attack on cyclohexene, in the major pathway. The rate law would not be altered if the major osmium species were bis(pinanediol) osmate(VI) [5 as $OsO(O_2C_{10}H_{16})_2$] instead of the monoester 3. In accord with this interpretation, oxidations of α-pinene result in a very dark purplish solution, in contrast to the much lighter yellows or browns characteristic of the cyclohexene or stilbene reactions.

Effects of Amines. The retardation of the oxidation of cyclohexene by pyridine and the even greater retardation by 2,2′-bipyridyl must be attributed to the formation of relatively unreactive amine complexes (11) of the osmium(VI) ester intermediates. The alternative hypothesis that the amines retard the cyclohexene reaction by diminishing the free OsO_4 concentration is contradicted by the observations that these amines accelerate the stoichiometric addition of osmium tetraoxide to alkenes.[5,7,12,13] The resistance of amine complexes of osmium(VI) esters to oxidation is in accord with the observations that pyridine and especially 2,2′-bipyridyl complexes of these esters are stable compounds.[7,13,14,32]

The lack of effect of pyridine on the rate of oxidation of α-pinene or of cyclohexene in the presence of α-pinene is consistent with the possibility that both processes involve 2:1 diol/osmium(VI) esters (5) and that these do not complex with pyridine.

The fact that triethylamine only slightly retards the reaction of either alkene provides assurance that the trimethylamine evolved in the reaction probably did not have a gross effect on the kinetics. Even so, the amount of trimethylamine escaping from the solution, which depends on the void volume of the container and leakiness of the seal, could lead to some minor differences. This as well as other unidentified variables make it impossible to compare sets of data from one table with those in another.

It would have been desirable to measure the production of diol as well as the consumption of alkene, but gas chromatographic analyses for diols and α-hydroxy ketones were relatively difficult and somewhat erratic. We have never observed the α-hydroxy ketone production to approach that of diol and consider this potential source of error in our kinetics to be minor.

(32) (a) Daniel, F. B.; Behrman, E. J. *J. Am. Chem. Soc.* **1975**, *97*, 7352-7358. (b) Chang, C. H.; Beer, M.; Marzilli, L. G. *Biochemistry* **1977**, *16*, 33-38.

Conclusions

The observed kinetics require that the mechanism of the osmium tetraoxide catalyzed reactions of α-pinene and cyclohexene with trimethylamine *N*-oxide involve oxidation of a relatively substitution-inert osmium(VI) ester to a substitution-labile osmium(VIII) species in the rate-determining step. Reaction of osmium(VIII) with the alkene to form osmium(VI) ester must be rapid.

The observation that the trimethylamine *N*-oxide directly attacks osmium(VI) esters is in accord with earlier findings that amine oxides are superior to other oxidizing agents for preparative purposes.[1,2] If the oxidizing agent merely converted inorganic osmium(VI) to osmium(VIII), the differences in performance between different oxidizing agents would be difficult to rationalize.

Pyridine and similar amine additives greatly retard the reaction of cyclohexene, and for that reason these additives are undesirable for preparative reactions involving relatively unhindered alkenes. Pyridine promotes the reaction of α-pinene enough to provide significant shortening of reaction time, and our results indicate a beneficial effect on the diol to α-hydroxy ketone ratio. Higher concentrations of trimethylamine *N*-oxide also appear to be beneficial for suppressing overoxidation of α-pinene to α-hydroxy ketone.

Reactions in which α-pinene is present appear to involve a catalytic cycle having hydrolytically stable pinanediol osmium(VIII) ester 4 as the active oxidizing agent and osmium(VI) bis(diol esters) 5 as the major osmium species. The relative slowness of osmium tetraoxide catalyzed oxidations of highly substituted alkenes may be attributed to the intermediacy of bis(diol esters) resembling 5, which are sterically hindered at osmium and provide opportunities for other modes of oxidative attack leading to side products.

Acknowledgment. We thank NATO for grant No. 038.80 and the National Science Foundation for grant No. CHE8400715.

