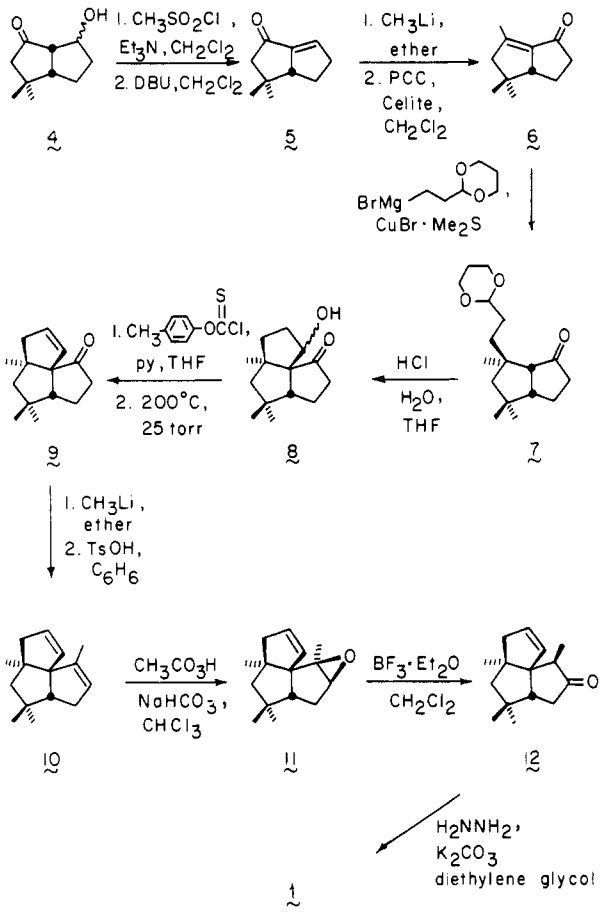
Scheme I



hydrogen in **6** is the only stereochemical anchor in the molecule, it as usual proved adequate to direct clean entry of the cuprate reagent from the β face. Following the isolation of **6** (68%), its exposure to aqueous acid afforded in turn the tricyclic hydroxy ketone **8** (71%).

With ample quantities of **8** in hand, dehydration of this intermediate was next broached. The more customary conditions for effecting elimination of water could not be implemented here because of ready retroaldolization. To our delight, however, condensation of **8** with 4-methylphenyl thiochloroformate in dry pyridine led quantitatively to the thiocarbonate ester whose pyrolysis at 200 °C and 25 torr delivered **9** with preservation of the tricyclic framework (84%).[13]

Following arrival at **9**, stereocontrolled introduction of a secondary β-methyl group was undertaken. Ample precedent exists to suggest that any scheme involving catalytic hydrogenation would generate the α isomer predominantly if not exclusively.[4,5] Such methodology had, therefore, to be avoided for this reason and because the second lesser substituted double bond had to be preserved. On the other hand, no difficulty in the form of structural isomerization was encountered during acid-catalyzed dehydration of the tertiary alcohol produced by methyllithium addition to **9**. When diene **10** (73%) was in turn subjected to the action of buffered peracetic acid (1 equiv) in $CHCl_3$ at 0 °C, the β-epoxide **11** was obtained exclusively (100%). Evidently, the reactivity of the trisubstituted double bond in **10** is sufficiently heightened to be the sole detectable site of electrophilic attack.[14]

Exposure of **11** to BF_3·Et_2O in C_6H_6 at room temperature overnight[15] resulted in stereospecific rearrangement to **12** (95%), with the secondary methyl group occupying the thermodynamically more stable quasi-equatorial position. Epimer contamination was also not encountered during the ensuing Wolff–Kishner reduction of **12** with potassium carbonate and hydrazine hydrate in hot diethylene glycol.[16] Following isolation of the resulting hydrocarbon (83%) by preparative VPC, its spectra proved identical with those of natural silphinene.[17]

In summary, the first total synthesis of silphinene has been achieved in a fully stereocontrolled manner from **2** in 15 steps and 10% overall yield. The carbon skeleton **1** is developed by twofold conjugate addition of a functionalized organocopper reagent and subsequent aldol cyclization. In addition to highlighting the utility and efficiency of this methodology for polyquinane construction, the route also provides a practical solution to the ready introduction of vicinal quaternary carbon centers onto polycyclic frameworks.[18]

(12) For earlier precedent, consult the following: (a) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. (b) Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1980**, *64*, 104 and relevant references cited therein.

