Equation 7 illustrates several useful features of this novel annulation strategy. The methyl ketone **14** need not be stereohomogeneous since using the potassium hydroxide conditions for the ylide condensation effects epimerization faster than sulfur ylide addition to the carbonyl group.[5] The trans diastereomer which possesses the sterically more accessible carbonyl group assures the trans stereochemistry of **15** and consequently the annulation product **16**. Conjugate addition methodology makes the keto acetal **14** easily available from 1-acetylcyclopentene. The efficiency with which the vinylcyclopropanol composite functional group acts as a terminator in electrophilic cyclizations forming six-to-eight-membered rings, the possibility for further structural elaboration of the spirocyclobutanone products, and the high diastereoselectivity observed in the generation of quaternary carbons in the form of a spirocyclobutanone in compounds **10**, **12**, and **16** make this methodology especially useful for the synthesis of complex natural products containing these rings.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their generous support of our programs. We thank Dr. Bruce Adams and Rebecca Braslau for high-field NMR spectra (SPT difference, NOE, COSY, and CH correlation).

Registry No. 5a, 36727-64-7; **5b**, 115756-88-2; **6a**, 115796-54-8; **6b**, 115756-89-3; *trans*-**7a**, 115756-90-6; *cis*-**7a**, 115756-95-1; *trans*-**7b**, 115756-91-7; *cis*-**7b**, 115756-94-0; *trans*-**7c**, 115756-92-8; **8**, 115756-93-9; **9**, 115756-96-2; *trans*-**10**, 115756-97-3; *cis*-**10**, 115756-98-4; **11**, 115756-99-5; **12**, 115757-00-1; **12** (methoxy epimer), 115887-53-1; **13**, 16112-10-0; *trans*-**14**, 115757-05-6; *cis*-**14**, 115757-06-7; **15**, 115757-07-8; **16**, 115757-08-9; **16** (methoxy epimer), 115887-55-3; cyclopropyldiphenylsulfonium fluoroborate, 33462-81-6; *trans*-1-acetyl-2-(3,3-dimethoxypropyl)cyclopentane, 115757-01-2; *cis*-1-acetyl-2-(3,3-dimethoxypropyl)cyclopentane, 115757-02-3; *trans*-1-[1-[1-(trimethylsilyloxy)cyclopropyl]vinyl]-2-(3,3-dimethoxypropyl)cyclopentane, 115757-03-4; (3aα,4β,6β,8aβ)-6-methoxyperhydrospiro[azulene-4,1′-cyclobutane]-2-one, 115757-04-5; (3aα,4β,6α,8aβ)-6-methoxyperhydrospiro[azulene-4,1′-cyclobutane]-2-one, 115887-54-2.

Supplementary Material Available: Characterization data for **7a**, **7b**, **8**, **10**, **12**, **16**, and 4-methoxybicyclo[6.3.0]undecane-2-spiro-1′-cyclobutan-2′-one (3 pages). Ordering information is given on any current masthead page.

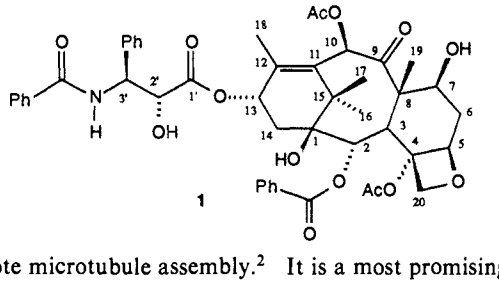
A Synthesis of Taxusin

Robert A. Holton,* R. R. Juo, Hyeong B. Kim,
Andrew D. Williams, Shinya Harusawa,
Richard E. Lowenthal, and Sadamu Yogai

Dittmer Laboratory of Chemistry
The Florida State University
Tallahassee, Florida 32306

Received April 8, 1988

The compound taxol (**1**)[1] has been the subject of extraordinary interest. It exhibits unique biological activity through its ability

