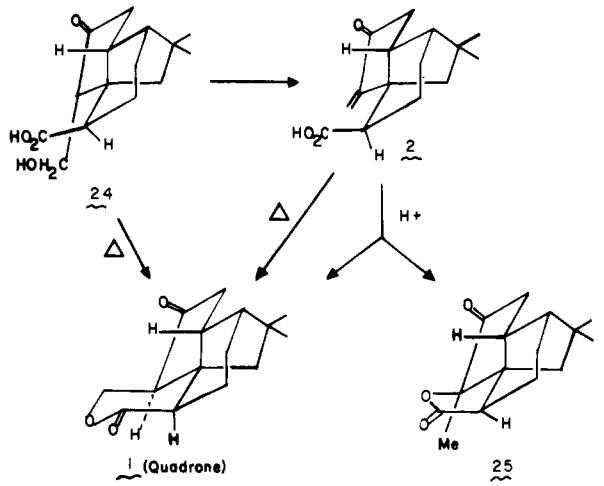
carbomethoxy group. NMR examination of the crude reaction mixture did not reveal the presence of epimeric tricyclic ketal ester.[15] The formation of **18** implies that the reacting enolate derived from **17** is in the rotameric state shown in **17a.** The reasons for this conformational specificity remain to be understood.

Deprotection (*p*-TsOH, acetone) of **18** afforded the keto ester **19**,[7] mp 49–51 °C, which upon alkaline hydrolysis (aqueous KOH, dioxane, reflux 1 h) gave acid **20**,[7] mp 132–135 °C, in 90% yield from **18.** A variety of experiments probing the regiochemistry of α-substitution reactions about the ketone in compounds **19** and **20** indicated the exclusive formation of products derived from enol **21.**[16-18] Accordingly, keto acid **20** was subjected to selenenylation[18] (PhSeCl, ethyl acetate, room temperature 2.5 h). Oxidative treatment (CH_2Cl_2, H_2O_2, pyridine, room temperature) of the resultant α-phenylseleno ketone afforded the enone acid, **22**,[7] mp 142–146 °C, in 87% yield from **20.** *It was our intention to use the α,β unsaturation in* **22** *to force enolization in the required α' sense. Thus, enolization in the extended mode is prohibited by the bridgehead nature of the γ carbon.*

Treatment of **22** with 3 equiv of lithium diisopropylamide (THF, −23 °C, 1 h), followed by quenching of the resultant dianion with gaseous formaldehyde, afforded a 62% yield of crystalline hydroxymethyl keto acid **23**,[7] mp 156–158 °C, which, upon catalytic reduction (H_2, Pd/C, EtOAc-MeOH, room temperature, ~1 atm), gave a nearly quantitative yield of **24**,[7,19] mp 153–155 °C.

Treatment of **24** with *p*-TsOH in benzene at 40–50 °C smoothly afforded the presumed biologically active intermediate **2**,[7] as a nicely crystalline solid, mp 177–179 °C. The stage was now set to conclude the total synthesis of quadrone. Treatment of **2**, so generated, with *p*-TsOH in benzene under reflux afforded the long sought *dl*-quadrone **1** (vide infra), but only as the minor product. Surprisingly, the major product of this reaction was its isomer **25**[7,20] (**25:1** ≃ 7:3).

Fortunately for our purposes, when **2** was heated in the absence of solvent from 190 to 195 °C for 5 min, there was produced *dl*-quadrone, mp 140–142 °C, free of its isomer **25.** Adding still further to the simplicity of the synthesis was the finding that pyrolysis of **24**[21] under the same conditions also afforded only *dl*-quadrone. The solution ($CHCl_3$) IR, NMR ($CDCl_3$, 270 MHz), and mass spectra of the *dl*-quadrone, as well as its chromatographic mobility, were indistinguishable from those obtained from a sample of the natural product furnished by Dr. Matthew Suffness of the National Cancer Institute.



The total synthesis of quadrone was thus achieved in 19 steps in 1.4% yield from cyclopentenone **5.** Efforts to improve the overall yield are in progress. The results of those investigations as well as a full description of the studies described herein will be provided in due course.

Acknowledgments. This research was supported by PHS Grant CA-12107. NMR spectra were obtained on facilities in Pittsburgh supported by NIH Grant RR-00292. We also acknowledge Fellowships from the Chaim Weizmann Foundation and from the National Cancer Institute to R.C.G. and from the Andrew Mellon Foundation to K.V. We gratefully acknowledge Dr. Matthew Suffness of the National Cancer Institute for providing us with a sample of authentic quadrone.

