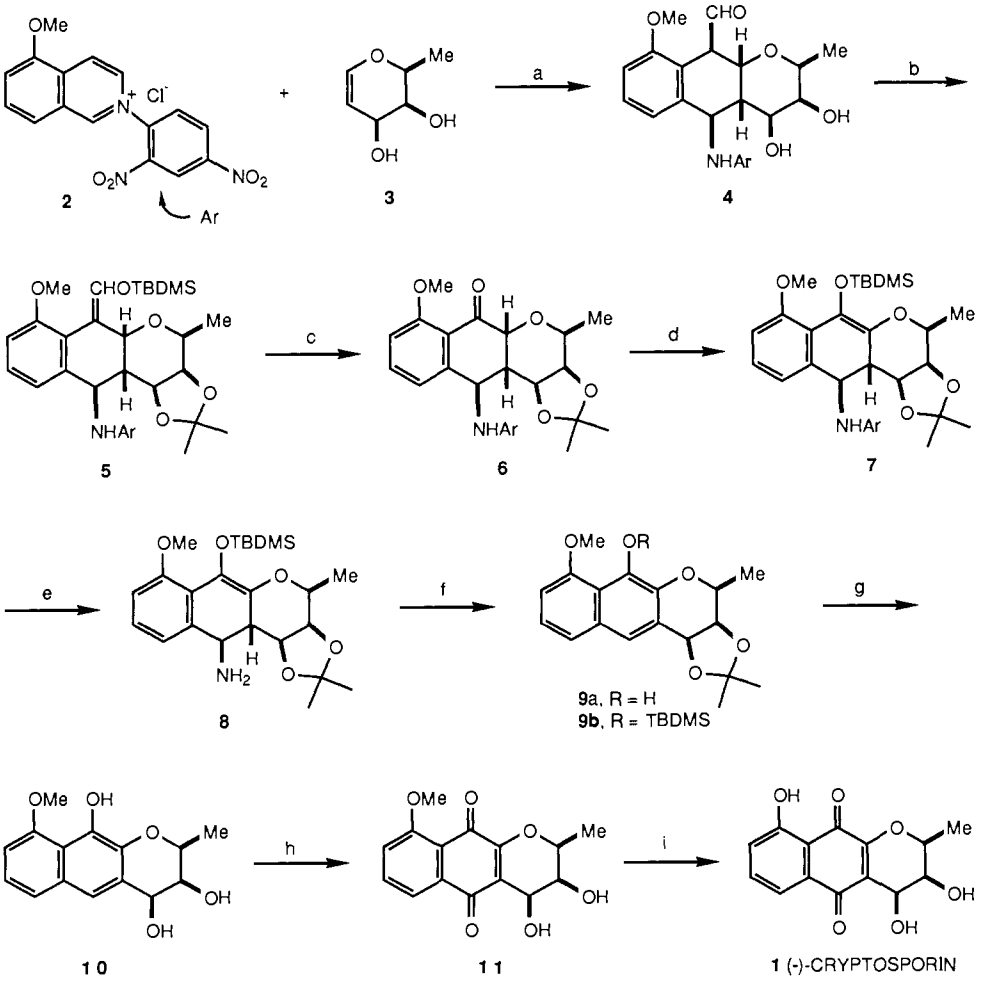
(+)-Cryptosporin, a yellow fungal metabolite with weak activity against gram-positive bacteria, can be isolated from the fermentation broths of *Cryptosporium pinicola* LINDER.[1] Its original structural assignment was based on an analysis of NMR data and a comparison of a degradation product with a hydroxyjuglone, and the peri-hydroxyl was located at C-6. Later, the hydroxyl was relocated to C-9, as shown in **1** when a confusion in the original samples of hydroxyjuglone reference samples was

† This paper is dedicated to William S. Johnson in the year of his 76th birthday and his Cope Medal award.

