corresponding lengths are 1.419 (7) and 1.410 (7) Å. In **2** they are 1.402 (8) and 1.384 (8) Å. The remaining benzyne ring C–C distances in **1** range from 1.416 (7) to 1.388 (8) Å and from 1.404 (9) to 1.380 (9) Å in **2**. Thus, all the benzyne bond lengths are relatively long and show, to some degree, an alternating pattern similar to the D_{3h} symmetry first noted by Schrock.[12a] The longer benzyne C–C bonds may be due to a number of factors. First, the group 5 metal centers in **2** and, especially, **1** are probably more electron rich than **3** or **4**. This can be attributed to the good σ-donor and poor π-acid properties of the phenyl coligands. The Nb and Ta metals are thus able to donate electron density more readily into antibonding benzyne orbitals giving the longer C–C distances seen throughout the benzyne ligands in **1** and **2**. Secondly, the many interactions between the Li^+ ions and the ligands serve to reduce bonding electron density in the benzynes even further.

It is also notable that the average benzyne C–C bond length in **1** is slightly longer than in **2**, 1.403 versus 1.396 Å. This is consistent with a more electron-rich center in the niobium compound as a result of its lower oxidation state. Further evidence for greater electron density is seen in the greater number of associated Li^+ ions; five for niobium versus two for tantalum.

Finally, we note that the complex **2** is very close to the structures for $[Ta(\eta^2\text{-}C_6H_4)_2Ph_4(Li{\cdot}OEt_2)_3]$ proposed on the basis of ^1H and ^7Li NMR data.[6] The major difference involves the number of complexes Li^+ ions. However, we believe that this difference is merely a consequence of the greater lattice energy obtained by crystallization as the ionic **2**. Apparently, two Li^+ ions suffice to stabilize the structure obtained. Attempts to remove the complexes Li^+ ions from either **1** or **2** to test their dependence on Li^+ for stability did not afford any material suitable for X-ray crystallography.

Acknowledgment. We thank the Petroleum Research Fund for financial support.

Supplementary Material Available: Summary of data collection and refinement and tables of atom coordinates, thermal parameters, bond distances and angles, and hydrogen coordinates (22 pages). Ordering information is given on any current masthead page.

Asymmetric Dihydroxylation via Ligand-Accelerated Catalysis†

Eric N. Jacobsen, István Markó, William S. Mungall, Georg Schröder, and K. Barry Sharpless*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

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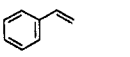
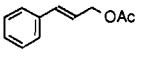
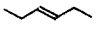
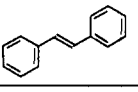
The addition of osmium tetroxide to olefins may be both the most selective and reliable of known organic transformations.[1] The added utility of stereospecifically imbedding two hydroxyl groups in a hydrocarbon framework (cis vicinal dihydroxylation) accounts for osmium tetroxide's popularity in organic synthesis, but osmium's expense and toxicity call for a catalytic solution.[1c,2]

Table I[a]

entry	olefin	ligand, % ee,[b] confgn of diol[c] sign of $[\alpha]_D^{25}$	time (h)
1		**1**, 62, *R*-(−)	3[d]
		1, 60, *R*-(−)	7[e]
		2, 53.6, *S*-(+)	7[e]
2		**1**, 65, *R,R*-(−)	5[d]
		2, 55.4, *S,S*-(+)	12[e]
3		**1**, 33, *R*-(−)	1.5[d]
4		**1**, 46, *R*-(+)	1[d]
5		**1**, 76, *R,R*-(+)	7[d]
6		**1**, 65, (−)	3[d]
7		**1**, 20, *R,R*-(+)	17[d]
8		**1**, 88, *R,R*-(+)	7[d]
		1, 85, *R,R*-(+)	15[e]
		2, 78.5, *S,S*-(−)	17[e]