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(4) While considerable progress in the direction of this esthetically commendable goal has been achieved (R. C. Gadwood, unpublished results), this objective has not been fully met. On the other hand, the method described here (**20** → **22** → **23** → **24** → **2**), while somewhat lengthy, is in fact easily carried out in high yield).
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(9) Welch, S. C.; Chayabunjonglerd, S. *J. Am. Chem. Soc.* **1979**, *101*, 6768.
(10) For a recent use of compound **6** as an alkylating agent see Stork, G.; Taber, D. F.; Marx, M. *Tetrahedron Lett.* **1978**, 2445.
(11) Typically the sequence **7** → **11** was carried out without purification of the intermediates; **11** was purified in only a preliminary fashion (silica gel flash chromatography) prior to cyclization. The overall yield from **7** → homogeneous **4** in this way was 40–42%.
(12) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163.
(13) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.
(14) With this decarboxylation, the potential for regiochemical control implicit in the β-dicarbonyl system was forfeited. The solution described here circumvents the need for this control. In ongoing investigations, we are still attempting to exploit more fully the functionality in **13.**[4]
(15) In addition to **18** there could be found smaller amounts of bromide **16** (due to incomplete Finkelstein reaction) and more complex material possibly arising from intermolecular alkylation.
(16) These included (i) reaction of either **19** or **20** with formaldehyde under various acidic conditions, (ii) reaction of **19** with Bredereck's[17] reagent, and (iii) selenenylation **19** (as well as **20**) under standard conditions.[18] It should also be noted that enol silylation of **19** using lithium diisopropylamide afforded the silyl enol ether corresponding to **21.**
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(19) The stereochemistry of the hydroxymethyl group in compounds **23** and **24** is not known. The nonspontaneity of lactonization may be taken to suggest an α configuration of this group, though this is not clear.
(20) The formation of **25** under acidic conditions may involve prior enolization of the ketone. Lactonization to **25** would occur via the allylic carbonium ion derived from protonation of this enol at the methylene carbon. The equilibria between **2**, **25**, and **1** are currently being studied.
(21) Careful TLC monitoring of this transformation demonstrated that it proceeds through intermediate **2**, rahter than by direct lactonization to **1.**[19]

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Asymmetric Induction in the Reaction of Osmium Tetroxide with Olefins

Sir:

Of the existing methods[1,2] for direct conversion of olefins into cis-vicinal diols, the most reliable method continues to be the reaction of an olefin with a stoichiometric amount of os-

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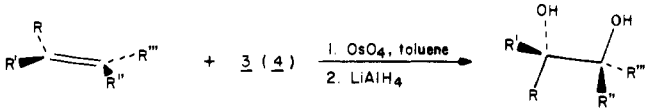
Table I. Oxidation of Olefins with OsO_4 in the Presence of **3** and **4**

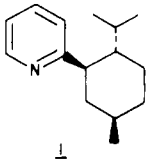


entry	olefin[a]	ligand	product	configuration[b]	% yield[c,d]	% ee[b,c]
1	styrene	3	phenylethane-1,2-diol	(*S*)-(+)	90	64.5
2		4		(*R*)-(−)	62	61.0
3	(*Z*)-1-phenylpropene	3	*erythro*-1-phenylpropane-	1(*S*),2(*R*)-(+)	82	26.8
4		4	1,2-diol	1(*R*),2(*S*)-(−)	85	25.5
5	(*E*)-1-phenylpropene	3	*threo*-1-phenylpropane-	1(*S*),2(*S*)-(+)	90	45.5
6		4	1,2-diol	1(*R*),2(*R*)-(−)	66	48.6
7	1-phenylcyclohexene	3	1-phenylcyclohexane-1,2-diol	1(*S*),2(*S*)-(−)	88	67.9
8		4		1(*R*),2(*R*)-(+)	87	67.1
9	(*E*)-stilbene	3	*threo*-hydrobenzoin	1(*S*),2(*S*)-(−)	90	83.2[e]
10		4		1(*R*),2(*R*)-(+)	85	82.0
11	3,3-dimethyl-1-butene	3	3,3-dimethylbutane-1,2-diol	(*S*)-(+)	87	26.2
12	(*Z*)-4,4-dimethyl-2-pentene	3	*erythro*-4,4-dimethylpentane-2,3-diol		78	<5
13	(*E*)-4,4-dimethyl-2-pentene	3	*threo*-4,4-dimethylpentane-2,3-diol		78	37
14	(*E*)-2,2,5,5-tetramethyl-3-hexene	3	*threo*-2,2,5,5-tetramethylhexane-3,4-diol		86	62
15	(*E*)-3-hexene	3	*threo*-hexane-3,4-diol	(*S*,*S*)-(−)	69	50.2

