Table I. Oxidation of Amines with Molecular Oxygen[13]

amine (concn, M)	solvent	P_{O_2}, bar	temp, °C	time, h	products, % yield (% NR_3 convn)
NMe_3 (0.5)	H_2O	14[a]	100	14	31.5% Me_3NO (32%)
NMe_3 (2.4)	H_2O	14	100	64	>95% Me_3NO (100%)
H^+NMe_3 (1.0)[b]	H_2O	86	100	64	0.4% Me_3NO
N,N-dimethyldodecylamine (0.22)	4:1 MeOH/H_2O	14	100	64	>95% *N,N*-dimethyldodecylamine oxide (100%)
N-methylmorpholine (0.20)	H_2O	71	115	72	62% *N*-methylmorpholine oxide (88%)
N,N-dimethylaniline (0.17)	4:1 MeOH/H_2O	71	104	23	<16% *N,N*-dimethylaniline oxide[c] (>90%)
pyridine	H_2O	71	100	16	0% *N*-oxide (0%)
N,N-dimethylbenzylamine (0.15)	2:1 MeOH/H_2O	71	116	7	56% *N,N*-dimethylbenzylamine oxide, 15% benzaldehyde (84%)

[a] 0.011 M O_2 in water.[12] [b] pH 2.2. [c] At low conversion (<20%) *N*-methylaniline is ~70% of converted amine.

transfer to yield an amine radical cation and superoxide (eq 1).[3] This accounts for the observed first-order de-

$$\underset{}{NR_3} + O_2 \rightleftarrows \underset{\mathbf{1}}{R_3N^{+}\cdot} + O_2^{-}\cdot \qquad (1)$$

pendence in NR_3 and O_2, as well as the slow reaction rates since this electron transfer is endothermic.[7] Such a rate-determining step is in accord with the studies of Beckwith et al. for low-pressure autoxidations in water.[3] The reactivity of amines in electron-transfer reactions has been well established by Smith[8] and Rosenblatt.[9]

The necessary divergence of mechanism must occur at the next step. Beckwith et al.[3] postulate α-deprotonation of the radical cation which is inconsistent with our results. In our case we believe the high oxygen concentration permits effective $^3O_2$ interception of the solvent-stabilized amine radical cation **1** before it can be deprotonated at the α-CH (eq 2). The alternative of a combination of **1** and

$$\underset{\mathbf{1}}{R_3N^{+}\cdot} + {}^3O_2 \rightleftarrows \underset{\mathbf{2}}{R_3N^{+}OO\cdot} \qquad (2)$$

superoxide to yield **3** is not supported by Beckwith et al.[3] and would be even more unlikely under the more strenuous conditions we employ. The hydroperoxy radical cation can be reduced either by a second tertiary amine moiety initiating a *chain reaction* or it might be reduced by superoxide directly. At this point our data do not allow us to distinguish between these possibilities. The net consequence of either of these steps is production of a zwitterionic species **3** analogous to that formed in the photooxidation of thioethers.[10] The zwitterion **3** would react with a second tertiary amine (in analogy to the thioether case[10]) to generate the *N*-oxide product (eq 3). The initial

$$\underset{\mathbf{3}}{R_3N^{+}OO^{-}} + NR_3 \rightarrow 2R_3NO \qquad (3)$$

electron transfer is the rate-limiting step in this mechanistic sequence. Our studies of the temperature dependence of the reaction for dimethyldodecylamine in 4:1 methanol/H_2O at 65 bar O_2 pressure yield an E_a = 19.1 kcal/mol and a $\Delta S^{\ddagger}$ -26.1 eu. These parameters are consistent with a bimolecular rate-determining step involving developing charge separation.[11]

In conclusion, we have shown that tertiary amines can be directly oxidized with molecular oxygen to give high yields of *N*-oxides. The mechanism appears to involve initial electron-transfer followed by oxygenation of the radical cation. Further mechanistic studies of this surprising reaction are in progress.

Registry No. NMe_3, 75-50-3; HN^+Me_3, 16962-53-1; Me_3NO, 1184-78-7; *N,N*-dimethyldodecylamine, 112-18-5; *N*-methylmorpholine, 109-02-4; *N,N*-dimethylaniline, 121-69-7; pyridine, 110-86-1; *N,N*-dimethylbenzylamine, 103-83-3; *N,N*-dimethyldodecylamine oxide, 1643-20-5; *N*-methylmorpholine oxide, 7529-22-8; *N,N*-dimethylaniline oxide, 874-52-2; *N,N*-dimethylbenzylamine oxide, 5400-82-8.