0002-7863/89/1511-7668$01.50/0

Scheme I[a]



[a](a) (i) MeOH, $CaCO_3$, 55–60 °C, 3 days; (ii) 1 N HCl, CH_3CN, 25 °C, 1 day, 95%; (b) (i), 2,2-dimethoxypropane, acetone, *p*-TsOH, 4 Å MS, 0–25 °C, 1 h; (ii) TBDMSOTf, Et_3N, CH_2Cl_2, 0–25 °C, 1 h, 91%; (c) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, 5–25 °C, 0.5 h, 78%; (d) TBDMSOTf, Et_3N, CH_2Cl_2, 0–25 °C, 4 h, 95%; (e) $LiBH_4$, EtOH, THF, H_2O, 25 °C, 20 h, 90%; (f) MeI, K_2CO_3, MeOH, 25 °C, 30 h, **9a** = 56%, **9b** = 12%; (g) 3 N HCl, CH_3CN, 45 °C, 4 h, 92%; (h) salcomine, CH_3CN, O_2, 25 °C, 45 min, 72%; (i) BCl_3, CH_2Cl_2, −78 °C to −40 °C, 6 h, 77%.

unearthed. The relocation was confirmed by a proton-coupled ^{13}C spectrum.[2] The relative configuration of groups in the pyran ring was assigned from NMR coupling constants, and the illustrated absolute configuration was chosen by interpreting the positive CD Cotton effect of the 3,4-dibenzoate according to the exciton-chirality rules of Harada and Nakanishi.[3] The only published work on the synthesis of the antibiotic was reported by Krohn and co-workers.[4] Their route led to a racemic 9-deoxy compound which confirmed the relative configuration assignment but not the absolute stereochemistry or the location of the peri-hydroxyl.

Cryptosporin belongs to an important class of naturally occurring 3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran-5,10-quinones which possesses a wide range of biological activities. No efficient method has been reported for the preparation of this family of compounds. The most common approach involves construction of the pyrano ring by cyclization of 2-hydroxy-3-alkenylated-1,4-naphthoquinones.[4-7] We wish to report an entirely new methodology for making the required pyranonaphthoquinones as illustrated by an efficient total synthesis of cryptosporin (**1**) via cycloaddition of isoquinolinium salt **2** with L-fucal **3**. Our sample of cryptosporin has a rotation and CD spectrum opposite to that of a sample obtained from natural sources. Thus, we conclude that natural cryptosporin must have the 2*R*,3*R*,4*R* configuration, enantiomeric to formula **1**.

Our synthesis begins with the key Bradsher cycloaddition[8] of **2** and **3** which requires 3 days at 55–60 °C. Workup with aqueous acid affords aldehyde **4** in 95% yield (Scheme I).[9,10] After ketalization of the diol, the aldehyde is converted to its enol silyl derivative **5** with TBDMSOTf and Et_3N. Oxidative cleavage of