[a] All reactions were performed essentially as described for the molar scale process with stilbene. Specific notes and exceptions: (1) 1–5 mmol of olefin; (2) in small (ca. 7 mL) screw-cap vials (avoid rubber septa); (3) a temperature of 0 °C was maintained by storing the vials in an ice-bath for the duration of the reaction; (4) either 1 or 2 M in olefin as indicated (i.e., *d* or *e*). In all cases the isolated yield of the diol was 80–95%. [b] The enantiomeric excesses were determined by HPLC separation of the mono MTPA ester (entry 3), bis MTPA esters (entries 1, 2, 4–7), or the bis acetates (entry 8) in all cases by using a chiral Pirkle column (type 1A, preparative version) and eluting with *i*-PrOH/hexane. [c] The absolute configurations of the diols were established as described in ref 5. For case 6, the correlation is not yet accomplished. Rotations were measured in EtOH except entry 5 which was taken in $CHCl_3$. [d] [olefin] = 1 M and [Os] = 4×10^{-3} M. [e] [olefin] = 2 M and [Os] = 4×10^{-3} M.

We report a new catalytic process achieving substantially improved rates and turnover numbers[2] as well as useful levels of asymmetric induction.

Knowing that certain tertiary amines accelerate the stoichiometric reaction between OsO_4 and olefins,[1a,b] in the late seventies we developed an asymmetric osmylation of olefins by using cinchona alkaloid derivatives as the chiral ligands;[3] improvements and variations followed.[4,5] Our stoichiometric procedure[3] becomes a highly effective catalytic process (Scheme I) with the apparently trivial act of combining it with the well-known Upjohn, N-oxide-based, catalytic method.[2a] Table I and the experimental details given for the molar-scale asymmetric dihydroxylation of (*E*)-stilbene[6] illustrate the procedure's simplicity and effectiveness.

† Dedicated to Professor Hans Wynberg on the occasion of his 65th birthday.

(1) (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75. (b) Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99. (c) Schröder, M. *Chem. Rev.* **1980**, *80*, 187–213.

(2) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. F. *Tetrahedron Lett.* **1976**, 1973. (b) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986. (c) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063. (d) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449. (e) Myers, R. S.; Michaelson, R. C.; Austin, R. G., U.S. Patents 4 496 778 and 4 496 779 and others cited therein.

(3) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

(4) The 4-chlorobenzoyl derivatives **1** and **2** are not previously described.[3] For comparison, **1** was tried with stilbene under the original[3] stoichiometric conditions (in toluene at room temperature) and yielded (*R,R*)-*threo*-hydrobenzoin of 99% ee. Upon reexamination, however, all the enantiomeric excesses reported in ref 3 are low (unpublished results of present authors, see also ref 5c). The acetate analogue of **1**, for example, affords the *R,R*-diol from stilbene in 94% ee not in 83% ee as recorded in ref 3. Alkaloid **1** is the best of 20 related derivatives examined. The structure given for dihydroquinine acetate in ref 3 is wrong: the configuration at carbon-9 should be *R* not *S*.

(5) Stoichiometric, asymmetric osmylations involving external chiral amine ligands reported by other groups: (a) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131. (b) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Stefanelli, S. *Tetrahedron Lett.* **1987**, *28*, 3139. (d) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. Asymmetric osmylations involving internal chiral ligands: (e) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459. (f) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458. (g) Hassine, B. B.; Gorsane, M.; Pecher, J.; Martin, R. H. *Bull. Soc. Chim. Belg.* **1985**, *94*, 759. Catalytic asymmetric osmylation: (h) Kokubo, T.; Sugimoto, T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1983**, *769*.

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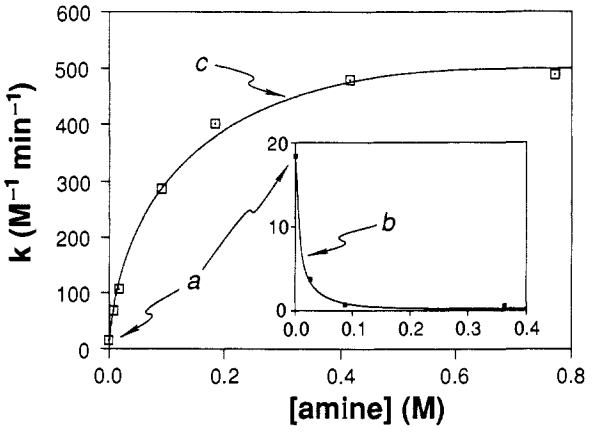


Figure 1. Plot of amine concentration versus second-order rate -constant k for the catalytic *cis*-dihydroxylation of styrene at 25 °C: point a, no added amine; line b, with quinuclidine; line c, with **1**. k is defined as $k_{obsd}/[OsO_4]_0$ where rate = $-d[\text{styrene}]/dt = k_{obsd}[\text{styrene}]$.