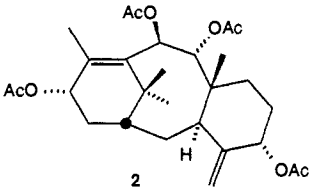


1

to promote microtubule assembly.[2] It is a most promising antitumor agent,[1,3] now in phase II clinical trials, obtained by isolation from the bark of the pacific yew tree.[1,4] The most recent harvest, which requires sacrifice of ca. 12 000 trees to obtain ca. 60 000 pounds of bark and 2.5 kg of taxol, threatens the survival of the pacific yew and its habitat, the virgin rainforest, and is a subject of considerable environmental concern.[5]

These factors combine with the skeletal and stereochemical complexity of the taxanes[6] to provide an enormous synthetic challenge. Although a number of synthetic approaches have been reported,[7] none of the natural products have heretofore been synthesized.

We now describe the first synthesis of taxusin (**2**).[8] The cornerstone of this work, like that of our taxane skeleton synthesis,[9] is the fragmentation of a bicyclic epoxy alcohol.[10]



2

The synthesis proceeds from the commodity chemical patchino (**3**),[11] which, upon treatment with *tert*-butyllithium (hexane, reflux, 5 h) gave rise to the sensitive tertiary allylic alcohol **4**, which typically was epoxidized (*t*-BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, 2 h) without purification to give **5**,[12] mp 97-99 °C $[\alpha]^{25}_{Hg}$ −5° (CH_3OH, *c* 11.91), in 98% yield from **3**. Epoxy alcohol **5** rearranged ($BF_3{\cdot}Et_2O$, CF_3SO_3H, CH_2Cl_2, −80 °C, 22 h) to diol **6**,[12] mp 100-101 °C $[\alpha]^{25}_{Hg}$ +67° ($CHCl_3$, *c* 0.50), in 93% yield at 75% conversion.[13] Oxidation of diol **6** (PDC, DMF; 94%) furnished ketone **7**,[12] mp 71-72 °C $[\alpha]^{25}_{Hg}$ +57° ($CHCl_3$, *c* 4.76),

(1) (a) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggan, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. (b) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr. *J. Org. Chem.* **1981**, *46*, 1469 and references contained therein.

(2) For leading references, see: (a) Manfredi, J. J.; Fant, J.; Horwitz, S. B. *Eur. J. Cell Biol.* **1986**, *42*, 126. (b) Solari, A. J.; Duschak, V. G. *Micro Sc. Electron. Biol. Cel.* **1985**, *9*, 163. (c) Bhattacharyya, B.; Ghoschaudhuri, G.; Maity, S.; Biswas, B. B. *Ann. N.Y. Acad. Sci.* **1986**, *466*, 791. (d) Horwitz, S. B.; Lothstein, L.; Manfredi, J. J.; Melcado, W.; Parness, J.; Roy, S. N.; Schiff, P. B.; Sorbara, L.; Zeheb, R. *Ann. N.Y. Acad. Sci.* **1986**, *466*, 733. (e) Wallin, M.; Nordh, J.; Deinum, J. *Biochim. Biophys. Acta* **1986**, *880*, 189.

(3) For leading references, see: (a) Riondel, J.; Jacrot, M.; Picot, F.; Beriel, H.; Mouriquand, C.; Potier, P. *Cancer Chemother. Pharmacol.* **1986**, *17*, 137. (b) Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83. (c) Hamel, E.; Lin, C. M.; Johns, D. G. *Cancer Treat. Rep.* **1982**, *66*, 1381. (d) Suffness, M.; Douros, J. D. *Methods Cancer Res.* **1979**, *16*, 73. (e) Fuchs, D. A.; Johnson, R. K. *Cancer Treat. Rep.* **1978**, *62*, 1219. (f) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561.

(4) Large scale isolation: Boettner, F.; Williams, M.; Boyd, R.; Halpern, B. D., preparation Report 9 on Contract N01-CM-77070, N.C.I.

