experiment. Molecular hydrogen, from total decomposition of some fraction of the adsorbate mixture, evolved in two peaks, at 370 and 580 K. Ethene, propene, and butene were detected at approximately 350 K. Because of overlapping mass spectral cracking fractions, the temperatures of the alkene peaks could not be accurately determined, but they were certainly very close and probably identical. Finally, ethane, propane, and butane evolved in peaks of identical line shape at 310 K (Figure 2A). The hydrocarbon yields were consistent with those previously measured for the individual thiols, based on the integrated mass spectral intensities.[1-3] Coadsorption of two different ethanethiol/1-propanethiol/1-butanethiol mixtures (ratios = 0:4:1, 15:3:1) resulted in alkane production at slightly different temperatures (315 and 320 K, respectively). However, for all of the thiol mixtures investigated, the ethane, propane, and butane temperatures were identical. Therefore, the kinetics of the process leading to alkane production from the three alkyl thiols are identical and are not affected by the length of the alkyl chain. The slight differences in the peak temperatures that are detected for different ratios of ethanethiol/1-propanethiol/1-butanethiol and when the thiols are reacted individually[1-3] are tentatively attributed to differences in the surface carbon, sulfur, and/or hydrogen stoichiometry, although the stoichiometries were not determined.

Similar coadsorption experiments were performed by coadsorbing one of the cyclic sulfides, tetrahydrothiophene, or trimethylene sulfide with a thiol. In Figure 2B are shown the temperature-programmed reaction spectra of ethane and butane from the coadsorption of ethanethiol and tetrahydrothiophene (ratio = 6:1) on Mo(110). The ethane and butane peak temperatures and line shapes were identical within experimental error. For the tetrahydrothiophene/ethanethiol ratio represented by Figure 2B, alkane evolution occurred at 300 K. The experiment was repeated for three different ethanethiol/tetrahydrothiophene ratios (6:1, 9:1, and 15:1), and in all cases the two alkanes evolved at the same temperature, although the peak temperature depended slightly on the adsorbate ratio. Figure 2C shows the temperature-programmed reaction of propane and butane from a 1:2 1-butanethiol/trimethylene sulfide mixture. Propane evolution from trimethylene sulfide proceeded at 315 K, as did butane evolution from 1-butanethiol. Again, the peak temperatures and line shapes were identical, regardless of the 1-butanethiol/trimethylene sulfide ratio in the coadsorbed mixture (1:9, 1:4, or 1:2). In both coadsorption experiments it was impossible to compare the temperatures of the alkene peaks because of overlapping mass spectral cracking products. Also, in the case of trimethylene sulfide, a cyclopropane peak at 190 K[5] partly overlapped with the propene peak, preventing accurate temperature determination. The relative yields in the coadsorption experiments are consistent with those measured for the individual reactants.[1-3]

These experiments are confirming evidence that tetrahydrothiophene and trimethylene sulfide decompose to alkanes and alkenes on Mo(110) by way of a common intermediate, proposed to be a surface thiolate. Furthermore, the coincidence of the alkane peak temperatures from the cyclic sulfides and the thiols suggests that the slow step in the desulfurization of trimethylene sulfide and tetrahydrothiophene to alkanes and alkenes is decomposition of the surface thiolate, not ring opening. Finally, the thiol coadsorption experiments demonstrate that the kinetics of alkane formation from the thiolate are independent of the number of carbon atoms in the thiolate. Differences in the hydrocarbon evolution temperatures observed when the individual thiols were adsorbed[1-3] are attributed to the effect of surface carbon, sulfur, and/or hydrogen coverage. Reaction of a coadsorbed mixture allows direct comparison of the reaction kinetics of the molecules in that mixture because coadsorbed molecules are by definition reacting on the same surface.

We are unaware of any instance where adsorbate coadsorption has been used to compare the relative kinetics of two related surface reactions. However, coadsorption experiments such as those described here may be of great use for that purpose when used with other surface chemical probes. The primary requirements for their success are that the coadsorbed molecules (a) not greatly affect each other's reaction kinetics and (b) not form islands of distinct phases.

Acknowledgment. This work was supported by the Department of Energy, Basic Energy Sciences, Grant no. DE-FG02-84ER13289.