(7) We have measured the irreversible oxidation potential of *N,N*-dimethyldodecylamine in 4:1 MeOH/H_2O (0.1 M TBATFB) by cyclic voltammetry to be $E_p \sim 0.87$ V. The reduction potential for oxygen under similar conditions is $E_{1/2} \sim -0.25$ V. This corresponds to an energy gap of ~1.12 V (26 kcal/mol). Since these are irreversible oxidations, the actual energy difference will be less than the measured potential differences.

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(13) In a typical procedure, a homogeneous solution containing the tertiary amine in a glass line is placed in a high-pressure rocking autoclave fitted with sampling controls (all wetted parts see only glass or Teflon). The reaction samples are analyzed by reverse-phase HPLC techniques (0.02 N NH_4OAc + 0.02 N NH_4NO_3 in methanol/water) and analytical GC using fused silica capillary columns with FID.

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The Oxahydrindene Component of the Avermectins[1]

Summary: An intramolecular nitrile oxide cycloaddition involving a vinyl group at C3 and a nitrile oxide at C6 of a derivative of diacetone glucose provides a route to the oxahydrindene **2** stereochemically pure and appropriately functionalized for further elaboration.

Sir: The milbemycins[2] and avermectins[3] are relatively new families of broad spectrum, antihelminthic, antiparasitic agents, which are currently the foci of considerable biological and chemical interest. The avermectins, reported by Merck, Sharp and Dohme in 1979,[3a] are the more potent, and a patent medicine, Ivermectin, has recently been released for use in veterinary medicine.[4] The complex

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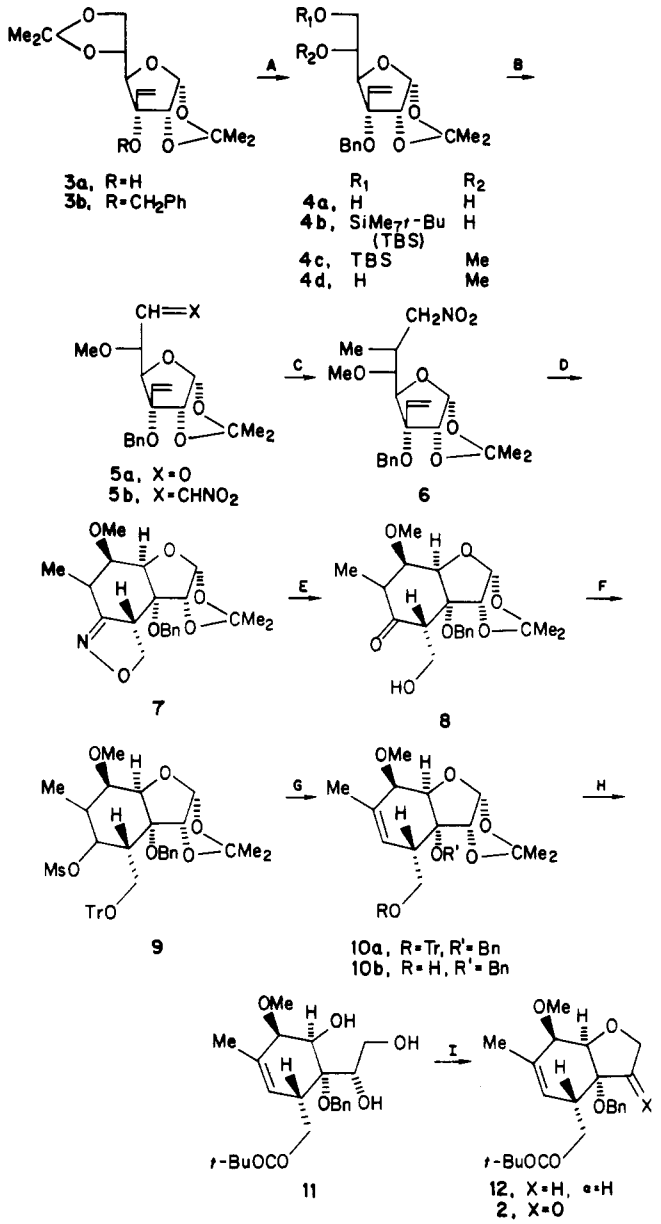
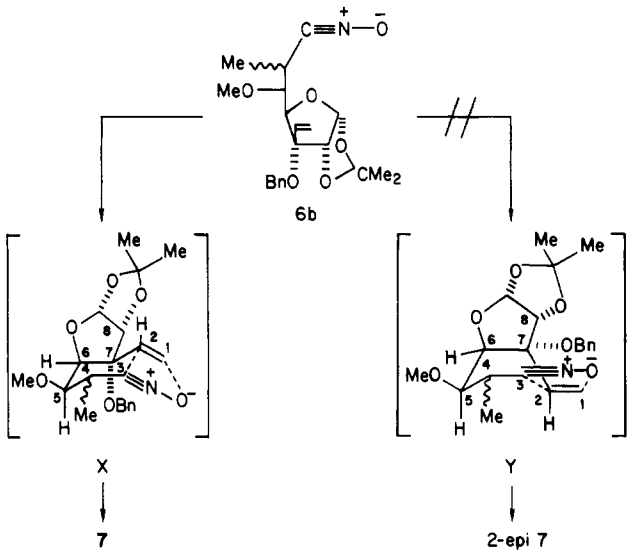
Scheme I[a]