(5) A large number of articles describing this situation have appeared in U. S. and Canadian newspapers and magazines. For leading references, see: (a) *The New York Times*, **1987**, May 3, I, 29:1. (b) Strycker, L. *The Register-Guard* (Eugene, OR), **1987**, *120* (*166*), 1B. (c) Brooks, B. *Tallahassee Democrat* (FL) **1987**, *82* (*270*), 1E. (d) *Audubon*, 9/87. (e) Boling, R. *Equinox* **1988**, *37*, 7:1, 107.

(6) Review: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(7) Synthetic studies from over 20 different laboratories have been described. See: (a) Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275. (b) Kraus, G.; Thomas, P. J.; Hon, Y. S. *J. Chem. Soc., Chem. Commun.* **1987**, 1849. (c) Pettersson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 2753. (d) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (e) Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. (f) Winkler, J. D.; Hey, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6425 and references cited therein.

(8) (a) Miyazaki, M.; Shimizu, K.; Mishima, H.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546. (b) Liu, C. L.; Lin, Y. C.; Lin, Y. M.; Chen, F. C. *T'ai-wan K'o Hsueh* **1984**, *38*, 119. (c) Erdtman, H.; Tsuno, K. *Phytochemistry* **1969**, *8*, 931. (d) Lee, C. L.; Hirose, Y. *Nakatsuka Mokuzai Gakkaishi* **1975**, *21*, 249. (e) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1966**, 923.

(9) Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731.

(10) Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.* **1984**, *25*, 4455.

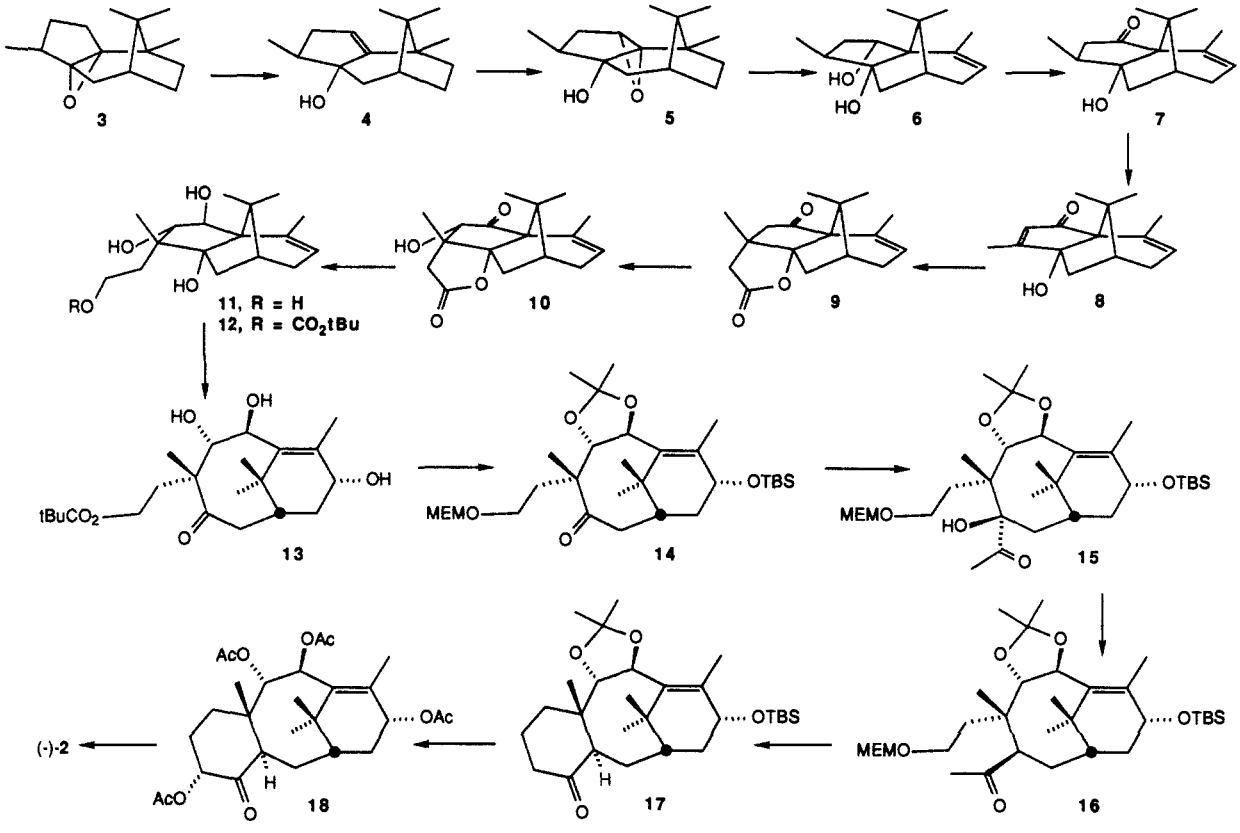
(11) Patchino (**3**) is the International Flavors and Fragrances, Inc. trade name for β-patchoulene oxide, $[\alpha]^{25}_{Hg}$ −10°; $[\alpha]^{25}_{Na}$ −8° ($CHCl_3$, *c* 1.12).[21]