Registry No. 1, 7785-70-8; 2, 18680-27-8; 2 (ketone), 1845-25-6; 7, 110-83-8; 10, 1792-81-0; Me_3NO, 1184-78-7; O_5O_4, 20816-12-0; Et_3N, 121-44-8; *trans*-stilbene, 103-30-0; (+)-hydrobenzoin, 52340-78-0; 2,2′-bipyridyl, 366-18-7; cholesterol, 57-88-5.

Notes

Preparation of Cyclic Ethers via a Transacetalization-Cationic Cyclization Sequence

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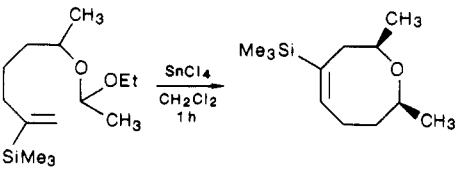
Received July 12, 1988

There is current interest in the preparation of cyclic ethers by way of Lewis acid promoted carbon–carbon bond-forming cyclizations of unsaturated acetals. An illustrative example reported by Overman et al.[1] of the facility and selectivity of these reactions is shown in eq 1



(1)

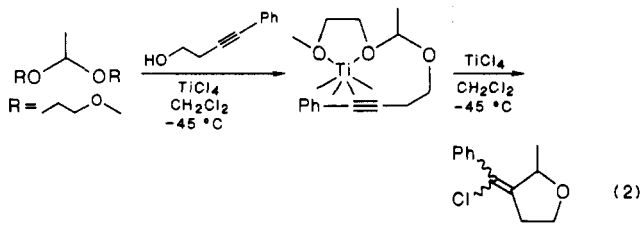
where the cyclization proceeds rapidly under mild conditions to give essentially a single diastereomeric eight-membered cyclic ether. Itoh,[2] Kay,[3] Kocienski,[4] Overman,[5]

(1) Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516.

0022-3263/89/1954-2748$01.50/0

and Thompson[6] with their co-workers have reported similarly efficacious acetal–olefin cyclizations leading to five- through nine-membered rings. These oxonium ion initiated cyclizations in both endo- and exocyclic modes are a significant addition to existing methods for the preparation of cyclic ethers. The Taddei,[7] Tagliavini,[8] and Chan[9] groups have reported related reactions that involve Lewis acid promoted condensation of olefins and aldehydes with subsequent cyclization to cyclic ethers. All of the above reactions have roots in the chemistry of the classic Prins reaction and modifications thereof.[10]

During investigations of the formation of 3-alkylidenetetrahydrofurans from the acid-promoted cyclization of acetals of internal homopropargyl alcohols, we[11] found that the preparation of the acetal derived from ethyl vinyl ether and 4-phenyl-3-butyn-1-ol was plagued by polymerization problems that could not be resolved satisfactorily. Since we were anxious to have 2-methyl-3-(phenylchloromethylidene)tetrahydrofuran, we envisaged preparing the symmetric acetal of 2-methoxyethanol and acetaldehyde, which could then be used as a reagent with 4-phenyl-3-butyn-1-ol in a single-vessel synthesis of the cyclic ether as shown in eq 2. This reaction involves the Lewis acid



(2)

catalyzed exchange of one methoxyethoxide for the unsaturated substrate alkoxide; the mixed acetal formed in situ should then rapidly cyclize. Reference to the table shows that this transacetalization/cyclization approach was fruitful.

Our inititial success led us to investigate further generality of the transacetalization route to cyclic ethers for several reasons. First, transacetalization represents a simplification of existing procedures by eliminating the need to isolate intermediate olefinic acetals. Secondly, the ready preparation of acetals and ketals from aldehydes and ketones, respectively, should allow greater flexibility for introducing substituents at the 2-position of tetrahydrofuran and tetrahydropyran rings. Finally, we have noticed in previous work that the yields from the cyclizations of the ethyl vinyl ether acetals are often lower than those from the methoxyethoxy acetals.[12] The higher yields for the MEM acetals may be due to bidentate coordination of the methoxyethoxy fragment to the Lewis acid, which is not possible for the ethyl vinyl ether analogues. Formation of symmetric acetals with alcohols such as ethylene glycol or 2-methoxyethanol allow bidentate coordination to the acid during cyclization.