[a] 3a → 3b, NaH, $PhCH_2Br$, $Bu_4N^+Br^-$ (76%); (A) (i) H_3O^+, (95%); (ii) *t*-$BuMe_2SiCl$, Et_3N, (98%); (iii) CH_3I, NaH, $Bu_4N^+I^-$ (98%); (iv) $Bu_4N^+F^-$ (98%); (B) $(COCl)_2$, Me_2SO, Et_3N (90%); (ii) CH_3NO_2, *t*-BuOK (77%); (iii) MsCl, (77%); (C) MeLi (60%); (D) PhNCO, Et_3N, C_6H_6, reflux (74%); (E) H_2, Ni (67%); (F) (i) $LiAlH_4$ (65%); (ii) Ph_3CCl (90%); (iii) MsCl (86%); (G) (i) NaOAc, HMPA, 100 °C, 3–4 days (50–55%); (ii) camphorsulfonic acid, MeOH, room temperature, (94%); (H) (i) *t*-BuCOCl, (80%); (ii) 0.5% H_2SO_4 (85%); (iii) $NaBH_4$, (60%); (I) (i) TsCl (70%); (ii) $(COCl)_2$, Me_2SO, Et_3N (70%).

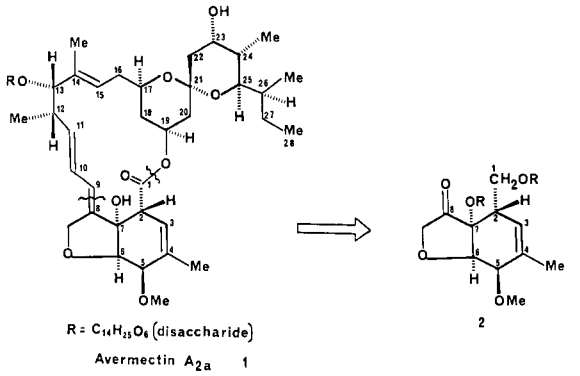
molecular framework of these compounds presents a variety of challenges to the synthetic organic chemist, and Smith[5] and Williams[6] have responded with elegant total syntheses of the milbemycins. Those achievements, buttressing the seminal investigations of Deslongchamps[7] and

Scheme II



pioneering syntheses by Evans,[8] have set a pattern for dealing with the spiroketal moiety of the series, and recent reports from the laboratories of Hanessian[9] and Baker[10] have been concerned with this component of the avermectins and/or milbemycins.

However, there have been no reports so far on the crucial "southern" oxahydrindene portion[11] of avermectin A_{2a} (1)



which, given the secure prototypes[5-8] for the "northern half" is clearly the more challenging. The stability of this component is surprising, since two β-eliminations (of water and methanol from 1) would lead to a benzenoid ring, and a subsequent prototropic shift (from C8a) would afford a benzofuran. However, these aromatizations do not occur in spite of isolation procedures that include standing overnight in methanolic HCl.[3b] Furthermore, heating with pyridine and acetic anhydride at 100 °C for 24 h caused only 30% aromatization.[12] Our objective was therefore to develop a secure, versatile route to the oxahydrindene segment, so that systematic studies on its stability could be carried out. The work accomplished features a [3 + 2] intramolecular nitrile oxide cycloaddition (INOC)[13] applied

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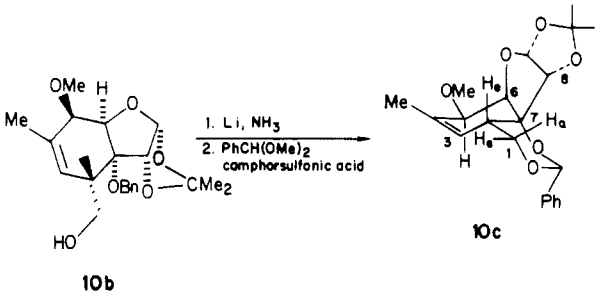
Scheme III



to a readily prepared derivative of "diacetone glucose", whereby the oxahydrindene **2** is obtained optically active, with the correct stereochemistry, and appropriately functionalized for further elaboration.