(12) Characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS or elemental analysis.

(13) Diol **6** is the kinetic product of this rearrangement: Holton, R. A.; Juo, R. R.; Lowenthal, R. E.; Goedken, V., manuscript in preparation.

0002-7863/88/1510-6558$01.50/0

Scheme I



which was then converted[14] (LDA/TMSCl; PhSeCl; H_2O_2; MeOH K_2CO_3; 95%) to enone **8**,[12] mp 103–104 °C $[\alpha]^{25}_{Hg}$ +33° ($CHCl_3$, *c* 3.70).

Prior experience[9] led us to pursue introduction of C6 and C7 (taxane numbering) before fragmentation. Hydroxy enone **8** reacted with 1,2-dibromoethyl methyl ether ($PhN(Me)_2$, CH_2Cl_2, 25 °C, 2.3 days; 93%) to provide a diastereomeric mixture of bromoacetals which, upon radical cyclization[15] (Bu_3SnH, AIBN, PhH, reflux, 3 h; 98%), hydrolysis, and oxidation (Jones; 90%), led to keto lactone **9**,[12] mp 159–162 °C $[\alpha]^{25}_{Hg}$ +47° ($CHCl_3$, *c* 3.56). Stereospecific introduction of the C9, C10 trans diol functionality was readily accomplished due to the severe steric encumbrance of the β-face of **9** and **10** by the geminal methyl groups. The silyl enol ether of **9** (LDA/TMSCl) reacted with peracetic acid (CH_2Cl_2, 25 °C, 2 h) to give hydroxy ketone **10**,[12] mp 180–183 °C $[\alpha]^{25}_{Hg}$ +65° ($CHCl_3$, *c* 3.12), in 92% yield. Reduction of **10** (Red-Al, 1:9 THF:PhH, reflux, 12 h; 95%) revealed tetraol **11**,[12] mp 146–148 °C $[\alpha]^{25}_{Hg}$ −15° (CH_3OH, *c* 2.97), which was converted (*t*-BuCOCl, pyridine; 99%) to monopivalate **12**,[12] mp 118–120 °C $[\alpha]^{25}_{Hg}$ −10° ($CHCl_3$, *c* 3.81). Although Sharpless epoxidation of **12** failed, use of a large excess of anhydrous peracetic acid (CH_2Cl_2, 25 °C, 30 min) was effective, and the crude unstable epoxide was treated directly with $Ti(OiPr)_4$ (CH_2Cl_2, reflux, 45 min) to give triol **13**,[12] mp 154–157 °C $[\alpha]^{25}_{Hg}$ −74° ($CHCl_3$, *c* 0.17), in 90% yield from **12**. Protection of **13** (2,2-dimethoxypropane, *p*-TsOH; *tert*-butyldimethylsilyl triflate, pyridine; K_2CO_3, CH_3OH; MEMCl, $(iPr)_2NEt$, CH_2Cl_2) then provided ketone **14**,[12] $[\alpha]^{25}_{Hg}$ −113° ($CHCl_3$, *c* 1.55), in 97% yield.

