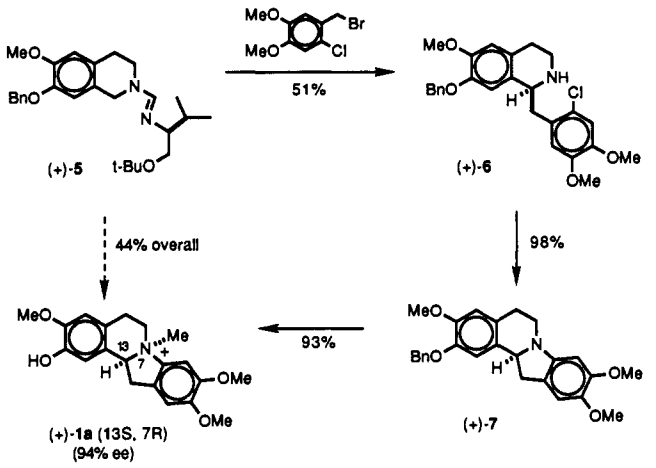
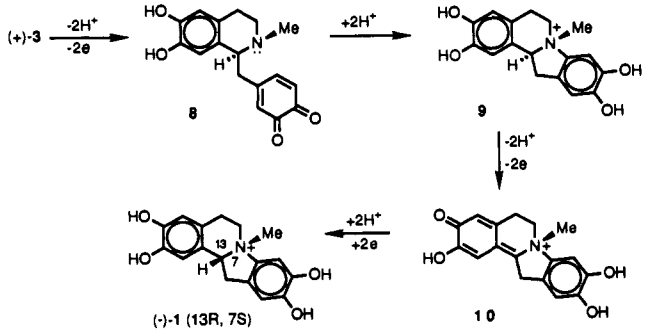



question arose whether or not the natural alkaloid **1a** had been correctly assigned. As mentioned above, Brossi et al.[7] had shown that (*S*)-(+)-laudanosoline (**3**) had given optically active **1** (R = OH) when treated with horseradish peroxidase (Scheme I) and, after exhaustive methylation, provided the tetramethoxy derivative (Scheme I, **1**, R = Me). Furthermore, they methylated (-)-**1a**, the naturally isolated compound, to also provide the tetramethoxy derivative. Comparison of optical rotation of the material from both sources was in good agreement, which led to the reasonable conclusion that cryptaustoline possessed the *S* configuration at C-13. In attempts to clarify this obvious discrepancy, Cotton curves were examined for our intermediates (+)-**6**, (+)-**7**, and the final product, (+)-**1**. In all cases a positive Cotton curve was obtained (Table I). However, when we examined the Cotton curves for the route to cryptaustoline using horseradish peroxidase or the chloranil oxidation, we found that the coupled cyclized quaternary salts **1** (Scheme I) exhibited a negative Cotton effect. Furthermore, generation of the tetramethoxy derivative **1** (R = Me) also showed a negative Cotton effect (Table I). Thus, it was clear that *even though both routes to cryptaustoline derivatives began with a 1-benzylisoquinoline with the S configuration* [(+)-*3 and* (+)-*6*], *the oxidative route gave inverted stereochemistry at C-13 whereas the benzyne route retained stereochemistry*. Since the oxidative route may also be the most likely biosynthetic pathway,[3,7-9] nature has played a devious game which caused two scientific groups to misassign the stereochemistry of these alkaloids, and only through a rational asymmetric synthesis was this uncovered.

We propose that the (1*S*)-(+)-1-benzylisoquinoline **3** undergoes oxidation to the quinone **8**, which adds in a Michael fashion to the enone in **8**, affording the trans-fused dibenzopyrrocoline **9**.