[a] In each case, 0.5 mmol of olefin was mixed with 0.55 mmol of **3** or **4** in 2.6 mL of dry toluene and the mixture was then allowed to react with 0.55 mmol of OsO_4 in 1.4 mL of dry toluene. After stirring 12 h at room temperature, the green solutions were diluted with 10 mL of dry ether and treated with 3 mmol of $LiAlH_4$. The reduction was quenched by the method of Mićović and Mihailovic.[10] After filtration and evaporation of solvent, the diols were purified by preparative layer or column chromatography on silica followed by sublimation (hydrobenzoin was not sublimed). At no time were the diols purified by crystallization. [b] Enantiomeric excess and absolute configurations were determined in most cases (entries 1-11, 15) by comparison of optical rotations with literature values.[11] In three cases (entries 12-14) the diols are known only in racemic form.[12] In these cases, enantiomeric excesses were measured by conversion of the diols into the corresponding bis esters of (*R*)-(+)-α-methoxytrifluoromethylphenylacetic acid[11a,13] and determination of the ratio of diastereomers by GLC and/or ^1H NMR. [c] Each value is the average of at least two parallel experiments. [d] No attempt was made to recover **3** or **4**. [e] This number was also determined by ^1H NMR using tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) as a chiral shift reagent. An enantiomeric excess of ~80% was measured by integration.

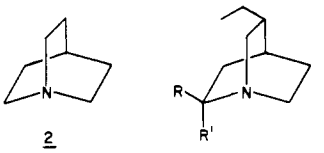
mium tetroxide in pyridine, followed by reductive hydrolysis.[2b,c] In spite of the cost and toxicity of osmium tetroxide, this method is routinely applied to small-scale reactions owing to its mildness and generality. As a means of increasing the utility of this reaction and to probe its mechanism, we have sought to modify the reaction to produce chiral vicinal diols from prochiral olefins. We present here our initial results.[3]

Pyridine is known to accelerate the rate of reaction of OsO_4 with olefins.[2b,c] It most likely exerts its effect on the reaction by coordination to the metal center at some point along the reaction pathway. Although the mechanism of the reaction is not known, we reasoned that replacement of pyridine with a similar chiral ligand might induce chirality in the diol product, and thus provide a direct route to chiral vicinal diols as well as additional insight into the mechanism. Initial efforts focused on the effect of a chiral pyridine, *l*-2-(2-menthyl)pyridine (**1**), on the reaction of OsO_4 with olefins. However, the diols ob-

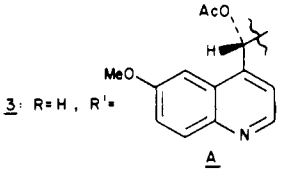


1

tained in these reactions were of low enantiomeric excess (3-18%).[3,4] Griffith and co-workers have observed that tertiary alkyl bridgehead amines, such as quinuclidine (**2**), form complexes with OsO_4[5,6] which are much more stable than the corresponding pyridine complex. To determine whether a chiral quinuclidine could also induce chirality in the diol products, samples of dihydroquinine acetate (**3**) and dihydroquinidine acetate (**4**) were prepared.[7] It was expected that **3** and **4** would bind to OsO_4, through the quinuclidine nitrogen,[8] much more tightly than does **1**, which is only very weakly bound.[9] Since **3** and **4** have a chiral center adjacent to the site of coordination, we hoped that the enantiomeric yields obtained