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(17) Copies of these spectra were kindly provided to us by Professor Bohlmann whom we thank.

(18) This research was generously financed by the National Institutes of Health (Grant GM-28468) to whom we are indebted.

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Micelle-Induced Chemoselectivity: A Probe for Sites of Solubilization and Water Penetration

Summary: The potential and limitations of micellar differentiation between reactive sites in a molecule are delineated and then related to questions of micelle structure and sites for solubilization.

Sir: As part of our study of micelle-induced selective chemistry, we have previously demonstrated the ability of anionic micelles to promote both the selective monomercuration of nonconjugated dienes and the micelle-enhanced transformation of dienes into cyclic ethers.[1] Both of these observations were attributed to the anisotropic solubilization of an initially formed alkylmercurial in a relatively water-poor environment. The work we report herein further elucidates the requirements for reaction-site selectivity in terms of substrate structure and demonstrates that this selectivity is a new diagnostic for substrate solubilization that may help interpret data bearing on the question of water penetration into micellar aggregates.

In earlier work[1] we used 1 equiv of $Hg(OAc)_2$ in sodium lauryl sulfate (SLS) micelles to bring about the monofunctionalization of limonene (I) and 4-vinylcyclohexene

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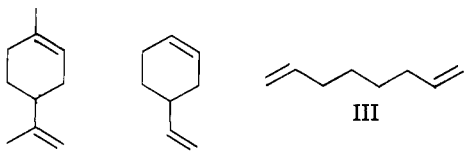
Table I. Hydroxymercuration of IV

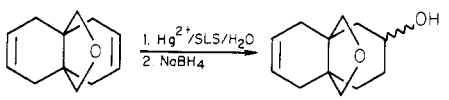
reaction medium	Hg^{2+} consumed, equiv	10^3[IV]	% diene	% mono-ol	% diols + cyclic ethers
THF (50% aq)	1.08	2.2	19	53	28
THF (50% aq)	1.10	5.7	25	40	36
SLS (3.5×10^{-2} M)	1.03	8.9	7	83	10
SLS (5.0×10^{-2} M)	1.03	5.7	7	79	16
SLS (5.0×10^{-2} M)	1.14	5.7	4	78	18

(II). At that same time, the contrasting inability to monofunctionalize 1,7-octadiene (III) was suggested to be due



I II III

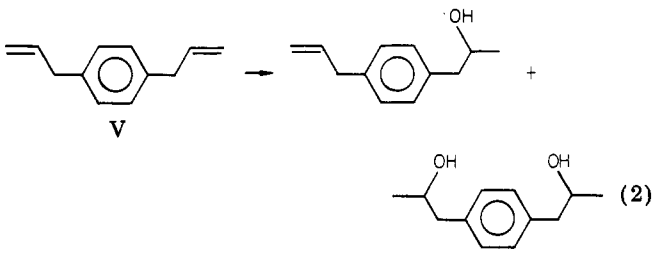
to the flexibility of that substrate. We alleged that this flexibility made the micelle–substrate complex unable to effectively sequester the second reaction site in the micelle interior. To ascertain whether substrate rigidity is the only necessary feature to allow micelle-induced protection of a second reaction site in a molecule, we sought an additional substrate that, like 1,7-octadiene, had chemically equivalent functional groups but was still relatively rigid. We have therefore investigated the hydroxymercuration of 12-oxa[4.4.3.]propella-3,8-diene (IV).[2] Representative data are shown in Table I. They reveal a clear contrast between the nonselective reaction of this compound in the water/THF solvent system and its successful monofunctionalization in aqueous SLS as per eq 1.[3]



IV (1)

The kinetics for the reaction of IV in both micellar and nonmicellar medium are similarly revealing. With use of reaction conditions that allow for pseudo-first-order reaction of IV, the measured rate constants for the disappearance of IV (k_1) is more than 10^2 larger in SLS than in THF/H_2O. Moreover, while the ratio of k_1/k_2 (where k_2 is the rate of disappearance of monoreacted material) is 1.5 in THF/H_2O, it is $>2.5 \times 10^2$ in SLS. The magnitude of the ratio of k_1/k_2 in SLS makes it very clear that in SLS the first double bond of IV reacts much faster than does the remaining double bond in the incipient (hydroxyalkyl)mercurial. This is not the case in the nonmicellar reactions and is thus consistent with the suggestion that micelle-induced chemoselectivity results from anisotropic solubilization of monoreacted substrate molecules in micellar sites that allow for varying degrees of penetration by water and/or water-soluble reagents. This selectivity does not rely on any intrinsic difference in substrate reactivity.