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[5] Cyclopropane formation[2] occurs via a competing pathway at low temperature. Increased ring in trimethylene sulfide strain may account for the selectivity change observed.

Total Synthesis of (±)-2-Desoxystemodinone. A Novel Hydroxyl-Assisted, Intramolecular Ene Reaction[†]

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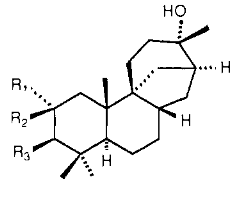
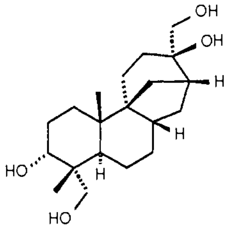
Structural elucidation in 1973 of a pair of novel tetracyclic diterpenes, stemodin (**1**) and stemodinone (**2**),[1] launched numerous synthetic ventures directed at these substances[2] and their congeners 2-desoxystemodinone (**3**)[3] and maritimol (**4**).[2b,4] A stereochemical variant of the stemodane ring system found in the antiviral, tumor inhibitory fungal metabolite aphidicolin (**5**)[5] has likewise provided a focus of intense synthetic interest.[6,7]



1, R_1 = OH, R_2 = R_3 = H
2, R_1 = R_2 = O, R_3 = H
3, R_1 = R_2 = R_3 = H
4, R_1 = R_2 = H, R_3 = OH



5

The preparation of **6** in eight steps from geraniol was reported recently,[8] and we now describe an efficient conversion of this tricyclic ketone to (±)-**3**. The key transformation in this sequence is a unique hydroxyl-assisted ene reaction that establishes the stemodane framework from a conformationally restricted aldehyde precursor.

[†] Dedicated to Professor George Büchi on the occasion of his sixty-fifth birthday.

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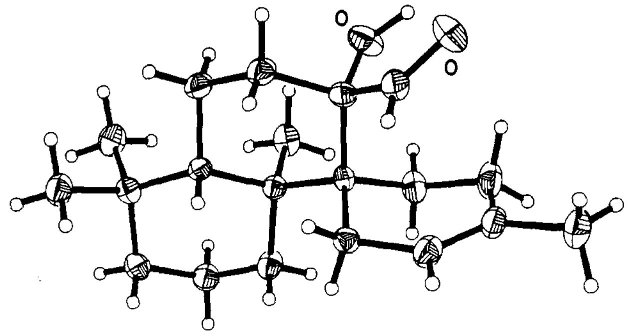
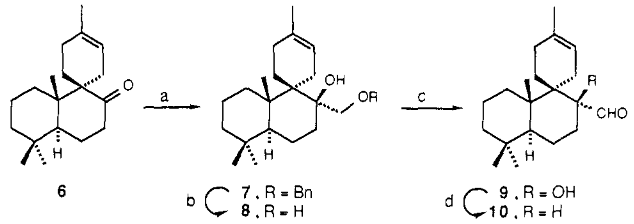


Figure 1. ORTEP plot of the X-ray crystal structure of **9**.

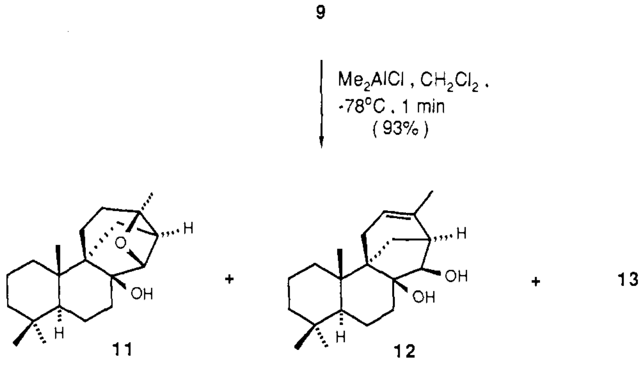


(a) BnOCH$_2$Cl, SmI$_2$, THF, 25 °C, 20 h (92%); (b) Na/NH$_3$/THF (94%); (c) Me$_2$SO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$, -60 °C (93%); (d) SmI$_2$, *t*-BuOH, THF, 25 °C, 14 h (63%).

