Bleomycin as an Oxene Transferase. Catalytic Oxygen Transfer to Olefins

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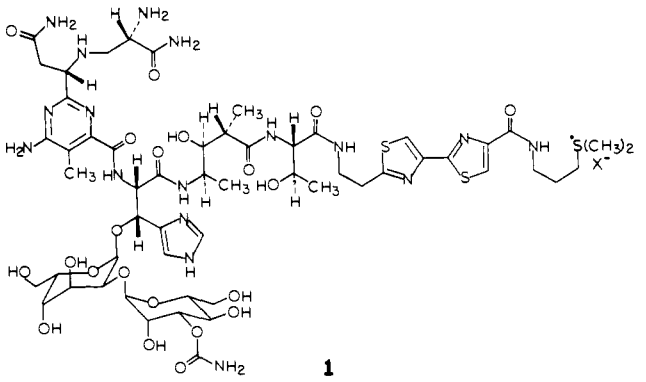
Abstract: Admixture of oxidants such as iodosobenzene and sodium metaperiodate to solutions of Fe(III)–bleomycin and Cu(II)–bleomycin effected activation of these species. The active complexes thus formed were found to be capable of transferring oxygen to certain olefinic substrates, including *cis*-stilbene, styrene, norbornene, and cyclohexene. *cis*-Stilbene was converted to *cis*-stilbene oxide reasonably efficiently by bleomycin, but *trans*-stilbene was shown to be a poor substrate for bleomycin-mediated oxidation. The stereoselectivity of olefin oxidation was thus similar to that observed for cytochrome P-450 model systems, a characteristic also found for a number of other bleomycin-mediated transformations. Also analogous to observations made previously for cytochrome P-450 was the bleomycin-mediated *N*-demethylation of *N*,*N*-dimethylaniline and the oxidation of *p*-deuterioanisole to *p*-methoxyphenol with concomitant 1,2-migration of deuterium (NIH shift). However, in contrast to cytochrome P-450, which has been reported to induce asymmetry during the oxidation of certain prochiral substrates, bleomycin-mediated oxidation of styrene resulted in the formation of racemic styrene oxide. Also tested for their oxygen-transfer properties were a number of structural analogues of bleomycin, including epibleomycin, isobleomycin, deglycobleomycin, and *N*-acetylbleomycin. All of the tested species were found to be capable of effecting oxygen transfer to olefins with the exception of *N*-acetylbleomycin, which was also the only analogue dysfunctional in DNA degradation. Although investigated in less detail, it was also shown that oxidation of olefins could be achieved with Fe(II)–bleomycin + O_2, provided that a suitable reducing agent was present. The results obtained are consistent with a mechanism in which the same activated species can be derived from suitable metallobleomycins via the agency of O_2 and reducing agents or oxygen surrogates such as iodosobenzene and periodate.

The bleomycins are a family of glycopeptide-derived antitumor antibiotics used clinically for the treatment of squamous cell carcinomas and malignant lymphomas. Individual bleomycins differ structurally at the C-terminus; bleomycin A_2 (**1**) is the main



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component of the clinically used mixture of bleomycins.[1,2] Current interest in the chemistry of bleomycin (BLM) is reflected in efforts to understand the mechanistic nature of DNA strand scission,[3] which is the presumed therapeutic locus of bleomycin,[1] and in the characterization of structural analogues of bleomycin which may have modified biochemical and biological properties.[4] DNA strand scission by bleomycin is an oxidative process that can be demonstrated in vitro by using Fe^{II}·BLM + O_2[5] or Cu^{I}·BLM + O_2.[6] The nature and structures of the oxygen-activated species have eluded exact definition and remain an area of active research.[5b,7]

Cytochrome P-450 is a group of widely distributed heme-containing proteins that mediate the oxidative metabolism of a number of substances, including many xenobiotics.[8] Cytochrome P-450 is a mixed-function monooxygenase; although normally activated by NADPH-ferricytochrome oxidoreductase, NADPH, and O_2, activation can also be effected by the use of oxygen surrogates such as iodosobenzene.[8,9] The latter approach has been particularly useful mechanistically in facilitating elucidation of the mechanism of oxygen activation and transfer,[9,10] in part because the active complexes so formed from a number of P-450 model systems catalyze a wide variety of oxidation reactions, including aliphatic hydroxylations and alkene epoxidation.[8]