2



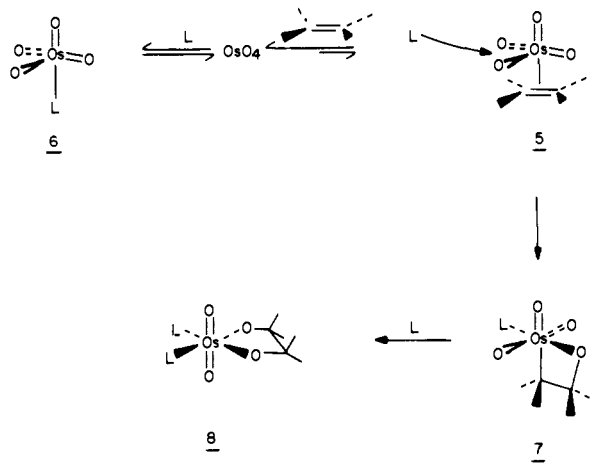
3: R = H, R' = **A**

4: R = **A**, R' = H

with **3** and **4** would be substantially higher than those obtained with **1**, in which the nearest chiral center is two carbons removed from the site of coordination. As shown in Table I, addition of 1 molar equiv of **3** or **4** to reactions of olefins with OsO_4 in toluene, at room temperature, resulted in the formation of vicinal diols of fair to high enantiomeric excess. In preliminary work, we have found that the enantiomeric yields can be increased by performing the reactions at −78 °C. For example, oxidation of (*E*)-stilbene with OsO_4 in toluene at −78 °C, in the presence of **3**, yields the corresponding diol, after reductive hydrolysis, with an enantiomeric excess of 89.7%. The opposite stereoselectivities exhibited by the diastereomers **3** and **4** are of special synthetic and mechanistic interest.

A few years ago, we proposed a new mechanism for the reaction of OsO_4 with olefins[14] which involved an organometallic intermediate containing an Os-C σ bond. With the additional data provided by this study, we now favor the modified mechanism shown in Scheme I. The first step in this mechanism is the coordination of the olefinic π bond to the metal center to give complex **5**. With more basic ligands, such as pyridine[2c] and quinuclidine,[5] isolable 1:1 adducts **6** are reversibly formed.[15] We assign the geometry of **5** in analogy to the known structure of **6** (L = quinuclidine).[16] It is worth noting that **5** is formally a coordinatively saturated 18-electron complex. Reaction of **5** with a ligand, such as pyridine, triggers insertion of the olefin into the Os=O bond to give the metallocycle **7**, also an 18-electron complex. Finally, reaction of **7**

Scheme I



with a second ligand induces formation of the final product **8**, again an 18-electron complex.[17]

Following Scheme I, the stereoselectivity, when L is a chiral ligand, can be seen to arise in the conversion of **5** into **7**. Coordination of a prochiral olefin, such as a symmetrical trans olefin, to OsO_4 gives a pair of enantiomeric intermediates **9** and **10**.[18] Reaction of **9** and **10** with a chiral ligand would be

expected to proceed with different rates owing to differential steric interactions in the pair of diastereomeric transition states. The source of this steric effect may be in the interaction of the methoxy quinoline moiety of **3** and **4** with the olefin substituents.[19] Through examination of molecular models we have been able to rationalize the stereochemical outcome of this reaction, including the opposite stereoselectivities exhibited by **3** and **4**. Although the mechanism is still speculative[20] we have found that this mechanism can at least provide a useful model for prediction of the absolute configuration of the diol products.[21]

In our continuing studies, we are extending the reaction to a wider variety of olefins and alkaloid derivatives and also examining possible catalytic schemes.[22]

Acknowledgment. We are grateful to the National Institutes of Health (GM24551-01) for financial support and to Professor Harry S. Mosher for many helpful discussions.

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(4) Details of these reactions and the preparation of **1**, $[\alpha]^{21}_D$ −43.82° (*c* 3.25, EtOH), will be reported in a future publication.

(5) Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 941.

(6) More recently, we have isolated 1:1 complexes of *t*-$BuNOsO_3$ with ligands such as **2**. These complexes are also much more stable than the corresponding pyridine complex, which is not detectable in this case: Hentges, S. G.; Sharpless, K. B. *J. Org. Chem.*, in press.

(7) (a) Hesse, O. *Justus Liebigs Ann. Chem.* **1887**, *241*, 255; (b) *Ibid.* **1882**, *214*, 1.

(8) Evidence for coordination through the quinuclidine nitrogen was obtained by comparison of the colors of solutions containing OsO_4 (0.14 M) and an equimolar amount of a ligand in toluene. Solutions made with **2**, **3**, or **4** are all a very similar red-orange color, whereas solutions made with quinoline are bright yellow.

(9) Examination of the oxo-stretch region (Os=O) of the IR spectrum of a toluene solution containing 0.14 M OsO_4 and 0.14 M **2** reveals that the 1:1 adduct **6** (L = **2**) is the predominant species (98%). Similarly, a toluene solution containing 0.10 M OsO_4 and the more sterically hindered **3** (0.10 M) contains a mixture (~1:1) of the adduct **6** (L = **3**) and free OsO_4. In contrast, solutions of OsO_4 and **1** give no evidence for complex formation (<5%). However, **1** apparently does coordinate to the metal center at some point along the reaction pathway, since chiral diols are obtained in reactions of olefins with OsO_4 in the presence of **1**.