Although the sterically encumbered keto group of **6** resisted attack by many nucleophilic reagents (methyllithium, for example, led only to enolate formation), benzyl chloromethyl ether in the presence of samarium diiodide[9] reacted with this ketone to give **7** in virtually quantitative yield. Reductive debenzylation of **7** afforded diol **8**, which was oxidized to α-hydroxy aldehyde **9** under Swern conditions. NMR evidence[10] suggested a conformation for **9** in which the aldehyde carbonyl and hydroxyl substituent are bridged by an intramolecular hydrogen bond, and an X-ray crystal structure (Figure 1) verified that these functionalities are indeed coplanar with the aldehyde carbonyl oriented parallel to the π bond of the cyclohexene ring. This alignment sets the stage for an extremely facile, intramolecular ene reaction,[11] in which **9** is converted to diol **13** in nearly quantitative yield upon refluxing in toluene.

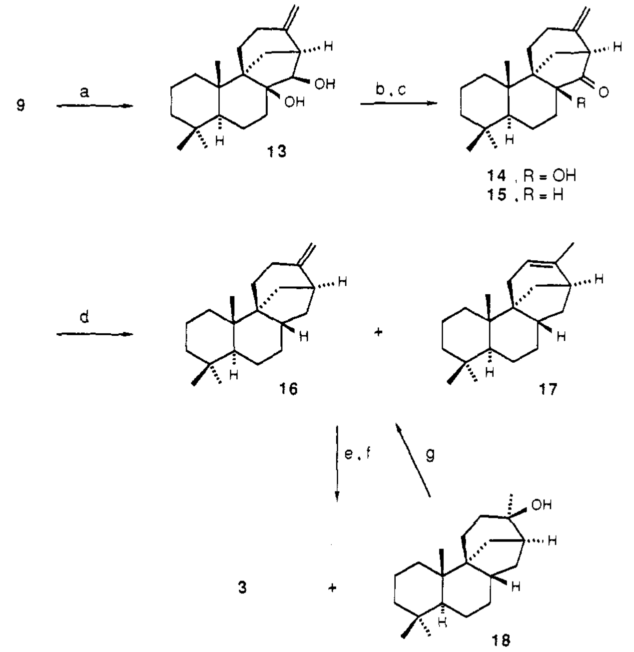
The pivotal role of the hydroxyl substitutent in this process was verified by its reductive removal from **9** with samarium diiodide.[12] The resulting aldehyde **10**, in contrast to **9**, failed to yield any trace of an ene product either thermally (toluene, 250 °C, 8 h) or in the presence of a Lewis acid[13] (e.g., Me$_2$AlCl, CH$_2$Cl$_2$, 25 °C).

Somewhat surprisingly, rearrangement of **9** in the presence of Me$_2$AlCl took a quite different course from the thermal reaction, the major product being the pentacyclic oxetane **11**.[14] Two tetracyclic compounds, **12** and **13**, were also isolated from this reaction and, although these can be formally derived by an ene reaction, they more likely arise from an ionic process that terminates at the endo and exocyclic olefin isomers via a tertiary carbocation intermediate.



11 : 12 : 13 2.4 : 1.2 : 1

The synthesis of (±)-2-desoxystemodinone was concluded by first oxidizing **13** to hydroxy ketone **14** under Swern conditions. Treatment of **14** with samarium diiodide effected a rapid and exceptionally clean removal of the α-hydroxy substituent,[12] provided *tert*-butyl alcohol was present as a proton source, to give **15**. Wolff–Kishner reduction of **15** unavoidably yielded a mixture of exo (**16**) and endo (**17**) olefins (2.5:1, respectively), which were inseparable. This mixture was treated with *m*-chloroperbenzoic acid to yield exo and endo epoxides, which were reduced directly with lithium triethylborohydride[15] to (±)-2-desoxystemodinone (**3**) and its easily separated epimer **18** in a 1.4:1 ratio. *epi*-2-Desoxystemodinone (**18**) was recycled by dehydration to a mixture of **16** and **17**, thereby providing a route that converts **15** to **3** in 55% overall yield. The TLC properties, infrared and mass spectra, and ^{1}H and ^{13}C NMR spectra of **3** were identical with those recorded with an authentic sample. However, the melting point measured for (±)-**3** (108–109.5 °C) is in serious disagreement with two values (144 °C[3a] and 146–147 °C[2b]) reported in the literature. In order to remove any ambiguity, an X-ray structure determination was carried out on our synthetic material that fully confirmed its identity as 2-desoxystemodinone (**3**).[16]