The entries in the table suggest that the initially successful transacetalization/cyclization sequence does have general utility. Acetals **1** and **2**, derived from 2-methoxyethanol and formaldehyde and acetaldehyde, respectively, react with 3-buten-1-ol and *trans*-3-hexen-1-ol to give good yields of tetrahydropyrans, which have been made previously via cyclization of the isolated MEM and ethyl vinyl ether–olefin acetals. In addition to satisfactory yields, the transacetalization procedure yields essentially the same distribution of stereoisomers as the isolated acetal–olefin systems run at similar tempeeratures. (We have observed in earlier work that lower temperatures favor slightly the trans and trans-trans isomers.[12]) This similarity of stereoselectivity is expected if the pathway outlined in eq 2 is operative. Acetal **3** reacts very smoothly with 4-penten-2-ol at low temperature to give the cis isomer (>98% by GLC). This selectivity is expected due to unfavorable 1,3-diaxial interaction if the alkenol methyl group does not occupy a pseudoequatorial position in a chairlike conformation just prior to ring formation[13] and if there is strong preference for trans addition across the double bond. The preference for trans addition in similar systems is well established.[13]

Spirocyclic compounds (**12–17**) are formed from ethylene glycol acetals (**4**, **5**) of cyclohexanone and cyclopentanone. Again, yields are good except for the reaction of **5** with 3-butyn-1-ol. We have periodically observed that some alkynols, for no obvious reason, give uncharacteristically low yields. The stereochemistry of **13** is essentially cis as has been observed when this compound is formed from the cyclization of the ethyl vinyl ether acetal of 1-allylcyclohexanol with titanium tetrachloride. As expected, 7-methyl-9-chloro-6-oxaspiro[4.5]decane, **16**, has the cis stereochemistry as well.

Experimental Section

Preparation of Acetals and Ketals. I. Bis(2-methoxyethoxy)methane. MEM chloride (40 g, 0.32 mol) and 2-methoxyethanol (71 g, 0.93 mol) were stirred together under a nitrogen atmosphere at room temperature for 4 h. Excess Na_2CO_3 was added to neutralize dissolved HCl. Distillation over Na_2CO_3 gave a center cut of the title compound, which was >98% pure by GLC: bp 88–91 °C (5 Torr); ^{1}H NMR ($CDCl_3$) δ 3.39 (s, 6 H), 3.57 (m, 4 H), 3.72 (m, 4 H), 4.76 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 59.0, 66.8, 71.8, 95.7.

II. 1,1-Bis(2-methoxyethoxy)ethane. 2-Methoxyethanol (35 g, 0.46 mol) and acetaldehyde (27 g, 0.61 mol) were added to a nitrogen-purged 100-mL three-neck round-bottom flask at −45 °C equipped with a gas effusion tube and a dry ice condenser. Dry HCl was passed through a sulfuric acid wash into the reaction flask for ca. 2 h. After this time uptake of hydrogen chloride ceased as evidenced by a marked increase in flow through an exit bubbler. The reaction mixture was allowed to warm to room temperature and then slowly poured into 500 mL of *n*-pentane at 0 °C. Substantial HCl was liberated as the solution was stirred for 1 h. Magnesium sulfate was added to the solution, which was filtered, stripped of pentane, and fractionally distilled; 33 g of

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(8) (a) Boaretto, A.; Marton, D.; Tagliavini, G. *Inorg. Chem. Acta* **1983**, *77*, L153. (b) Gambaro, A.; Gambaro, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1983**, *254*, 293.
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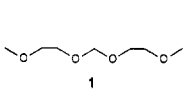
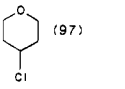
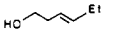
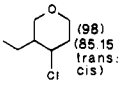
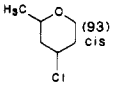
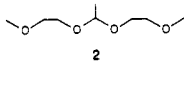
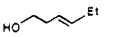
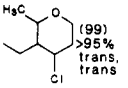
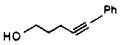
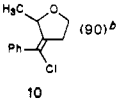
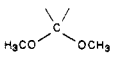
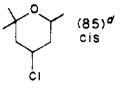
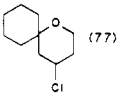
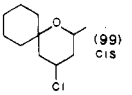
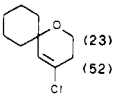
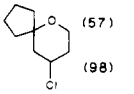
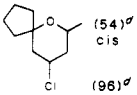
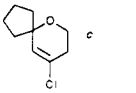
(10) (a) See Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505 and references therein. (b) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479.
(11) Thompson, D. W. *The Synthesis of ... Alkylidenetetrahydrofurans; Abstracts of Papers*, 193rd National Meeting of the American Chemical Society, Denver, CO; American Chemical Society: Washington, DC, 1987; ORGN 229.
(12) Thompson, D. W. Unpubished observations.
(13) (a) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) Barlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 341. (c) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517.