(1) Closse, A.; Sigg, H.-P. *Helv. Chim. Acta* **1973**, *56*, 619.
(2) Thomson, R. H. *Naturally Occurring Quinones, III*; Chapman and Hall: New York, 1987; pp 198–199. A report of a private communication from Dr. Closse.
(3) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983. On p 115 the authors comment on the cryptosporin assignment "However, in order to obtain a more definite conclusion, it would have been better to block the phenol group by methylation and to employ a para-substituted benzoate chromophore: this is in order to avoid interaction with the naphthoquinone chromophore."
(4) Krohn, K.; Bruckner, G.; Tietjen, H.-P. *Chem. Ber.* **1978**, *111*, 1284.
(5) (a) Thomson, R. H. *Naturally Occurring Quinones, III*; Chapman and Hall: New York, 1987. (b) Thomson, R. H. *Naturally Occurring Quinones*, 2nd, ed.; Academic Press: New York, 1971.
(6) For a review of synthetic methods, see: *Houben-Weyl Methoden der Organischen Chemie, Chinon-I*; George Thieme Verlag: Berlin, 1979; Vol. VII-3a, pp 373–384.
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the enol ether using a Sharpless method[11] affords ketone **6** in 71% yield from **4**. Aromatization to the key naphthol **10** requires four manipulations/enol silylation of the ketone[12] to produce **7**; cleavage of the DNP group to form **8**; modified Hofmann elimination to yield a mixture of naphthol and silyl ether **9a** and **9b**; and finally acid hydrolysis to obtain **10** in 53% overall yield from **6**. Salcomine oxidation[13] of **10** where the use of CH_3CN as solvent is critical, affords the methyl ether of *ent*-cryptosporin **11** in 72% yield. Finally, BCl_3/CH_2Cl_2 demethylation at −40 °C for 6 h gave *ent*-cryptosporin (**1**) mp 242–249 °C (dec) (lit. 244–250 °C (dec)),[1] identical in all respects, except for opposite rotation and mirror-image CD spectrum, to the natural product. It is interesting that the configuration proven by our synthesis validates Harada and Nakanishi's cautionary note[3] about the application of their dibenzoate rule as the basis for the assignment in the original experiment of Closse and Sigg.[1] Thus, the interaction of the naphthoquinone chromophore with the 4-benzoate dominates the CD Cotton effect producing the observed positive sign, whereas the original workers assumed that the 3,4-dibenzoate relationship was the determining factor. A similar interaction has been reported by Inouye in his lapachone studies.[14]

We believe that the methodology described will be generally applicable to the regiospecific synthesis of naturally occurring naphtho[2,3-*b*]pyrano- and [2,3-*b*]furanoquinones.[15]

Acknowledgment. We are indebted to the National Cancer Institute for Grant CA 39351, to the American Cancer Society for Grant CH 272, and to CUNY for PSC research awards which supported this work. NMR instruments used were obtained through Grants NSF-PCM 111745 and NIH RR 03214. We thank Dr. Katta of the Rockefeller University Mass Spectrometric Biotechnology Resource for obtaining the mass spectra. We are indebted to Dr. Rene Traber of the Biotechnology and Natural Product Chemistry division of Sandoz Ltd., Basle, for a sample of natural cryptosporin.

Supplementary Material Available: CD spectra of natural and synthetic cryptosporins (1 page). Ordering information is given on any current masthead page.

(8) For a recent paper with an up-to-date bibiliography on the Bradsher cycloaddition, see: Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 5393.

(9) All yields reported are for isolated materials, homogeneous on TLC, and characterized by ^1H and ^{13}C NMR. Compounds **1**, **4**, **6**, **9a**, and **10** were also characterized by exact mass determination high-resolution mass spectrometry.

(10) Adduct **4** is a homogeneous material with seven homochiral centers, the relative configurations of which were established by extensive decoupling experiments. Full details of our study of a variety of isoquinolinium salt/glycal cycloadducts will be described separately: Gupta, R. B.; Franck, R. W., manuscript in preparation.

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(14) Inouye, H.; Okuda, T.; Hayashi, T. *Chem. Pharm. Bull.* **1975**, *23*, 384.

(15) Our work in progress on the first syntheses of kigelinone, diodantunezone, and 8-hydroxy-2-isopropenylnaphtho[2,3-*b*]furan-4,9-quinone will resolve the ambiguities about the location of the peri-hydroxyls in these antibiotics, see ref 5a. For recent work in the furanoquinone field, see: Zani, C. L.; de Oliveira, A. B.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 6561. Lopes, C. C.; Lima, E. L. S.; Monteiro, A. J.; Costa, P. R. R. *Synth. Commun.* **1988**, *18*, 1731. Lopes, C. C.; Lopes, R. S. C.; Pinto, A. V.; Costa, P. R. R. *J. Heterocycl. Chem.* **1984**, *21*, 621. Ghera, E.; Maurya, R.; Ben-David, Y. *Tetrahedron Lett.* **1986**, *27*, 3935. Kang, W. B.; Nanya, S.; Toru, T.; Ueno, Y. *Chem. Lett.* **1988**, 1415.