The introduction of C4 and C5 was accomplished by the addition of α-methoxyvinyllithium[16] (hexane, −13 °C, 12 h) to **14** followed by in situ hydrolysis (2:1:1 THF:HOAc:H_2O) to give hydroxy ketone **15**,[12] $[\alpha]^{25}_{Hg}$ −121° ($CHCl_3$, *c* 0.79), stereospecifically (>30:1) in 90% yield. *The observed stereospecificity is due to a novel directing effect exerted by the MEM ether protecting group.*[17] Hydroxy ketone **15** was reduced (SmI_2, THF, 0 °C, 2 h, 90%)[18] to ketone **16**,[12] $[\alpha]^{25}_{Hg}$ −112° ($CHCl_3$, *c* 0.91), which underwent base-promoted deuterium exchange without epimerization. Removal of the MEM ether ($FeCl_3$, Ac_2O, −45 °C, 4 h; $NaOCH_3$, CH_3OH, 25 °C, 1 h)[19] gave a mixture of hemiketals and hydroxy ketone which, through an unstable tosylate ($(Ts)_2O$, pyridine), was converted (NaO-*t*-Bu, THF, 25 °C) to ketone **17**,[12] mp 135–137 °C $[\alpha]^{25}_{Hg}$ −122° ($CHCl_3$, *c* 1.20), in 87% yield from **16**. Stereospecific oxidation (mCPBA, CH_2Cl_2) of the silyl enol ether (LDA, TMSCl) of **17** was followed by deprotection (Bu_4NF, THF; 0.25 N HCl, THF) and acetylation to provide tetraacetoxy ketone **18**,[12] mp 72–75 °C $[\alpha]^{25}_{Hg}$ −106° ($CHCl_3$, *c* 0.44), in 83% yield from **17**. Finally, olefination of **18** (Ph_3PCH_2, 1:1 toluene:hexane, 25 °C, 3 h; 70%) gave (−)-taxusin, $[\alpha]^{25}_{Hg}$ −120° ($CHCl_3$, *c* 0.40), which exhibited ^1H NMR, ^{13}C NMR, IR spectra, and mp (125–127 °C) identical with those of natural (+)-taxusin (**2**),[8] $[\alpha]^{25}_{Hg}$ +120° ($CHCl_3$, *c* 0.16).

The conversion of (−)-patchino into the enantiomer of the natural product, (−)-taxusin, is described here.[20] In view of Buchi's preparation of (−)-patchino from (+)-camphor[21] and the ready availability of (−)-camphor, this work also describes a method for the preparation of (+)-taxusin.

We are now pursuing studies directed toward the synthesis of taxol. The results of these endeavors will be reported in due course.

(14) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(15) For example, see: Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

(16) Baldwin, J. E.; Hofle, G. A.; Lever, Jr., O. W. *J. Am. Chem. Soc.* **1974**, 96, 7125.

(17) This directing effect is currently being investigated in our laboratory. Addition of α-methoxyvinyllithium to **14** in THF solution gave a 1:1 mixture of **15** and its C3 epimer.

(18) (a) The C3 epimer of **15** underwent skeletal rearrangement upon attempted reduction with SmI_2. Holton, R. A.; Williams, A. D., submitted for publication. (b) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. (c) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.

(19) (a) Ganem, B.; Small, Jr., V. R. *J. Org. Chem.* **1974**, *39*, 3728. (b) Gross, R. S.; Watt, D. A. *Synth. Commun.* **1987**, *17*, 1749.

(20) This synthesis requires about 30 reactions. However, it is most efficiently performed in approximately 24 laboratory operations. When the synthesis is carried out in this way, (−)-taxusin can be prepared from patchino in >20% overall yield.

(21) Buchi, G.; MacLeod, W. D., Jr.; Padilla, J. *J. Am. Chem. Soc.* **1964**, 86, 4438.