To extend these findings, we sought a better understanding of this anisotropic solubilization site by looking at substrates where independent analytical data are available. In particular, there seems to be general agreement that aromatic molecules are solubilized in a micellar region that is relatively more polar than the sites for solubilization of simple hydrocarbons.[5] The question we therefore posed was whether or not our chemoselectivity would persist with rigid substrates containing an aromatic moiety. To this end we synthesized *p*-diallylbenzene (V)[6] and reacted it with 1 equiv of $Hg(OAc)_2$ under the micellar (SLS) and nonmicellar (THF/H_2O) reaction conditions described above (eq 2). This reaction was essentially



V (2)

nonselective and produced comparable amounts of mono-ol and diol in both cases. We attribute the inability of the micelle to bring about selective monofunctionalization of this rigid substrate to the presence of an aromatic moiety and the fact that aromatics are solubilized into different, more polar, micellar sites than alkyl substrates; our chemoselectivity probe is sensitive to this difference.

We therefore suggest that any interpretation of the many recent experiments aimed at assessing the degree of water penetration into a micellar interior must be able to also explain our observation of chemically useful water poor environments in simple aqueous micelles. It also seems to be true that both spectroscopic evidence[5] and our chemoselectivity results suggest that aromatic probes may not be able to detect the existence of such an environment in the alkyl core of the micelle despite its presence. We call particular attention to this point since in the recent works of Engberts,[7] Fendler,[8] Menger,[9] Turro,[10] and

(2) (a) For nomenclature system and for properties of IV, see: Altman, J.; Babad, E.; Itzchaki, J.; Ginsburg, D. *Tetrahedron, Suppl.* **1966**, *8*, 279–304. (b) Our own synthesis of IV differed from that reported in ref 2a, and will be reported in due course. However, our material was identical in all respects with that reported in the literature. Both IV and its hydroxymercuration products (mono-ols, cyclic ethers, and diols) were fully characterized by ^1H and ^{13}C NMR, IR, and MS.

(3) As was the case with the dienes studied in ref 1, a mixture of mono-ols, diols, and cyclic ethers is possible. Control experiments using other mercurating agents ($HgSO_4$) and additives ($NaCH_3OSO_3$) were done to verify the dependence of monofunctionalization on the presence of SLS micelles.

(4) By resorting to long reaction times (>1 week) we can obtain, even in SLS reactions, reasonable yields of doubly reacted material. The distribution of these products, the cyclic ethers and diols, showed the same enhancement of cyclic ether formation as was reported for I and II in ref 1.

(5) (a) For an interesting discussion of this differentiation of solubilization sites, see: Mukerjee, P. *Pure Appl. Chem.* **1980**, *52*, 1317, and references therein. (b) Clear, brief summaries of data bearing on the question of aryl solubilization in micelles can be found in the following: Thomas J. K. *Acc. Chem. Res.* **1977**, *10*, 133. Turro, N. J.; Gratzel, M.; Braun, A. M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 675.

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Whitten,[11] the suggestion of extensive water penetration has been convincingly advanced. While we are not arguing against some level of water penetration into these micelles, we are concerned by the fact that all of these experiments have used aromatic probe molecules. In this respect our chemoselectivity test has the advantage that the same test can be applied to both aromatic and nonaromatic probes.

We feel that despite the recent proliferation of models[12] for micelle structure, the experiments cited above,[7-11] as well as those done by Menger using nonaromatic test systems,[13] raise many intriguing questions that must still be answered. In an effort to address some of these questions we are using various versions of our chemoselectivity test to assess the relationship of both probe structure and probe size to its ability to monitor micelle properties. These results will be published in due course.

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Registry No. IV, 15405-67-1; V, 2664-28-0; H_2O, 7732-18-5; SLS, 151-21-3; $Hg(OAc)_2$, 1600-27-7; $HgSO_4$, 7783-35-9; $NaCH_3OSO_3$, 512-42-5.

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