Only slightly soluble in the acetone–water solvent, stilbene is completely digested to a homogeneous solution of diol product when the suspension stands overnight in the refrigerator!

Preliminary studies of the process indicate rough guidelines of its scope.[7] Significantly, the most available cinchona alkaloids, quinine and quinidine, act more like enantiomers than diastereomers (Table I entries 1, 2, and 8), and the pseudoenantiomeric relationship of **1** and **2** is highlighted by their presentation in Scheme I. The scheme's face selection rule so far has no exceptions, but other substitution patterns still require testing. Among tested classes not included in Table I are *Z*-disubstituted olefins and unbranched terminal olefins which give poor results (<25% ee). Entry 4 gives a better enantiomeric excess, perhaps due to its α-branching. For aromatic substrates the presence of electron-withdrawing or electron-donating substituents barely affects the asymmetric induction (4-methoxy- and 4-nitrostyrene gave 67% and 51% ee, respectively).

Not just the straightforward marriage of known partners,[2a,3] this new catalytic asymmetric oxidation is revealed by the figure's kinetic data to be a dramatic example of ligand-accelerated catalysis.[8] Point a is the rate of the catalytic process in the absence of added amine ligands ($t_{1/2}$ = 108 min); line b shows the rates in the presence of varying amounts of quinuclidine, a ligand which substantially retards catalysis (at >0.1 M quinuclidine $t_{1/2}$ > 30 h). The observed effect of quinuclidine ("ligand-decelerated" catalysis[9]) led to line c's unexpected result: when the process occurs in the presence of the dihydroquinidine benzoate derivative **1**, the alkaloid, despite its quinuclidine moiety, strongly accelerates the catalytic process at all concentrations (with **1** = 0.4 M, $t_{1/2}$ = 4.5 min).

Comparing the rate of the stoichiometric reaction of styrene with osmium tetroxide and that of the corresponding catalytic process indicates that both have identical rate constants [k_{stoic} = (5.1 ± 0.1) × 10^2 M^{-1} min^{-1} and k_{cat} = (4.9 ± 0.4) × 10^2 M^{-1} min^{-1}] and that they undergo the same rate acceleration upon addition of **1**. Hydrolysis and reoxidation of the reduced osmium species, steps which accomplish catalyst turnover, are not kinetically significant in the catalytic process with styrene. It may be concluded that the limiting step is the same in both processes and consists of the initial addition reaction forming the osmate ester. A detailed mechanistic study indicates[10] that the observed rate acceleration by added **1** may be attributed to formation of an osmium tetroxide–alkaloid complex[11] which, in the case of styrene, is 23 times more reactive than free osmium tetroxide. The rate reaches a maximal and constant value beyond an ca. 0.25 M concentration of **1**. The onset of this rate saturation corresponds to a preequilibrium between **1** and osmium tetroxide with a rather weak[12] binding constant (K_{eq} = 18 ± 2 M^{-1} at 25 °C). Not surprisingly, increasing the concentration of **1** above 0.25 M also produces negligible increases in the enantiomeric excess of the product diol. At this concentration of alkaloid, virtually all of the catalyst reacts as the osmium tetraoxide–alkaloid complex and raising the concentration further has little effect.