Table I. Cyclic Ether Syntheses via a Lewis Acid Promoted Transacetalization–Cyclization Sequence

symmetric acetal	alkenol/ alkynol	conditions[a]	product (yield, %)	^{13}C NMR (δ $CDCl_3$)
 1		0 °C, 1 h (4:1:5)	 (97) 6	36.9 (t), 56.9 (t), 66.1 (d)
		0 °C, 1 h (2:1:3)	 (98) (85:15 trans:cis) 7	(cis) 10.7 (q), 21.5 (t), 34.8 (t), 42.1 (d), 60.1 (d), 62.6 (t), 67.0 (t); (trans) 11.0 (q), 22.3 (t), 36.4 (t), 46.2 (d), 61.5 (d), 67.2 (t), 70.8 (t)
		22 °C, 3 h (2:1:4)	 (93) cis 8	22.9 (q), 38.3 (t), 45.9 (t), 57.1 (d), 68.5 (t), 74.6 (d)
 2		22 °C, 3 h (2:1:4)	 (99) >95% trans, trans 9	9.2 (q), 20.0 (q), 21.1 (t), 38.1 (t), 51.8 (d), 60.4 (d), 67.1 (t), 76.9 (t)
		0 °C, 0.8 h (2:1:2)	 (90)[b] 10	18.6 (q), 34.5 (t), 65.5 (t), 76.0 (d), 122.9 (s), 128.20 (d), 128.24 (d), 128.15 (d), 138.0 (s), 142.7 (s)
 3		−45 °C, 2 h (2:1:2)	 (85)[d] cis 11	22.2 (q), 22.8 (q), 31.9 (q), 44.7 (t), 47.3 (t), 54.2 (d), 66.8 (d), 73.4 (s)
		22 °C, 4 h (2:1:2)	 (77) 12	21.5 (t), 21.9 (t), 26.4 (t), 30.5 (t), 37.6 (t), 39.9 (t), 46.7 (t), 53.9 (t), 60.3 (d), 73.7 (s)
 4		22 °C, 4.25 h (1.5:1:2) 0 °C, 4 h (2:1:2)	 (99) cis 13	21.8 (t), 22.1 (t), 22.5 (q), 26.3 (t), 31.0 (t), 40.2 (t), 44.8 (t), 46.1 (t), 54.1 (d), 65.1 (d), 74.0 (s)
		22 °C, 4 h (2:1:2) 0 °C, 4 h (2:1:2)	 (23) (52) 14	22.1 (t), 25.5 (t), 33.3 (t), 35.7 (t), 59.2 (t), 74.3 (s), 129.3 (s), 131.5 (d)
		22 °C, 4 h (1.5:1:2) 0 °C, 6 h (2:1:2)	 (57) (98) 15	23.4 (t), 24.5 (t), 33.5 (t), 37.1 (t), 41.0 (t), 46.1 (t), 54.9 (d), 61.5 (t), 84.9 (s)
 5		22 °C, 4 h (2:1:2) 22 °C, 9 h (1.5:1:2)	 (54)[d] cis (96)[d] 16	22.1 (q), 23.4 (t), 24.9 (t), 33.4 (t), 41.9 (t), 44.8 (t), 46.0 (t), 54.9 (d), 67.5 (d), 85.0 (s)
		0 °C, 6 h (1.5:1:2)	 [c] 17	