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Recently, we demonstrated that Fe^{III}·BLM and Cu^{II}·BLM could also be activated by C_6H_5IO and that the derved activated species could be employed for oxygen transfer.[11] We also demonstrated that both Fe^{III}·BLM and Cu^{II}·BLM could be activated enzymatically by NADPH-ferricytochrome oxidoreductase, NADPH, and O_2.[12] In addition to mediating the oxidative degradation of DNA, C_6H_5IO-activated Fe^{III}·BLM and Cu^{II}·BLM were also shown to oxidize *cis*-stilbene (to *cis*-stilbene oxide), but not *trans*-stilbene;[11] the selectivity observed in these transformations was strongly reminiscent of results obtained previously with cytochrome P-450 and analogues such as chloro($\alpha,\beta,\gamma,\delta$-tetraphenylporphyrinato)iron(III).[10d]

In an effort to better define the nature of oxygen activation and transfer by bleomycin, we have attempted to extend our observations of bleomycin activation and reactivity and to test further the apparent analogy between the chemistry of bleomycin and that of cytochrome P-450. Presently, we provide a complete analysis of the products formed from *cis*-stilbene and *trans*-stilbene by (anaerobically activated) Fe·BLM and Cu·BLM, as well as the effect of the specific oxygen surrogate and reaction solvent on the extent of transformation and ratio of products formed. Reported for the first time are the attempted oxidations of cyclohexene, norbornene, styrene, indene, and *trans*-cinnamic acid with Fe^{III}·BLM + C_6H_5IO; to facilitate comparison with comparable transformations mediated by cytochrome P-450 analogues, some of these substrates have also been oxidized using (tetraphenylporphyrinato)iron(III) (Fe^{III}·TPP) + C_6H_5IO. Also reported for the first time are the N-demethylation of *N,N*-dimethylaniline by Fe^{III}·BLM + C_6H_5IO, a BLM-mediated NIH shift, a study of the chirality of oxygen transfer from activated Fe·BLM to styrene, and the explicit identification of the source of oxygen transferred to the olefinic substrates studied here. In addition, we define an experimental system in which BLM can be used catalytically for the activation of O_2 and from which the same reaction products are produced as observed following admixture of metallobleomycin + C_6H_5IO. To date, only bleomycin[11] and deglycobleomycin[13] have been shown to mediate oxygen transfer to olefins. Reported herein are the oxygen-transfer properties of a number of bleomycin analogues previously shown to effect DNA strand scission when activated aerobically, including decarbamoyl bleomycin, isobleomycin, epibleomycin, and tallysomycin.

Results and Discussion

Cytochrome P-450 is a group of monooxygenases that can catalyze the oxidation of a wide variety of substrates in the presence of NADPH-cytochrome P-450 reductase, NADPH, and O_2. The mechanism of oxygen fixation by these heme proteins and the way in which the oxygen is transferred to other molecules have been subjects of much interest.[8] There is a growing body of evidence which suggests that a perferryl ion is present as the active oxygen-transfer agent formed as part of a catalytic cycle; the initial step is envisioned as reductive activation of molecular oxygen by the heme proteins.[8] The nature of the active species was deduced, in part, from extensive studies with model systems using monooxygen donors such as iodosobenzene, peroxide, etc.;[10] the active intermediates thus formed were found to oxidize a wide variety of organic molecules.[8,10] It may be noted that the type of oxidation accomplished in vitro by these model systems is believed to bear a close resemblance to the related enzymatic processes.

In analogy with cytochrome P-450, Fe^{II}·BLM chelates molecular oxygen, and an active intermediate derived from this complex effects DNA strand scission by an oxidative process.[5,7] BLM can also be activated with Fe^{III} and ethyl hydrogen peroxide and the two activated complexes have been reported to be similar in nature.[7d] To facilitate a better understanding of the chemistry of bleomycin, it was of interest to study the oxidation of simple organic substrates by bleomycin following activation of bleomycin with oxygen surrogates such as iodosobenzene.