(6) **(+)-*threo*-Hydrobenzoin.** A 2-L clear-glass bottle or flask was charged with 180.2 g (1.0 mol) of *trans*-stilbene (Aldrich, 96%), 62.4 g (0.134 mol, 0.134 equiv) of dihydroquinidine *p*-chlorobenzoate (**1**), 450 mL of acetone, 86 mL of water (the solution is 0.26 M in alkaloid before addition of olefin; the binding constant of **1** to osmium tetroxide increases substantially at lower temperature,[10] resulting in lower levels of alkaloid required to reach rate and ee saturation; as is apparent in the figure, 0.26 M in fact corresponds to the onset of rate saturation at 25 °C; we have recently found that at 0 °C, the temperature used in this general procedure, the concentration of **1** can be reduced to 0.067 M (i.e., only 15.6 g of **1**) with no loss in ee), and 162 g (1.2 mol, 1.2 equiv) of *N*-methylmorpholine *N*-oxide (anhydrous NMO, Aldrich 97%). [Alternatively, the inexpensive 60% (wt) solution of NMO in water (Aldrich) is equally effective as a source of the oxidant if it is brought up to 62% concentration by dissolving 57 g of anhydrous NMO per 1000 mL of the 60% solution. In the present one mole scale process one adds 234 mL (1.2 equiv) of the prepared 62% solution, which also contains the required 86 mL of water (so with this modification the separate addition of water is omitted).] The bottle was capped, shaken for 30 s, and cooled in an ice-bath until the contents reached 0–4 °C, and then 0.002 equiv of OsO_4 [0.51 g (4.25 mL of a solution prepared by dissolving 1 g of OsO_4 in 8.3 mL of toluene); 0.002 mol%—more or less catalyst can be used, and the time to reach completion changes accordingly] was injected as a solution in toluene. [Identical results were realized by using 0.593 g (0.002 mol%) of solid $OsCl_3$ (Strem Chemical) as the source of the catalyst, thus completely avoiding the hazard of handling volatile OsO_4]. The bottle was shaken (30 s) and placed in a refrigerator at ca. 4 °C with occasional shaking during the ca. 15–17 h reaction time. A dark purple color developed and slowly was replaced by deep orange; the heterogeneous reaction mixture gradually became homogeneous, giving in the end a clear orange solution. The reaction was monitored by TLC. After 17 h, 100 g of solid sodium metabisulfite ($Na_2S_2O_5$) was added to the cold solution, and the mixture was shaken (1 min) and then left standing at ambient temperature for 1 h with occasional shaking (the solution changes from deep orange to yellow-orange, and the reduced osmium species turn the solids pink). The mixture was then diluted with an equal volume of CH_2Cl_2, and anhydrous Na_2SO_4 (100 g) was added. After another 30 min of standing with occasional shaking, the solids were removed by filtration through a pad of Celite and washed 3 times with 250-mL portions of CH_2Cl_2. The combined extracts were concentrated to give an oily solid which was dissolved in ethyl acetate (750 mL), extracted 3 times with 500-mL portions of 2 M HCl, dried over Na_2SO_4, and concentrated to leave 190 g (89%) of crude diol as a pale yellow solid. The enantiomeric excess of the crude diol was determined by HPLC analysis (Pirkle 1A chiral column using 5% isopropyl alcohol/hexane as eluant) of the derived bis-acetate to be 78% [Note that this is ~7% lower than the ee value in the table for the same process on a small scale where the temperature was maintained at 0 °C. In fact for stilbene, process optimization has given a crude ee of >95% (unpublished results).] Recrystallization of the crude diol from ca. 1000 mL of CH_2Cl_2 gave 150 g (70%) of (+)-*threo*-hydrobenzoin (mp 135–137 °C, $[\alpha]^{23}_D$ +84° (*c* 1.0, EtOH), 90% ee). A second recrystallization from CH_2Cl_2 afforded 115 g (55%) of optically pure diol (mp 147–8.5 °C, $[\alpha]^{23}_D$ +90.1° (*c* 1.0, EtOH), >99% ee). The alkaloid **1** was recovered in 91% yield by neutralization of the HCl extracts (see Supplementary Material).

(7) To date about 20 olefins have been subjected to catalytic asymmetric dihydroxylation.

(8) We know of no previous reports of cinchona alkaloid derivatives accelerating a transition-metal-catalyzed process. However, due mainly to the contributions of the Wynberg group in Groningen, this family of alkaloids has had an important influence on the development of abiological asymmetric catalysis, see: Smaardijk, Ab. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135. Wynberg, H. "Asymmetric Catalysis by Cinchona Alkaloids" In *Topics in Stereochemistry*; Eliel, E., Wilen, S., Eds.; Wiley-Interscience: New York, 1986; Vol. 16.