[a] All reactions were run with 10–20 mmol of unsaturated alcohol in ca. 70–140 mL of methylene chloride, respectively. For the 22 °C reactions the reagents were added at 0 °C. Yields are by GLC and are corrected for response factors. [b] Both *E* and *Z* isomers are present in an 83:17 ratio. We assume that the major isomer is *E* due to the strong preference for trans addition in cationic olefin cyclizations. [c] In these two reactions we observed a peak in the GLC in the expected product region. However, yields were poor at ca. 10%. The product was not characterized. [d] Compounds 11 and 16 have not been prepared previously. ^{13}C NMR methyl peaks at δ 22.2 and 22.8 for 11 and at 22.1 for 16 ensure equatorial 6- and 7-methyl groups, respectively.[15] ^{1}H NMR spectra unambiguously indicate equatorial chlorine substitutents by exhibiting a "triplet of triplets" for the 4- and 9-protons of each compound, respectively: $J_{aa} \approx 4.5$ Hz and $J_{ae} \approx 12$ Hz for both compounds.

a 70:30 mixture of 1-(2-methoxyethoxy)-1-chloroethane and 1,1-bis(2-methoxyethoxy)ethane was isolated. (We were never successful in the production of the pure MEM chloride analogue at this stage.) The 33 g of the 70:30 mixture was stirred with additional 2-methoxyethanol (19 g, 0.25 mol) for 1.5 h. Sodium carbonate was added to this mixture, which was then distilled to yield a center cut of the title compound, which was 96% pure by GLC: bp 72–76 °C (2 Torr); ^{1}H NMR ($CDCl_3$) δ 1.34 (d, 3 H), 3.38 (s, 6 H), 4.08 (band, 8 H), 4.65 (q, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.3, 61.5, 63.7, 71.9, 99.6.

III. 1,4-Dioxospiro[4.5]decane. This compound was prepared by the *Organic Syntheses*[14] procedure: ^{1}H NMR ($CDCl_3$) δ 1.41

(br, 2 H), 1.59 (band, 8 H), 3.93 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 24.0, 25.2, 35.2, 64.1, 109.0.

IV. 1,4-Dioxospiro[4.4]nonane. This compound was prepared in the same manner as in III above: bp 68–71 °C (28 Torr); ^1H NMR ($CDCl_3$) δ 1.68 (band, 4 H), 1.77 (band, 4 H), 3.90 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 23.6, 35.9, 64.2, 118.5.

General Procedure for the Preparation of Cyclic Ethers by Transacetalization Reactions. Cyclic ethers were prepared by allowing ketals **1–5** to react with the appropriate alcohols in the presence of titanium tetrachloride as described below.

A 250-mL three-neck round-bottom flask was equipped with a gas inlet, a 25-mL addition funnel, and a septum. The system was purged with dry nitrogen after which methylene chloride (7 mL/mmol ROH) distilled from phosphorus pentoxide was added to the reaction flask, and 0.7 mL CH_2Cl_2/mmol $TiCl_4$ was added to the addition funnel. The flask was cooled to the appropriate temperature (0 or −45 °C). Weighed quantities of alcohol (10–20 mmol) and ketal (20–40 mmol) were added to the flask via syringe through the septum. Titanium tetrachloride (20–40 mmol) was added to the addition funnel. After thermal equilibrium the acid solution was added dropwise. (For cyclizations run at room temperature the titanium tetrachloride was added at 0 °C.) Reactions were run for ca. 1–4 h under nitrogen. Upon completion, reactions were quenched with 10 mL of methanol followed by 50 mL of 1 N hydrochloric acid saturated with sodium chloride. After coming to the ambient temperature, the organic layer was separated, and the aqueous phase was extracted with ether. The organic layers were combined and dried over magnesium sulfate, and the products were concentrated at the aspirator. Samples were isolated for analysis by preparative GLC or Kugelrohr distillation.

Characterization. Gas chromatographic analyses were performed with Hewlett-Packard Models 5710 and 5790 instruments equipped with electronic integrators and 10 ft × $^1/_8$ in. 10% SP1000 and 25 m methyl silicone (capillary) columns, respectively. NMR spectra were taken with General Electric QE-300 and Varian FT-80A instruments.

Acknowledgment. Financial support from the National Science Foundation (Grant CHE 8512477) is gratefully acknowledged. We also thank E. I. du Pont de Nemours and Co. and the National Science Foundation for funds used to purchase the gas chromatographs.