Oxidation of Olefins by Fe^{III}·BLM and Cu^{II}·BLM Following Activation with Iodosobenzene. As shown in Table I, when treated with 30–35 equiv of iodosobenzene in aqueous methanol, Fe^{III}·BLM effected its conversion to iodobenzene in ~80% yield within 30 min. In the presence of olefinic compounds, Fe^{III}·BLM effected the net transfer of oxygen from iodosobenzene to the substrates and, depending upon the structure and reactivity of the individual olefin, oxidized products could be isolated in varying yields. The products obtained with several olefin substrates are recorded in the table.

The greater reactivity of *cis*-stilbene relative to the trans isomer under the reaction conditions was evident from the yields of the products formed. *cis*-Stilbene, when used as a substrate, provided a number of products, the *cis*-oxide (25%) being the major one. The *trans*-oxide was produced only in 1% yield, demonstrating the stereoselectivity of the "oxygen transfer". In contrast, *trans*-stilbene was found to be a poor substrate under the same conditions as those used for *cis*-stilbene. Only 3% *trans*-oxide (and no *cis*-oxide) could be detected. As shown in the table, these results paralleled those obtained with (tetraphenylporphyrinato)iron(III) and C_6H_5IO under similar experimental conditions. In view of the recent report[14] that C_6H_5IO exists as the dimethoxide in methanolic solution, the expoxidation of *cis*-stilbene was attempted in anhydrous methanol to permit assessment of the nature of the oxidant responsible for BLM activation. In the absence of water, no *cis*-stilbene oxide was formed from *cis*-stilbene, consistent with the belief that BLM is activated by C_6H_5IO per se. Also consistent with this interpretation was the successful epoxidation of *cis*-stilbene in aqueous CH_3CN (Table II).

Norbornene proved to be a better substrate for activated Fe·BLM than stilbene, affording the *exo*-epoxide in 31% yield as determined by gas chromatography–mass spectrometry. Cyclohexene, when used as a substrate for Fe^{III}·BLM + C_6H_5IO, provided the oxide (9%), cyclohex-1-en-3-ol (12%), and cyclohexane-1,2-diol monomethyl ether (39%) as major products. The stereochemistry of cyclohexane 1,2-diol monomethyl ether was studied on the chance that it might provide useful information concerning the mechanism of bleomycin-mediated oxygen transfer. Direct comparison with authentic samples of *cis*- and *trans*-cyclohexane 1,2-diol monomethyl ether established that the bleomycin-derived material was exclusively of the trans configuration. While this result is entirely consistent with the suggested mechanism outlined below, it must be noted that the same product was also formed from cyclohexene oxide when the latter was treated with Fe^{III}·BLM + C_6H_5IO under the same experimental conditions. Thus *trans*-cyclohexane 1,2-diol monomethyl ether may not be a primary product of BLM-mediated oxygen transfer to cyclohexene.

Also employed as substrates for Fe^{III}·BLM A_2 + C_6H_5IO were styrene and indene, which were mainly converted to the respective epoxides. As described below, the former was of interest for the evaluation of possible chiral oxygen transfer by bleomycin.

It is interesting to note that unlike the reaction of activated Fe–bleomycin with DNA, for which it has been difficult to establish a catalytic role for bleomycin, as many as ~20 turnovers of bleomycin are indicated by the amounts of products formed in these experiments.

Cu^{I}·BLM undergoes aerobic activation and the redox-active species thus formed cleaves DNA.[6] We therefore attempted to study oxygen transfer from Cu^{II}·BLM following activation with C_6H_5IO. The oxidation of *cis*-stilbene with this reagent provided *cis*-stilbene oxide, as noted previously.[11] Although the yields of *cis*-stilbene oxide were occasionally as high as those obtained with Fe^{III}·BLM, more typically the oxide was isolated in 3–7% yields along with larger amounts (~10%) of *O*-methylhydrobenzoin.