Acknowledgment. We thank Dr. William Schrieber of International Flavors and Fragrances, Inc. for a generous continuing supply of patchino, Professor David Watt for suggesting the use of $FeCl_3/Ac_2O$ for MEM ether cleavage, Professor Fa-ching Chen, National Taiwan University, for providing a sample of natural taxusin, and the National Cancer Institute and the donors to the Taxol Research Fund, Florida State University Foundation, for generous financial support.

Formation of Two-Component Surfaces by the Spontaneous Assembly of Monolayers on Gold from Solutions Containing Mixtures of Organic Thiols[1]

Colin D. Bain[2] and George M. Whitesides*

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received April 29, 1988
Revised Manuscript Received July 5, 1988

The formation of ordered, oriented, organic monolayer films by adsorption of long-chain thiols, $HS(CH_2)_nX$, onto gold provides a means of controlling the chemistry and structure of surfaces on an angstrom scale.[3,4] Monolayers formed from a single thiol present a densely packed array of a single functional group at the interface between the monolayer and a liquid or vapor. A controlled degree of disorder can be introduced at this interface by coadsorbing thiols of different chain lengths, with the same[5] or different[6] terminal functionality. Here we demonstrate the synthesis of surfaces comprising a mixture of organic functional groups by the coadsorption of thiols with the *same* chain length but with different tail groups, X. The ability to control the composition of highly structured, multicomponent interfaces has particular potential for examining the interactions between organic functional groups in quasi-two-dimensional systems.

We have studied three simple, binary systems, $HS(CH_2)_{10}CH_3$ and $HS(CH_2)_{10}Z$ (Z = $-CO_2H$, $-CH_2OH$, $-CH_2Br$), chosen to have one polar and one nonpolar component.[7] These pairs were selected for ease of analysis by contact angle and by X-ray photoelectron spectroscopy (XPS). Monolayers were prepared by immersing evaporated gold films, supported on silicon wafers, in solutions of thiols in deoxygenated ethanol overnight at room temperature.[8] The ratio of the two components was varied while maintaining a total concentration of thiol of 1 mM. The compositions of the monolayers were determined from the normalized areas of the O(1s) and Br(3p) peaks in XPS.[9] Carboxylic acids, alcohols, and alkyl bromides coordinate only weakly to gold and do not form monolayers that are stable to washing with ethanol. Consequently, the tail groups do not compete with the thiol in binding to the gold.

Figure 1 (lower) plots the mole fraction in the monolayer, $\chi^P_{surface}$, of the polar component, $HS(CH_2)_{10}Z$, as a function of its mole fraction in solution. In general the compositions of the solution and of the monolayer are not equal: the relationship between $\chi^P_{surface}$ and $\chi^P_{solution}$ depends on the nature of the tail group.[10] Since the intermolecular interactions within a monolayer