This is consistent with molecular mechanics calculations, which show that, of the four lowest energy conformations, only **8** has the correct orbital alignment to allow Michael addition. After ring closure had occurred, we examined the relative energies of trans-fused **9** and the cis-fused observed end product, **1**. According to annealed molecular dynamics calculations, the trans-fused system was 9.3 kcal (±2) less stable than the cis-fused system, the greatest contribution (~7 kcal) comining from angle strain in **9**. This energy difference could be responsible for a second phenolic oxidation of **9** leading to the quinone, **10**. With the NMe quaternary center as the newly installed stereocenter, this anchors the absolute stereochemistry and then allows reprotonation of the reduced form, furnishing the more stable cis-ring-fused and final natural product, (-)-**1**.[12-14] In summary, the natural alkaloid cryptaustoline is (13*R*,7*S*)-(-)-**1** due to the heretofore unprecedented inversion while the formamidine route led to the expected (13*S*,7*R*)-(+)-**1**.

**Acknowledgment**. We are grateful to Dr. Arnold Brossi for his cooperation and discussions during the course of this study. Thanks are due to Ms. Laurie Castonguay for her assistance in performing the MM2 calculations. Financial support for this work was provided by the National Science Foundation, to whom we express our gratitude.

(12) Another route of stereochemical inversion of (+)-**3** to (-)-**1** was suggested to us by Dr. Arnold Brossi. The negative gegenion ($I^-$ or $Br^-$) in **9** could attack the C-13 position to produce a nine-membered ring,[13] which could reclose, giving the more stable optically active cis system. However, this experiment was attempted by placing (-)-**1** in aqueous solution, pH 4-5, similar to that employed[7] when horseradish peroxidase was used. The molecule slowly racemized after 48 h at room temperature whereas racemization was virtually complete at reflux in 1 h. Thus, ring opening is a viable process, but only leads to racemization.

(13) Nine-membered rings have been known to be conformationally stable, which may allow for ring closure to an optically active product; cf.: (a) Magnus, P.; Ladlow, M.; Elliot, J.; Kim, C. S. *J. Chem. Soc., Chem. Commun.* **1989**, 518. (b) Mislow, K.; Hyden, S.; Schaefer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1449.

(14) Another possible inversion route could involve the ylide of **9**. However, treatment of **9** in $D_2O$-$CDCl_3$ or $CF_3CO_2D$ for 1 h showed no evidence of D incorporation at C-13.

## Stereoselectivity in Guest Release from Constrictive Binding in a Hemicarceplex[1]

J. Kevin Judice and Donald J. Cram*

*Department of Chemistry and Biochemistry*
*University of California at Los Angeles*
*Los Angeles, California 90024*

*Received December 20, 1990*

We report the syntheses of enantiomerically pure $(R)_4$-**1**·$CHCl_3$[2] (12%) and $(S)_4$-**1**·$CHCl_3$[2] (13% yield) from rigid bowl-shaped cavitand **2**[3] and enantiomerically pure (*R*)-**3** and (*S*)-**3**, respectively.[4,5] All protons in the 500-MHz NMR spectrum of $(R)_4$-**1**·$CHCl_3$ in $CDCl_3$ (except those of the eight phenyl groups) were assigned, where necessary, by $^1H$-$^1H$ COSY[6a] or NOE difference experiments.[6b] When **1**·$CHCl_3$ isomers in neat solvents were heated at the temperatures indicated, guest exchange occurred to give **1**·G (1:1 hemicarceplexes, $^1H$ NMR integrations), with G = 1,4-$(CH_3)_2C_6H_4$ (100 °C, 18 h),[7] $CH_3CHICH_2CH_3$ (70 °C, 4 h), $CH_3CHOHCH_2CH_3$ (in 5-$(CH_3)_3$C-1,3-$(CH_3)_2C_6H_3$, 90 °C, 24 h), and $BrCH_2CH(CH_3)_2$ (90 °C, 4 h). The hemicarceplexes liberated their guests in $CDCl_3$ at 23 °C with $t_{1/2}$ values ($^1H$ NMR spectral changes) as follows: 1,4-

(1) We warmly thank the National Science Foundation for support through Grant NSF CHE 88 02800.

(2) Elemental analyses (C, H) were within 0.30% of theory, 500-MHz NMR spectra in $CDCl_3$ were structurally consistent, and FAB MS gave expected molecular ions.

(3) Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4527-4528.