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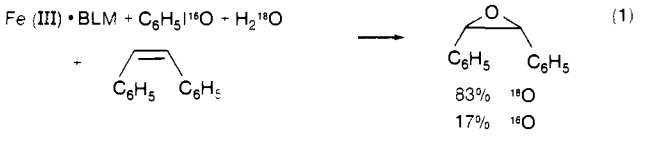
The latter was shown to be a secondary product that can form from *cis*-stilbene oxide under the reaction conditions, and its presence probably accounts for the low and variable[11] yield of the oxide. As observed in the case of Fe^{III}·BLM, *trans*-stilbene also proved to be a poor substrate of Cu^{II}·BLM in the presence of iodosobenzene.

As regards yields and stereoselectivity of epoxide formation, the results obtained here were in broad agreement with those reported by Groves et al.[10d] who used the cytochrome P-450 analogue chloro($\alpha,\beta,\gamma,\delta$-tetraphenylporphyrinato)iron(III) and iodosobenzene on similar substrates. Especially striking was the difference in reactivity between *cis*- and *trans*-stilbene in the BLM-mediated oxidations when the reactions were carried out in aqueous methanol.

Oxygen Transfer by Activated Bleomycin. The source of the oxygen atom incorporated into *cis*-stilbene oxide during bleomycin-mediated epoxidation was studied by carrying out the transformation in the presence of ^{18}O-labeled H_2O and C_6H_5IO. As shown in eq 1, the epoxidation of *cis*-stilbene with Fe^{III}·BLM



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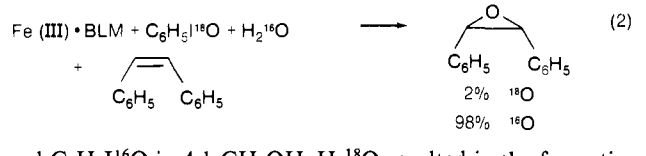
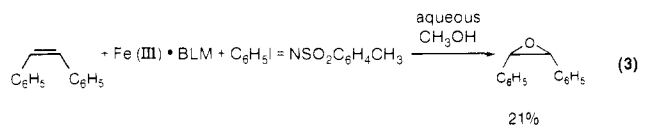


(2)

and $C_6H_5I^{16}O$ in 4:1 CH_3OH–$H_2{}^{18}O$ resulted in the formation of *cis*-stilbene oxide (~18% yield, based on consumed C_6H_5IO) containing 83% ^{18}O, as judged by mass spectral analysis. In comparison, when the expoxidation was carried out in aqueous methanol employing $C_6H_5I^{18}O$[15] as an oxidant, the resulting epoxide contained no more than 2% ^{18}O (eq 2). Incorporation of ^{18}O label into product was shown not to be due to $H_2{}^{18}O$–$C_6H_5I^{16}O$ exchange;[16] that iodobenzene dimethoxide[14] was not an obligatory intermediate in the exchange process reflected in eq 1 and 2 was established by repetition of the experiments in water–CH_3CN.[17]

Breslow and Gellman have described the tosylamidation of hexane by the use of (tosyliminoiodo)benzene and either Mn^{III}- or Fe^{III}·TPP(Cl)[18] in CH_2Cl_2. When *cis*-stilbene was incubated in the prescence of Fe^{III}·BLM + $C_6H_5I{=}NSO_2C_6H_4CH_3$-*p* in aqueous methanol, the major product isolated (21% yield) was *cis*-stilbene oxide (eq 3); no product containing the tosylamido



(3)

functionality could be detected. Clearly, this observation was also consistent with the results of the ^{18}O-incorporation experiments described above.

The C_6H_5IO-mediated hydroxylations of cyclohexene[19] and camphor,[20] carried out by cytochrome P-450 from rat liver and *Pseudomonas putida*, respectively, have also been shown to proceed with incorporation of label from solvent, but not from C_6H_5IO. In common with these cytochrome P-450 mediated transformations, it seems likely that the activated Fe·BLM that mediates the epoxidation of *cis*-stilbene contains a single oxygen atom bound to Fe, which is capable of undergoing exchange with solvent.