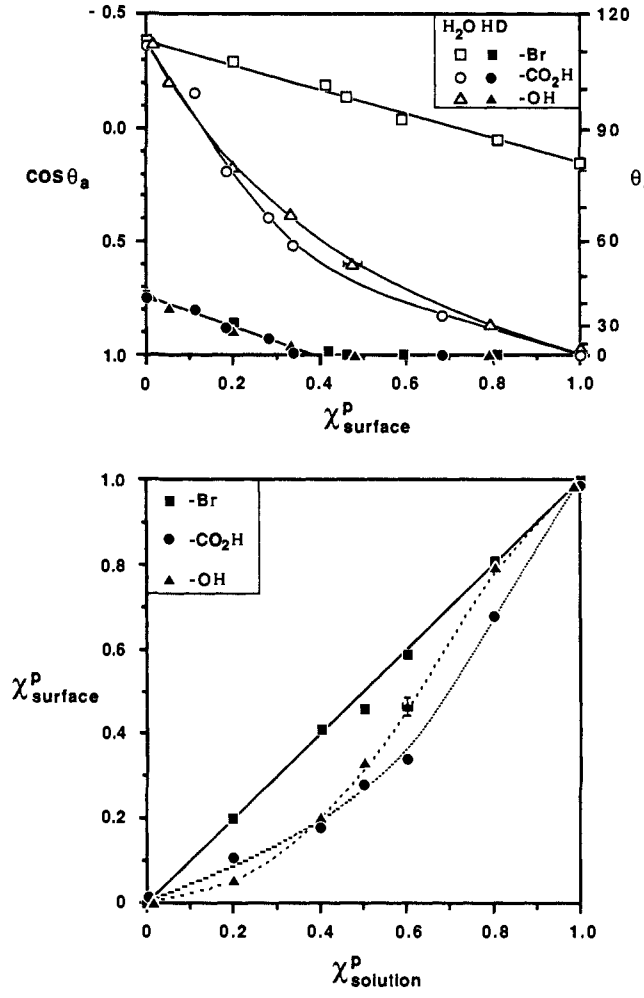


Figure 1. (lower) Composition of monolayers of thiols as a function of the composition of the solutions from which they were adsorbed; (upper) advancing contact angles, θ_a, of water and hexadecane (HD) as a function of the composition of the monolayer. $\chi^P_{surface}$ is the mole fraction on the surface of $HS(CH_2)_{10}Z$ (Z = $-CH_2Br$, $-CH_2OH$, $-CO_2H$) in binary mixtures with $HS(CH_2)_{10}CH_3$; it was determined from the areas of the O(1s) or Br(3p) peaks obtained by XPS. The error bars shown are indicative of the standard deviation of the random errors occurring in the preparation of adsorbate solutions, and in the collection and analysis of XPS data. The errors in the contact angles lie within the symbols.

are often similar to those in a crystal, solubility provides a useful guide to which component will be adsorbed preferentially.[11] $\chi^P_{surface}$ and $\chi^P_{solution}$ are not always related, however, by the simple equilibrium expression expected for an ideal two-dimensional solution; specific interactions within the monolayer clearly play a role in determining the composition.

Figure 1 (upper) shows the advancing contact angles, θ_a, of water and hexadecane as a function of surface composition for the three systems studied. The contact angles vary smoothly with surface composition between the values characteristic of the pure, one-component monolayers.[4] Cassie[12] has shown that if the two components of the surface act independently, then $\cos\theta_a$ is a linear function of the composition of the surface, in the absence of hysteresis. Cassie's law appears to hold for the contact angles of hexadecane on all three pairs over the limited range we could observe and for water on the brominated surfaces, for which dispersion forces are the principal intermolecular interaction. The

(1) Supported in part by the ONR and DARPA.
(2) IBM Pre-Doctoral Fellow in Physical Chemistry 1985-1986.
(3) Nuzzo, R. G.; Allara, D. L. *J. Am. Chem. Soc.* **1983**, *105*, 4481-4483. Porter, M. D.; Bright, T. B.; Allara, D. L.; Chidsey, C. E. D. *J. Am. Chem. Soc.* **1987**, *109*, 3559-3568.
(4) Bain, C. D.; Troughton, E. B.; Tao, Y.-T.; Evall, J.; Whitesides, G. M.; Nuzzo, R. G. *J. Am. Chem. Soc.*, in press.
(5) Bain, C. D.; Whitesides, G. M. *Science* (Washington, D. C.) **1988**, *240*, 62-63.
(6) Bain, C. D.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 3665-3666.
(7) The principle of these studies is generalizable to mixtures of two polar or two nonpolar tail groups or to systems with more than two components.
(8) Reference 4 contains experimental details.
(9) We also measured the intensity of the $Au(4f_{7/2})$ peak as a check on the focus of the spectrometer. The area of the bromine peak collected on the pure $HS(CH_2)_{11}Br$ was corrected by 6% for an abnormally low gold intensity.
(10) The composition of the monolayer appears to be controlled largely by thermodyamics: frequently the minor component in solution is the major component in the monolayer. For longer chains the role of kinetics appears to increase.
(11) Consequently, the choice of solvent has a major influence on the monolayer composition.
(12) Cassie, A. B. D. *Discuss. Faraday Soc.* **1948**, *3*, 11-16.

0002-7863/88/1510-6560$01.50/0