The known[14] allylic alcohol **3a** was prepared from diacetone glucose, and standard operations on the corresponding benzyl ether **3b** were applied to methylate the C5 hydroxyl group (glucose or avermectin numbering) and to expose the primary hydroxyl group in **4d**.[15] Swern oxidation[16] gave the aldehyde **5a**, and a Henry reaction, followed by sulfonation and β-elimination led to the nitroalkene **5b** which underwent conjugate addition with methyllithium to afford the epimeric mixture **6** (Scheme I).

The prospective INOC reaction[13] was the key step in our sequence, and the stereochemistry thereof was central to our plans, since the crucial C2 center of **1** is created in this process. Of the possible modes of cyclization, X and Y, shown in Scheme II, the former seemed more likely, since it proceeds through a chair transition state. In the event, treatment of **6** under the Mukaiyama conditions for generating a nitrile oxide[17] *yielded 7 as single C2 isomer* (74%) whose reduction, under the conditions prescribed by Curran,[18] afforded ketone **8** which was processed without event to the methanesulfonate **9**. The regioselectivity of the up-coming β-elimination was an obvious point of speculation; however, conditions were found where a single olefin, **10a**, was obtained.

Although the above transition-state analysis (Scheme II) seemed rational, it was essential to establish the C2 configuration unambiguously. Accordingly **10b** was converted into the benzylidene derivative **10c** as outlined in Scheme III. The 250-MHz ^{1}H NMR spectrum of **10c** shows the H1 protons at 4.34 and 4.22 ppm with couplings of 3.9 and 0.0 Hz, respectively, to H2. With respect to the benzylidene ring, the latter data rule out trans diaxial relationships, and given the fact that the C7 configuration is known, the parameters can *only* be accommodated by the representation shown in Scheme III.

After protecting group adjustments, the Gray procedure for reductive cleavage of glycosides[19] was then applied to **10b** and to the corresponding hemiacetal obtained by hydrolysis of the acetonide; but in both cases, complex mixtures resulted. A less direct procedure was therefore employed involving the triol **11**, which underwent sulfonation in the presence of pyridine to give **12**[15] directly. Oxidation to compound **2**[15] followed.

The INOC route illustrated in Scheme I has been shown to provide a simple secure route to the oxahydrindene **2**, and given the ready availability of the starting material **3a**, a variety of analogues of **2** can be readily envisaged. Studies along this line are underway and will be reported in due course.

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Selective Addition of Unsaturated Carboxylic Acids to Terminal Acetylenes Catalyzed by Bis(η^5-cyclooctadienyl)ruthenium(II)-Tri-*n*-butylphosphine. A Novel Synthesis of Enol Esters

Summary: Unsaturated carboxylic acids such as methacrylic acid, crotonic acid, vinylacetic acid, and sorbic acid and aromatic carboxylic acids reacted with terminal acetylenes in the presence of a catalytic amount of bis(η^5-cyclooctadienyl)ruthenium-P-*n*-Bu_3 in benzene at 80 °C to give enol esters having a terminal methylene group in excellent yields with high regioselectivity.

Sir: Enol esters have proven to be extremely valuable intermediates in organic synthesis.[1] Major methods for preparing enol carboxylates are (1) conversion of ketones or aldehydes into enolates followed by their treatment with acylating agents,[2] (2) the palladium-promoted acetoxylation of olefins,[3,4] and (3) addition of carboxylic acids to alkynes.[5] The last one is known to be catalyzed by mercury salts and strong acids[5a] or Lewis acids.[5b] In many cases stoichiometric quantities of mercury salts are used.[6,7] Recently, addition of carboxylic acids to internal alkynes catalyzed by $Ru_3(CO)_{12}$ and $[Ru(CO)_2(CH_3CO_2)]_n$ at 145 °C was reported.[8]

We now report a novel selective synthesis of enol esters through the addition of unsaturated carboxylic acids to

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