Oxygen Transfer to Prochiral Olefins. Recent reports of enantioselective sulfide oxidation by cytochrome P-450,[21] and of catalytic asymmetric epoxidations with chiral iron porphyrins,[22] prompted us to effect the epoxidation of two prochiral olefins with activated bleomycin. Oxidation of styrene with Fe^{III}·BLM + C_6H_5IO afforded styrene oxide in 18–20% yield. The material obtained did not have an optical rotation; determination of optical purity with the chiral shift reagent Eu(hfc)$_3$ indicated that the product was racemic.[23]

Activation of Fe–Bleomycin. Studies utilizing cytochrome P-450 have shown that, in addition to iodosobenzene, both iodobenzene diacetate and sodium metaperiodate function as oxygen surrogates in cytochrome P-450 dependent oxidation reactions.[10a] Therefore, these reagents were tested for their ability to support bleomycin-mediated olefin epoxidations.

When employed for Fe^{III}·BLM activation in the same fashion as C_6H_5IO, iodobenzene diacetate produced the same products from *cis*-stilbene in essentially the same relative amounts, albeit in significantly lower overall yields. Even when the reaction time was increased substantially (1.5 → 12 h), the yield of *cis*-stilbene was only 7%. In contrast, when periodate was employed for the activation of Fe^{III}·BLM the products included *cis*-stilbene oxide (12–18%), deoxybenzoin (10–15%), and benzaldehyde (~5%), but not *trans*-stilbene oxide. Activation of Fe^{III}·BLM A_2 with ethyl hydrogen peroxide was also studied; products included *cis*-stilbene oxide (17%), *trans*-stilbene oxide (~2%), and deoxybenzoin (7%). Although the ratios of products obtained from *cis*-stilbene following Fe^{III}·BLM activation with the four oxidants studied here were not absolutely identical, the HPLC product profiles were quite similar, suggesting that the individual BLM A_2 mediated olefin oxidations were basically analogous. These observations, though not conclusive, are consistent with the formation of a common activated complex fromFe^{III}·BLM A_2 and each of the four oxygen surrogates studied.

Although the active complex formed from BLM·Fe^{II} + O_2 has been reported to be the same as the reactive species derived from BLM·Fe^{III} + ethyl hydrogen peroxide,[7d] initial attempts to oxidize olefins with BLM·Fe^{II} following aerobic activation were not successful. In the belief that this might be due to an insufficiency of reducing equivalents,[6b] several different reducing agents were utilized in an effort to increase the extent of reaction. The reducing agents employed included dithiothreitol, dithionite, 2-mercaptoethanol, and ascorbate. In each case the extent of reaction increased dramatically; typically, several products were formed, including those obtained with anaerobically activated Fe^{III}·BLM and others that must have arisen by reaction of the reducing agents with initially formed reaction products or intermediates. Activation of Fe^{II}·BLM in the presence of O_2 and ascorbate gave the results most nearly analogous to those obtained via anaerobic activation.

Other Bleomycin-Mediated Transformations. Microsomal monoxygenases have been shown to mediate the hydroxylation of a number of aromatic substrates.[8] That these oxidations can proceed via arene oxide intermediates has been inferred from the

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(16) Incubation of $C_6H_5I^{16}O$ in methanolic solution in the presence of $H_2{}^{18}O$ under the conditions used for BLM-mediated formation of *cis*-stilbene oxide resulted in ~40% incorporation of ^{18}O into C_6H_5IO (as judged by mass spectral analysis of $(C_6H_5)_3PO$ following treatment of the incubation mixture with $(C_6H_5)_3P$[14]). Analogous incubation of $C_6H_5I^{16}O$ in CH_3CN–$H_2{}^{18}O$ gave only ~5% ^{18}O exchange into C_6H_5IO. While the limited exchange observed into methanolic solution presumably involves the intermediacy of iodobenzene dimethoxide, this species is clearly insufficient to account for the observed ^{18}O content of *cis*-stilbene oxide (eq 1).