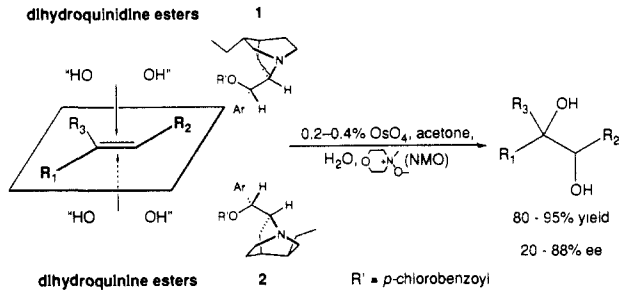
(9) Given the architecturally interesting ligands needed to influence the stereochemical course of a catalytic process, one intuitively expects ligand-decelerated catalysis to prevail, but, though probably rare, ligand-accelerated catalysis has intriguing implications for selective catalysis. In fact the titanium-catalyzed asymmetric epoxidation is another example of a process dependant on ligand-accelerated catalysis (Finn, M. G. Ph. D. Dissertation, Massachusetts Institute of Technology, Cambridge Massachusetts, 1985).

(10) Jacobsen, E. N.; France, M. B.; Sharpless, K. B., manuscript in preparation.

(11) X-ray structure determined for the osmium tetroxide complex of the dimethyl carbamate analogue of **1** (Rao, P.; Jacobsen, E. N.; Lippard, S. J.; Sharpless, K. B., unpublished results).

(12) Quinuclidine binds to osmium tetroxide with $K_{eq} \approx 13000$ M^{-1} in acetone/H_2O (10:1).[10]

Scheme I



At least in the case of styrene, the rate acceleration in the presence of the alkaloid is completely accounted for by facilitation of the initial osmylation step.[13] The strikingly opposite effects of quinuclidine and **1** on the catalysis can be related to the fact that although quinuclidine also accelerates the addition of osmium tetroxide to olefins,[10] it binds too strongly to the resulting osmium(VI) ester intermediate and inhibits catalyst turnover by retarding the hydrolysis/reoxidation steps of the cycle. In contrast, the alkaloid appears to achieve a balancing act which renders it near perfect for its role as an accelerator of the dihydroxylation catalysis. It binds strongly enough to OsO_4 to accelerate addition to olefins, but not so tightly to the osmate esters that it interferes (as does quinuclidine) with subsequent stages of the catalytic cycle. As expected from their known affinity for forming stable octahedral osmium(VI) glycolate ester complexes,[14] we find that chelating tertiary amines [e.g., 2,2'-bipyridine and (−)-(*R*,*R*)-*N*,*N*,*N'*,*N'*-tetramethyl-1,2-cyclohexanediamine][5b] at 0.2 M completely inhibit the catalysis. Perhaps more surprising is the observation that pyridine at 0.2 M has the same effect; pyridine is also an excellent ligand for osmate esters, which probably accounts for its deleterious effect here.[15]

This catalytic asymmetric oxidation has noteworthy features: (1) unlike asymmetric epoxidation and asymmetric hydrogenations, it requires no directing functional group (though so far aromatic olefins give better results); (2) thanks to the ligand-acceleration phenomenon, very little osmium catalyst is needed (as little as one part in 50000 to date), thus making it, asymmetric induction aside, the most active known catalytic osmylation; (3) the two readily available cinchona alkaloid diastereomers (quinine and quinidine) essentially fulfill the function of enantiomers and are easily recovered; (4) being insensitive to air and water and seeming actually to work better under conditions of high concentration (indicating little or no product inhibition), the process is simple to perform on any scale.

In summary, what this transformation lacks in uniformly high asymmetric inductions it makes up for in broad applicability and ease of execution. Among existing catalytic asymmetric reductions and oxidations involving olefins, this process seems to have the largest pool of potential substrates.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM 28384) and Eli Lilly. E.N.J., G.S., and K.B.S., respectively, thank the National Institutes of Health, NATO, and the John Simon Guggenheim Memorial Foundation for fellowships. K.B.S. is especially grateful to the California Institute of Technology for a Sherman Fairchild Fellowship during the tenure of which the idea of ligand-accelerated catalysis took hold.