(a) 110 °C, toluene, 16 h (94%); (b) Me$_2$SO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$, -60 °C (98%); (c) SmI$_2$, *t*-BuOH, THF, 25 °C, 12 h (87%); (d) H$_2$NNH$_2$, KOH, O(CH$_2$CH$_2$OH)$_2$, 25 → 140 °C, 1 h; 205 °C, 2 h (76%); (e) *m*-CPBA, benzene, 25 °C, 10 h; (f) LiEt$_3$BH, THF, 25 °C, 4 h (82%, two steps); (g) POCl$_3$, pyridine, 70 °C, 15 min (66%, **16**/**17** 1:1.7).

Acknowledgment. We are indebted to Dr. Percy S. Manchand and Louis Todaro, Hoffman-La Roche, Inc., for a sample of

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[10] The ^{1}H NMR spectrum of **9** (400 MHz, CDCl$_3$) displays a 1.5-Hz coupling between the aldehyde (δ 9.33) and hydroxyl (δ 3.73) protons.

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(+)-2-desoxystemodinone and for X-ray crystal structure determinations of **3** and **11**, respectively. The X-ray crystal structure of **9** was kindly provided by Dr. C. Campana, Nicolet Analytical Instruments (X-ray Division). Financial support for this research was provided by the National Science Foundation (CHE-8101223), and funds that assisted with the purchase of a Bruker AM-400 NMR spectrometer were obtained from the National Science Foundation (CHE-8216190) and the M. J. Murdock Charitable Trust.

Supplementary Material Available: Experimental data on compounds **3** and **7–18** (5 pages). Ordering information is given on any current masthead page.

Preparation and Characterization of Cu_2Ni_2 and Ag_2Ni_2 Superoxide Dismutase, Two New Metal-Substituted Derivatives

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Bovine copper–zinc superoxide dismutase, Cu_2Zn_2SOD, is a metalloprotein of molecular weight 31 200 which is comprised of two equivalent subunits, each of which contains a Cu^{2+} and a Zn^{2+} ion bound in close proximity and bridged by the imidazolate ring of a histidyl residue.[1] Spectroscopic studies of derivatives with Co^{2+} substituted at the zinc site have provided considerable information concerning the nature of this site.[1] We describe here the preparation and characterization of two new derivatives in which Ni^{2+} has been substituted at this same site. While the geometric preferences and ionic radii of Zn^{2+}, Co^{2+}, and Ni^{2+} are quite similar, their magnetic and spectroscopic properties are very different, and comparisons of results obtained from studies of each of these metal ions in identical or nearly identical ligand environments, including metalloprotein metal-binding sites,[3] have frequently provided complementary information, particularly in NMR studies.[2,3] The first new derivative is Cu_2Ni_2SOD, which contains Cu^{2+} in the native copper site and Ni^{2+} in the native zinc site. This derivative is EPR silent (at 90 K) and has a particularly rich ^1H NMR spectrum (at ambient temperature) consisting of isotropically shifted resonances from ligands bound to both metal ions. These observations are due to the fact that the fast relaxing electrons of the paramagnetic Ni^{2+} ion interact with the unpaired electron on the Cu^{2+} ion, causing its relaxation rate to increase. A similar phenomeon has been reported by Bertini and co-workers[4] for Cu_2Co_2SOD. The second new derivative is Ag_2Ni_2SOD, which contains Ag^+ in the native copper site and Ni^{2+} in the native zinc site and has allowed us to determine the spectroscopic properties of Ni^{2+} when bound to that site.