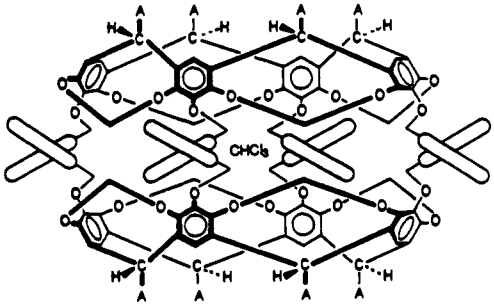
(4) (a) Hall, D. M.; Turner, E. E. *J. Chem. Soc., Chem. Commun.* **1955**, 1242-1251. (b) Harata, K.; Tanaka, J. *Bull, Chem. Soc. Jpn.* **1973**, *46*, 2747-2751.

(5) The reaction was run in pure, dry $(CH_3)_2NCOCH_3$-$Cs_2CO_3$ (40 °C, argon, 5 days, double syringe pump). After isolation (evaporation at 50 °C, chromatography), the carceplex was dissolved in $CHCl_3$, where guest exchange occurred rapidly. The product was precipitated by addition of pentane and was dried at 25 °C at $10^{-2}$ Torr, 3 h. For $(S)_4$-**1**·$CHCl_3$, $[\alpha]^{23}_{545}$ -52.4° (*c*, 0.042, $CHCl_3$); for $(R)_4$-**1**·$CHCl_3$, $[\alpha]^{23}_{546}$ +53.6° (*c*, 0.36, $CHCl_3$).

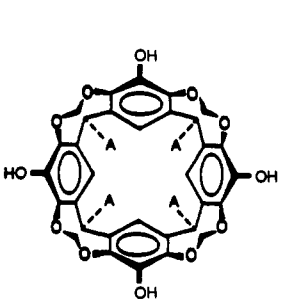
(6) (a) Derome, A. E. *Modern NMR Techniques for Chemical Research*; Pergamon Press: Oxford, 1987; Chapter 8; (b) Chapter 6.

(7) Heating **1**·$CHCl_3$ in $CH_3CH_2C_6H_4$ at 115-140 °C did not provide **1**·$CH_3CH_2C_6H_5$, whose CPK models cannot be assembled.

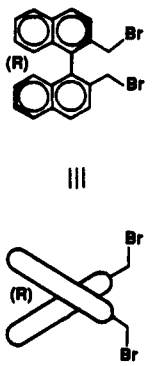
0002-7863/91/1513-2790$02.50/0 




$(R)_4$-**1**·$CHCl_3$, A = $CH_2CH_2C_6H_5$




**2**, A = $CH_2CH_2C_6H_5$




(R)-**3**

$(CH_3)_2C_6H_4$, 3 h; $CH_3CHICH_2CH_3$, ≈50 000 h; $CH_3CHOHCH_2CH_3$, 2 h; $BrCH_2CH(CH_3)_2$, 0.33 h. The $CH_3$ protons in the $^1H$ NMR spectrum of **1**·1,4-$(CH_3)_2C_6H_4$ are moved by incarceration upfield by 4 ppm and the Ar*H* protons by 2 ppm. A CPK molecular model of **1**·1,4-$(CH_3)_2C_6H_4$ can be constructed only with the long axes of each component coincident. Molecular model examination suggests that guest replacement occurs via four chiral equatorial portals generated by increasing the dihedral angles of the four binaphthyls.

For chiral selectivity studies during guest release, 1:1 hemicarceplexes were prepared.[8] From enantiomerically pure (*S*)-$BrCH_2CH(CH_3)CH_2CH_3$[9] were obtained $(R)_4$-**1**·(*S*)-$BrCH_2CH(CH_3)CH_2CH_3$[2] and $(S)_4$-**1**·(*R*)-$BrCH_2CH(CH_3)CH_2CH_3$.[2] The first-order rate constant for guest release[10] for the $(R)_4$-(*S*) isomer was $(4.4 \pm 0.3) \times 10^{-2}$ h$^{-1}$, and for the $(S)_4$-(*S*) isomer it was $(6.2 \pm 0.3) \times 10^{-3}$ h$^{-1}$, to provide $k_{R_4S}/k_{S_4S} = 7$.