Registry No. **2**, 10143-67-6; **3**, 77-76-9; **4**, 177-10-6; **5**, 176-32-9; **6**, 1768-64-5; *trans*-**7**, 25999-33-1; *cis*-**7**, 25999-40-0; **8**, 92826-98-7; **9**, 119568-20-6; *E*-**10**, 119568-21-7; *Z*-**10**, 119568-22-8; **11**, 119568-23-9; **12**, 53045-59-3; **13**, 119568-24-0; **14**, 119568-25-1; **15**, 119568-26-2; **16**, 119568-27-3; 4-phenyl-3-butyn-1-ol, 10229-11-5; 3-buten-1-ol, 627-27-0; *trans*-3-hexen-1-ol, 928-97-2; 4-penten-2-ol, 625-31-0; 3-butyn-1-ol, 927-74-2; bis(2-methoxyethoxy)methane, 4431-83-8; MEM chloride, 3970-21-6; 2-methoxyethanol, 109-86-4; acetaldehyde, 75-07-0; 1-(2-methoxyethoxy)-1-chloroethane, 119593-85-0.

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A New Route to Annelated Dihydrofurofurans. Synthesis of 6,8-Dideoxyversicolorin A

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Received September 27, 1988

The highly toxic fungal metabolite aflatoxin B_1 (**1**), and its carcinogenic biosynthetic precursor versicolorin A (**2**), are both annelated derivatives of 3a,6a-dihydro[2,3-*b*]-furofuran (**3**).[1]

A number of procedures have been described for the construction of the reduced furofuran skeleton.[2] The introduction of unsaturation into this system to give the enol ether functionality has generally been accomplished under vigorous pyrolysis conditions.[2a,e,f] We now report a new short and efficient protocol for the construction of an unsaturated furofuran based upon a key phenolic Claisen rearrangement step, as well as a mild selenoxide elimination for the generation of the cyclic enol ether function. The utility of this approach is illustrated by a synthesis of 6,8-dideoxyversicolorin A (**4**) from 1,3-dihydroxyanthraquinone (**5**).[3]

The required aliphatic reagent for this synthesis was 2,5-hexadien-1-ol (**6**). An inconvenient preparation of this alcohol has been reported.[4] We have found that it may be readily prepared by a two-step process with inexpensive precursors as starting materials. Thus, the coupling of allyl bromide with propargyl alcohol gave 5-hexen-2-yn-1-ol,[5] which was converted to **6** by reduction with lithium aluminum hydride.

1,3-Dihydroxyanthraquinone (**5**) was converted selectively into its 3-MOM ether (**7**) by reaction with methoxymethyl chloride and *N,N*-diisopropylethylamine. Mitsunobu condensation[6] of **7** with alcohol **6** afforded the corresponding ether **8** in 82% yield. The reductive Claisen rearrangement of **8** in aqueous DMF[7] proceeded smoothly to give the 2-dienylanthraquinone **9** (86%), which was deblocked by methanolic HCl to give the phenol **10** (78%). Oxidative cleavage of **10** by OsO_4–$NaIO_4$ directly furnished the lactol **12** (74%) through the spontaneous intramolecular cyclization of the intermediary dialdehyde **11**. Attempted conversion of lactol **12** to an α-phenylseleno ether with *N*-(phenylseleno)phthalimide[8] failed. However, treatment of **12** with benzeneselenol in refluxing benzene[9] gave the desired selenide **13** (81%) as a separable 3:2 isomer mixture. Either isomer readily underwent oxidative selenide elimination on treatment with hydrogen peroxide to 6,8-dideoxyversicolorin A (**4**) in 70% yield.

With an appropriately blocked 1,3,6,8-tetrahydroxyanthraquinone as starting material, the same methodology should be applicable to the synthesis of versicolorin A itself.

Experimental Section

General. All melting points are uncorrected. All NMR spectra were done in $CDCl_3$ solution. Elemental analyses (C, H, N, S) were carried out by Atlantic Microlabs, Atlanta, GA. Selenium analyses were done by Galbraith labs, Knoxville, TN.

2,5-Hexadien-1-ol (6). To a suspension of LAH (5.4 g, 0.14 mol) in THF (250 mL) was added dropwise a solution of 5-hex-

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