(17) Incubation of Fe(III)–BLM + $C_6H_5I^{16}O$ with *cis*-stilbene in a 4:1 mixture of CH_3CN–$H_2{}^{16}O$ provided *cis*-stilbene oxide containing 66% ^{18}O. While reflecting slightly less efficient exchange than that obtained in aqueous methanol (cf. eq 1 and ref 16), this observation excluded iodobenzene dimethoxide as an obligatory intermediate in the exchange.

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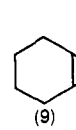
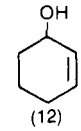
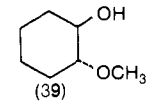
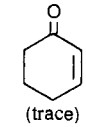
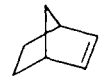
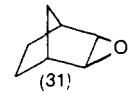
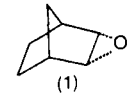
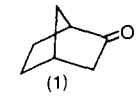
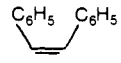
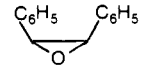
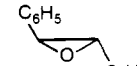
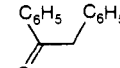
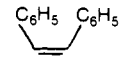
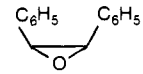
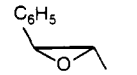
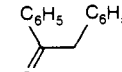
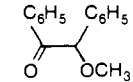
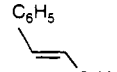
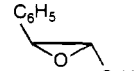
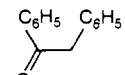
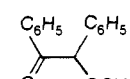
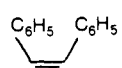
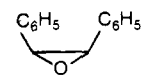
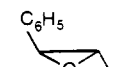
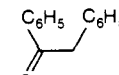
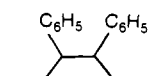
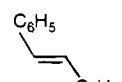
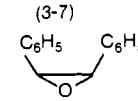
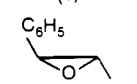
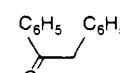
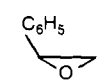
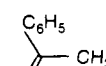
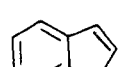
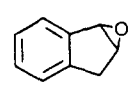
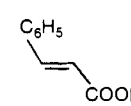
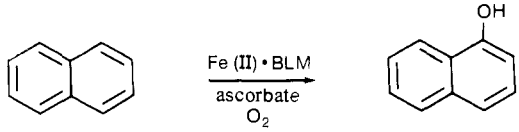
Table I. Olefin Oxidation by Fe(III) + BLM + C_6H_5IO and Cu(II) + BLM + C_6H_5IO

oxidant	substrate	products (yields)[a,b]				
Fe (III) • BLM A_2 + C_6H_5IO	None	C_6H_5I (78, 85)				1b
Fe (III) • BLM A_2 + C_6H_5IO		 (9)	 (12)	 (39)	 (trace)	1a
Fe (III) • BLM A_2 + C_6H_5IO		 (31)	 (1)	 (1)		1a
Fe (III) • TPP (Cl) + C_6H_5IO		 (40)	 (trace)	 (2)		1b
Fe (III) • BLM A_2 + C_6H_5IO		 (25, 22)	 (1)	 (7)	 (5-7)	C_6H_5CHO (5) 1b, 1c, 1d
Fe (III) • BLM A_2 + C_6H_5IO		 (3)	 (2)	 (2)		1b, 1c, 1d
Cu (II) • BLM A_2 + C_6H_5IO		 (3-7)	 (1)	 (1)	 (8-10)	1b, 1d
Cu (II) • BLM A_2 + C_6H_5IO		 (<1)	 (1)	 (2)		1b, 1d
Fe (III) • BLM A_2 + C_6H_5IO		 (9, 21)	 (trace)			1c
Fe (III) • BLM A_2 + C_6H_5IO		 (9)				1c
Fe (III) • BLM A_2 + C_6H_5IO		None				

[a] Yields were determined by (1a) gas chromatography–mass spectrometry, (1b) HPLC analysis, (1c) isolation, (1d) 360-MHz ^1H NMR analysis. [b] Yields based on amount of added iodosobenzene; quantitative conversion was assumed.

observed 1,2-shift of substituents from the site of oxidation concomitant with formation of the phenolic OH group.[8b,24] Initial efforts to effect facile monohydroxylations of substrates such as naphthalene and anisole[10g] using Fe^{III}·BLM + C_6H_5IO in aqueous methanol were largely unsuccessful, providing instead mixtures of (polyoxygenated) phenols. Subsequently, however, it was found that naphthalene could be converted predominantly to α-naphthol (162% yield, based on BLM) via the agency of Fe^{II}·BLM + O_2



+ ascorbate. Anisole was converted to *p*-methoxyphenol under the same conditions; both transformations were shown to be BLM dependent.