(10) Mićović, V. M.; Mihailovic, M. L. J. *J. Org. Chem.* **1953**, *18*, 1190.

(11) (a) Styrene: Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1970**, *35*, 4002. (b) (*Z*)- and (*E*)-1-phenylpropene: Fischer, F. *Chem. Ber.* **1961**, *94*, 893. (c) 1-Phenylcyclohexene: Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Chem. Soc. C* **1971**, 3371. (d) (*E*)-Stilbene: Berti, G.; Bottari, F.; Macchia, B. *Ann. Chim.* **1962**, *52*, 1101. Berti, G.; Bottari, F. *J. Org. Chem.* **1960**, *25*, 1286. (e) 3,3-Dimethyl-1-butene: Guetté, J.-P.; Spassky, N. *Bull. Soc. Chim. Fr.* **1972**, 4217. (f) (*E*)-3-Hexene: Cope, A. C.; Shen, T. Y. *J. Am. Chem. Soc.* **1956**, *78*, 5916.

(12) (a) (*E*)- and (*Z*)-4,4-Dimethyl-2-pentene: Katzenellenbogen, J. A.; Bowlus, S. B. *J. Org. Chem.* **1973**, *38*, 627. (b) (*E*)-2,2,5,5-Tetramethyl-3-hexene: Criegee, R.; Schröder, G. *Chem. Ber.* **1960**, *93*, 689.

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(14) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.

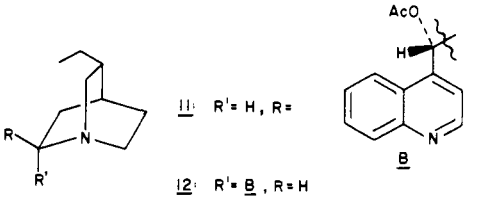
(15) A 1:1 OsO_4–PF_3 complex has also been reported: Hair, M. L.; Robinson, P. L. *J. Chem. Soc.* **1958**, 106.

(16) Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413. As shown in Scheme I, the structure of **6** (L = **2**) is a distorted trigonal bipyramid.

(17) The structure of bis(pyridine) osmate esters **8** have been determined to be that shown in Scheme I: Griffith, W. P.; Rossetti, R. *J. Chem. Soc., Dalton Trans.* **1972**, 1449. Conn, J. F.; Kim, J. J.; Suddath, F. L.; Blattmann, P.; Rich, A. *J. Am. Chem. Soc.* **1974**, *96*, 7152. Kistenmacher, T. J.; Marzilli, L. G.; Rossi, M. *Bioinorg. Chem.* **1976**, *6*, 347. Neidle, S.; Stuart, D. L. *Biochem. Biophys. Acta* **1976**, *418*, 226. The solid-state structure of the osmate ester from reactions in which the OsO_4:L ratio is restricted to 1:1 has also been determined: Cartwright, B. A.; Griffith, W. P.; Schröder, M.; Skapski, A. C. *J. Chem. Soc., Chem. Commun.* **1978**, 853. Schröder, M.; Nielson, A. J.; Griffith, W. P. *J. Chem. Soc., Dalton Trans.* **1979**, 1607.

(18) Unsymmetrical prochiral olefins give rise to two diastereomeric sets of enantiomers upon coordination to OsO_4.

(19) In preliminary experiments, we have observed that dihydrocinchonine acetate (**11**) and dihydrocinchonidine acetate (**12**) give rise to optically



active diols with enantiomeric purities substantially lower than those obtained with **3** and **4**. This indicates that the methoxy group of **3** and **4** is of some importance in determining stereoselectivity.

(20) Although we favor the mechanism shown in Scheme I, we have not eliminated the possibility that intermediate **7** is formed by reaction of **6** with the olefin via a direct [2 + 2] cycloaddition.

(21) A more detailed discussion of this stereochemical model will be given in a forthcoming publication.

(22) In preliminary work, we have found that the presence of **3** during the reaction of *t*-$BuNOsO_3$ with styrene results in production of an optically active vicinal amino alcohol with unknown enantiomeric excess.

(23) NSF Predoctoral Fellow, 1976–1979.

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Received December 27, 1979

Intramolecular [3 + 2] Cycloaddition Reactions in the Indole Series "The Nitrile Oxide Route to the Ergot Alkaloids". 1. Chanoclavine I

Sir:

The application of dipolar cycloaddition reactions to the synthesis of complex natural products has recently come to be recognized as a very powerful synthetic tool, one equally akin

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