From $(S)_4$-**1**·$CHCl_3$ and racemic $BrCH_2CH_2CHBrCH_3$ was prepared[8] a mixture of diastereomeric complexes (99% yield) in which one diastereomer dominated by a factor that varied in three identical runs from 1.5:1 to 2:1, reflecting a difference in free energies of association for the diastereomeric complexes of ~300 cal mol$^{-1}$ at 100 °C.[11] The dissociation rate constants[10] were $k_{fast} = (3.0 \pm 0.7) \times 10^{-1}$ h$^{-1}$ and $k_{slow} = (5.8 \pm 0.5) \times 10^{-2}$ h$^{-1}$ to give $k_{fast}/k_{slow} = 5$. The *less* thermodynamically stable isomer provided the *faster* rate. Similarly, from $(S)_4$-**1**·$CHCl_3$ and racemic $BrCH_2CHBrCH_2CH_3$ was prepared[8] an equilibrated diastereomeric mixture in a ratio of 2:1. The dissociation rate constants[10] were $k_{fast} = (1.21 \pm 0.06) \times 10^{-2}$ h$^{-1}$ and $k_{slow} = (1.3 \pm 0.4) \times 10^{-3}$ h$^{-1}$ to give $k_{fast}/k_{slow} = 9$. The *more* stable diastereomer provided the faster rate.

The $\Delta\Delta G^{\ddagger}$ values at 23 °C for the diastereomeric complexes dissociating were as follows: for $BrCH_2CH(CH_3)CH_2CH_3$, 1.1 kcal mol$^{-1}$; for $BrCH_2CH_2CHBrCH_3$, 1.0 kcal mol$^{-1}$; for $BrCH_2CHBrCH_2CH_3$, 1.3 kcal mol$^{-1}$. The $\Delta\Delta G°$ values at 100 °C for the latter diastereomers are ~300 cal mol$^{-1}$. Usually, $\Delta\Delta G°$ values for diastereomeric complexes decrease with increasing temperature.[12] If in the present study $\Delta\Delta G°$ remained at ~300 cal mol$^{-1}$ at 23 °C, the $\Delta\Delta G^{\ddagger}$ value for the *complexation diastereomeric transition state* would be 1.6 kcal mol$^{-1}$ for $BrCH_2CHBrCH_2CH_3$ ($k_{fast}/k_{slow} \sim 15$) and 0.7 kcal mol$^{-1}$ for $BrCH_2CH_2CHBrCH_3$ ($k_{fast}/k_{slow} \sim 3$).

Differences in steric repulsions in the diastereomeric transition states are probably responsible for the chiral selectivity in decomplexation. With each of the three chiral guests examined, the host discriminates between the steric requirements for $CH_3$ vs Br, or $CH_3CH_2$ vs $BrCH_2$. The relative sizes of covalently bound $CH_3$ and Br calculated from their volumes[13a] and surface areas[13b] differ by only 5-10%. The thermodynamic stereoselectivity of $\Delta\Delta G° \sim 300$ at 100 °C observed for the enantiomeric dibromides approximates that shown by Collet's chiral cyclotriveratrylene-based cryptophanes binding CHFClBr ($\Delta\Delta G°$ = 260 cal mol$^{-1}$ at 56 °C).[14]

(8) Enantiomers of **1**·$CHCl_3$ (8-15 mg) dissolved in 2.5-15 g of guest were heated to 100 °C for 18 h in the dark. The solutions were cooled and filtered into 30-50 mL of pentane. The precipitate was collected, washed, and dried (25 °C, $10^{-2}$ Torr, 2 h).

(9) Aldrich Chemical Co., Milwaukee, WI, 1989-1990 catalog, p 555.