In an effort to establish the mechanism by which these transformations proceeded, *p*-deuterioanisole[10g] (D content ~80%) was next treated with Fe^{II}·BLM + O_2 + ascorbate in aqueous methanol. Again, hydroxylation of the aromatic substrate was observed; the *p*-methoxyphenol produced from each of a few different experiments was analyzed for deuterium content of the product, and it was found to be somewhat variable (15–21%) but always much less than that of the starting material. These observations are consistent with partitioning of an intermediate of type i (eq 4), which has been invoked previously in aromatic hydroxylations.[25,26]

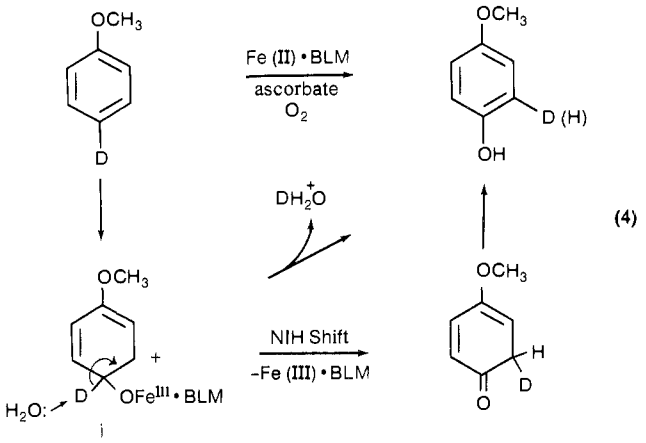
Cytochrome P-450 and related model systems have been shown to effect the oxidative N-demethylation of aromatic amines; the mechanism of the transformation has been studied in some detail.[8b,27] Interestingly, conversion of *N*,*N*-dimethylaniline to

(24) Jerina, D. M.; Daly, J. W. *Science (Washington, DC)* **1974**, *185*, 573.

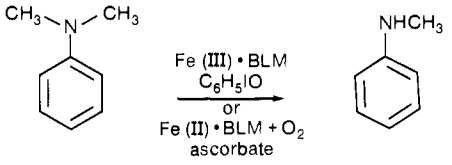
(25) Sheldon, R. A.; Kochi, J. K. "Metal-Catalyzed Oxidations of Organic Compounds"; Academic Press: New York, 1981; pp 254–255.

(26) Castle, L.; Lindsay-Smith, J. R.; Buxton, G. V. *J. Mol. Catal.* **1980**, *7*, 235.

(27) Shannon, P.; Bruice, T. C. *J. Am. Chem. Soc.* **1981**, *103*, 4580.



N-methylaniline proceeded cleanly in the presence of Fe^{III}·BLM



+ C_6H_5IO (40% yield based on C_6H_5IO; 1100% based BLM) or Fe^{II}·BLM + O_2 + ascorbate (140% yield based on BLM).

These additional bleomycin-mediated transformations extend the analogy between the chemistry of bleomycin and that of cytochrome P-450 and suggest strongly that bleomycin can function as a monooxygenase to effect the oxidative transformation of a variety of low molecular weight substrates also metabolized by cytochrome P-450.