Cu_2E_2SOD and Ag_2E_2SOD, derivatives in which either Cu^{2+} or Ag^+ is bound to the native copper site and the zinc site is empty (E = empty), were prepared in acetate buffer as previously reported.[5] The buffer was then changed to 50 mM phosphate, pH 6.5, and 2 equiv of Ni^{2+} was infused directly into each solution. For either solution, an increase of the absorbance near 500 nm indicated the formation of Ni-substituted SOD as shown in Figure 1A,E. The visible λ_{max} at ~700 nm in Cu_2E_2SOD was essentially unchanged by the addition of Ni^{2+}, indicating that Cu^{2+} remains in the copper site rather than migrating to the zinc site where it would be expected to give a λ_{max} instead at ~800 nm.[6] This conclusion is also supported by the observation that addition of azide or cyanide ion produced new absorption maxima at 475 and 530 nm, respectively, characteristic of derivatives in which Cu^{2+} is bound at the native copper site when those anions are bound to the protein.[1,4] The virtual disappearance (<5% remaining) of the EPR signal of Cu_2E_2SOD upon addition of 2 equiv of Ni^{2+} indicates that almost all of the Ni^{2+} was bound in the zinc site under those conditions. Addition of 2 equiv of Zn^{2+} to solutions of either oxidized or reduced Cu_2Ni_2SOD resulted in the complete disappearance of the absorbance near 500 nm, indicating that Zn^{2+} had displaced Ni^{2+} from the zinc site.[7] The Cu_2NiSOD derivative was found to have 26–45% of the activity of native SOD at pH 7.8[8] by using the cytochrome C–xanthine assay.[9]

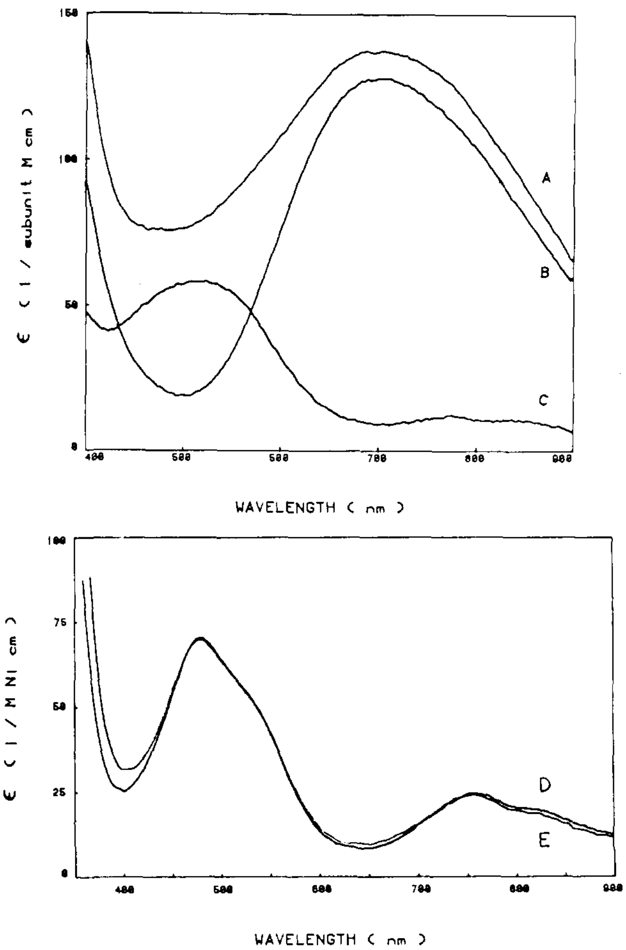

Figure 1. Electronic absorption spectra at room temperature of (A) Cu_2Ni_2SOD and (B) Cu_2E_2SOD, (C) the difference of Cu_2Ni_2SOD and Cu_2E_2SOD, (D) reduced Cu_2Ni_2SOD, and (E) Ag_2Ni_2SOD. Solutions were in 50 mM phosphate buffer, pH 6.5, referenced against deionized water.

The paramagnetically shifted ^1H NMR spectrum of Cu_2Ni_2SOD obtained in H_2O by the modified DEFT pulse sequence[10] on a Brucker WP200 spectrometer is shown in Figure 2B. At least 20 signals are detected (occurring over a range of about 120

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[7] The binding constant for Ni^{2+} to the zinc site of this derivative is apparently substantially less than that of Zn^{2+} or Co^{2+} based on our observation that the latter two metal ions are not removed by ultrafiltration while the Ni^{2+} is.

[8] The variability of the SOD activity of this derivative is reminiscent of the behavior of Cu_2E_2SOD and may be due to rearrangements of the metal ions in the protein as a function of pH.[8a] This question will be addressed in future studies. (a) Pantoliano, M. W.; Valentine, J. S.; Burger, A. R.; Lippard, S. J. *J. Inorg. Biochem.* **1982**, *17*, 325–341.

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