(10) The disappearance of hemicarceplex $^1H$ NMR (500 MHz, $CDCl_3$, 23 °C) spectral signals was followed. The signal integral for each point was compared with that of the 7,7′-binaphthyl protons at δ 7.6, whose clear multiplet was essentially guest independent. For the isomers of **1**·$BrCH_2CH(CH_3)CH_2CH_3$, the complexed host signal disappearance for the inward-turned $OCH_2O$ proton at δ 4.31 (doublet) was employed (six or seven points, $R^2 = 0.998$, both isomers). In the thermodynamic determinations and kinetic resolution of the isomers of **1**·$BrCH_2CH_2CHBrCH_3$, the bound guest doublet signals at δ -2.07 and -1.70 ($CH_3$) were employed (five points, $R^2 = 0.999$ for the rapidly and 0.997 for the slowly dissociating isomer). Similarly, for the isomers of **1**·$BrCH_2CHBrCH_2CH_3$, the bound guest triplets of $CH_3$ at δ -3.01 and -2.86 were employed (eight points, $R^2 = 0.999$ for the rapidly and 0.947 for the slowly dissociating isomer).

(11) Times that varied from 0.75, 1, 24, and 336 h gave ratios between the above limits, showing that equilibrium was established.

(12) For example, see: Kyba, E. P.; et al. *J. Am. Chem. Soc.* **1978**, *100*, 4555-4568.

(13) (a) Gavezzotti, A. *J. Am. Chem. Soc.* **1964**, *68*, 441-451. (b) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441-451.

(14) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993-6996.

## Stable $\eta^4$-Silatrimethylenemethane Transition-Metal Complexes by the Reaction of Alkylidenesilirane with Metal Carbonyl

Wataru Ando,* Takao Yamamoto, Haruo Saso, and Yoshio Kabe

*Department of Chemistry, University of Tsukuba Tsukuba, Ibaraki 305, Japan*

*Received November 30, 1990*

The coordination of transition metals has been well-known to stabilize many reactive species, e.g., carbenes, carbynes, cyclobutadiene, and trimethylenemethane. By analogy along this line, remarkable progress has been made in the synthesis of stable transition-metal complexes of unsaturated silicon species, e.g., silylene ($L_nM{=}SiR_2$),[1a-h] silene ($L_nM[\eta^2\text{-}R_2C{=}SiR_2]$),[1i-k] and disilene ($L_nM[\eta^2\text{-}R_2Si{=}SiR_2]$)[1l-n] complexes, respectively. Recently we have found the reaction of allene episulfide (II, X =

(1) For silylene complexes: (a) Straus, D. A.; Tilley, T. D.; Rheingold, A. L.; Geib, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5872. (b) Zybill, C.; Muller, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 669. (c) Zybill, C.; Wilkinson, D. L.; Muller, G. *Ibid.* **1988**, *27*, 583. (d) Zybill, C.; Muller, G. *Organometallics* **1988**, *7*, 1368. (e) Ueno, K.; Tobita, H.; Shimoi, M.; Ogino, H. *J. Am. Chem. Soc.* **1988**, *110*, 4092. (f) Zybill, C.; Wilkinson, D. L.; Leis, C.; Muller, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 203. (g) Tobita, H.; Ueno, K.; Shimoi, M.; Ogino, H. *J. Am. Chem. Soc.* **1990**, *112*, 3415. (h) Straus, D. A.; Grumbine, S. D.; Tilley, T. D. *Ibid.* **1990**, *112*, 7801. For silene complexes: (i) Campion, B. K.; Heyn, R. H.; Tilley, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 7558. (j) Campion, B. K.; Heyn, R. H.; Tilly, T. D. *Ibid.* **1990**, *112*, 4079. (k) Koloski, T. S.; Carroll, P. J.; Berry, D. H. *Ibid.* **1990**, *112*, 6405. For a disilene complex: (l) Pham, E. K.; West, R. *J. Am. Chem. Soc.* **1989**, *111*, 7667. (m) Pham, E. K.; West, R. *Organometallics* **1990**, *9*, 1517. (n) Berry, D. H.; Chey, J. H.; Zipin, H. S.; Carroll, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 452.

0002-7863/91/1513-2791$02.50/0 