Supplementary Material Available: Details for the preparation and recovery of the alkaloid ligands **1** and **2** (4 pages). Ordering information is given on any current masthead page.

(13) For more highly substituted olefins, steps involving the osmate ester may become turnover limiting. The presence of the alkaloid also seems to affect such cases, but its mode(s) of action remain to be established.

(14) Resch, J. F.; Meinwald, J. *Tetrahedron Lett.* **1981**, *22*, 3159, and references therein.

(15) However pyridine has also been reported[2d] to facilitate, albeit at higher temperatures, a catalytic osmylation process.

Probing Ergot Alkaloid Biosynthesis: Identification of Advanced Intermediates along the Biosynthetic Pathway

Alan P. Kozikowski* and Jiang-Ping Wu

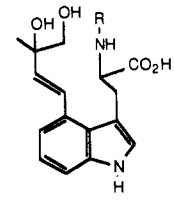
Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

Masaaki Shibuya and Heinz G. Floss*

Department of Chemistry, The Ohio State University Columbus, Ohio 43210

Received September 28, 1987

The biosynthesis of ergot alkaloids, e.g., chanoclavine-I (I) and elymoclavine (II) from L-tryptophan, methionine, and dimethylallyl pyrophosphate via *N*-methyl-4-(γ,γ-dimethylallyl)-tryptophan (III) is well established.[1-3] While the conversion of I to II is well understood,[1,4] the detailed mode of closure of ring C, i.e., the conversion III → I, is still obscure. In an effort to shed light on this matter we recently prepared a labeled version (IVc)



IVa, R=H
IVb, R=CH_3
IVc, R=CD_3

of a proposed[1,2] intermediate, the diol IVb.[5] However, feeding of both diastereomers of IVc to replacement cultures of *Claviceps sp.* strain SD58 failed to reveal any incorporation into II.[6] In view of this negative result it was decided to synthesize the monohydroxylated dimethylallyltryptophan derivative Vb (Scheme II) to examine its possible incorporation into II.

As shown in Scheme I, the required indole was prepared in labeled form from *N*-tosylindole-4-carboxaldehyde (**1**) by the addition of isobutenylmagnesium bromide, protection of the resulting alcohol **2** as its SEM ether, cleavage of the tosyl group, and then gramine formation with use of *N*,*N*-dimethyl(methylene)ammonium chloride. Next, the gramine intermediate was condensed with dimethyl [*N*-trideuteriomethyl-*N*-(2,2,2-trichloroethoxycarbonyl)amino]malonate[6] in the presence of tri-*n*-butylphosphine to produce the amidomalonate **5**. Intermediate **5** was treated in turn with pyridinium *p*-toluenesulfonate to afford the tertiary alcohol **6**. This acid-catalyzed process thus served to remove the SEM ether group with concomitant allylic rearrangement. The nitrogen-protecting group was now cleaved under reductive conditions, and the diester decarbomethoxylated by using 5% aqueous potassium hydroxide followed by acid treatment. Lastly, the monoester **7** was saponified with use of 2 N KOH in a mixture of methanol and tetrahydrofuran to provide the racemic amino acid Vb.

(1) Floss, H. G. *Tetrahedron* **1976**, *32*, 873.

(2) Floss, H. G.; Anderson, J. A. In *The Biosynthesis of Mycotoxins*; Steyn, P. S., Ed.; Academic Press: New York, NY, 1980; pp 17-67.

(3) Otsuka, H.; Quigley, F. R.; Gröger, D.; Anderson, J. A.; Floss, H. G. *Planta Med.* **1980**, *40*, 109.

(4) Floss, H. G.; Tcheng-Lin, M.; Chang, C.-j.; Naidoo, B.; Blair, G. E.; Abou-Chaar, C.; Cassady, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 1898.

(5) The original proposal[1] suggested the intermediacy of IVa; this had to be modified to IVb when it was discovered[3] that N-methylation precedes C-ring closure.

(6) Kozikowski, A. P.; Okita, M.; Kobayashi, M.; Floss, H. G. *J. Org. Chem.*, in press.

0002-7863/88/1510-1970$01.50/0