Oxygen Transfer from Several Activated Bleomycin Congeners. The generality of the oxygen-transfer properties noted for bleomycin A_2 was studied by the use of several congeners of bleomycin. The analogues studied included the Fe(III) chelates of *N*-acetylbleomycin,[28] epibleomycin,[1] isobleomycin,[1] decarbamoylbleomycin,[1] deglycobleomycin,[29] and tallysomycin.[30] All of these bleomycin derivatives were studied in the presence of equimolar $Fe(ClO_4)_3 \cdot 9H_2O$ following activation with ~30 equiv of C_6H_5IO. *cis*-Stilbene was employed as a substrate in each case, and the products were analyzed by HPLC. *N*-Acetylbleomycin, which does not cause DNA degradation,[28] was also found to be incapable of mediating the oxidation of *cis*-stilbene. Each of the other analogues tested did effect *cis*-stilbene oxidation, producing a mixture of products the main constituents of which were the same as those obtained with Fe(III)–bleomycin A_2 (Table II).

As anticipated, the active bleomycin derivatives were also capable of oxygen transfer to olefins such as cyclohexene and norbornene, but none of the analogues tested produced any oxidative product from *trans*-stilbene in >1–2% yield. Cu^{II}·deglyco-BLM A_2 + C_6H_5IO was also employed as a potential oxidant for *cis*-stilbene; as also noted for Cu^{II}·BLM A_2, oxidation of the olefin did occur, but the yields of *cis*-stilbene oxide were generally lower (~5%) than those obtained with Fe^{III}·deglyco-BLM A_2 + C_6H_5IO (cf. Tables I and II).

Although each of the bleomycin derivatives produced the same major products from *cis*-stilbene, and in yields that did not vary widely, a more substantial variety of products present at lower abundance was observed in each case, and these products were not the same for each bleomycin tested. Consequently, the HPLC chromatograms were very characteristic of the particular bleomycin derivative employed for the oxidation of *cis*-stilbene. These characteristic patterns, which were found to be quite reproducible in replicate experiments with single bleomycins, are illustrated in Figure 1 for bleomycin A_2 and deglycobleomycin A_2, two species that are known[13,31] to effect DNA degradation following aerobic or anaerobic activation and that form ternary complexes of fundamentally different structure with Fe(II) + CO.[31] The additional observation that some of the bleomycin congeners studied gave very similar product profiles (data not shown) suggests that these data may well reflect metal coordination geometries and provide a sensitive probe of this metallobleomycin characteristic. Since there are additional bleomycin congeners that are thought to possess altered metal coordination geometries,[32] comparison of product elution profiles following olefin oxidation may well facilitate the characterization of these species.

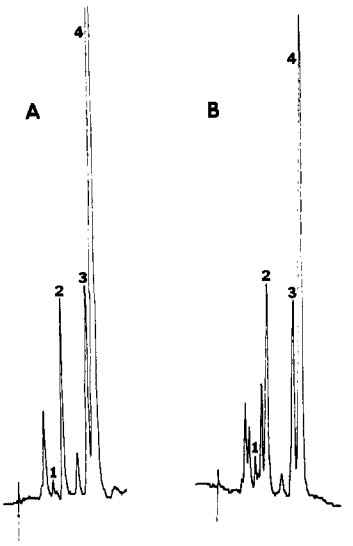
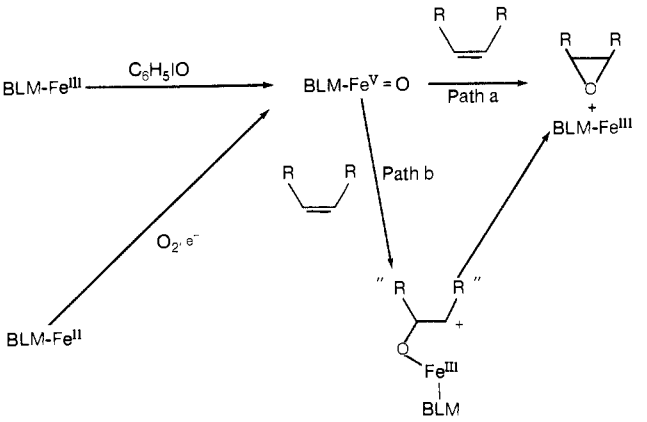


Figure 1. HPLC profiles of products formed from *cis*-stilbene following treatment with activated Fe–bleomycin (A) and Fe–deglycobleomycin (B). The response factors of individual products differed substantially. Compounds **1**, **2**, **3**, and **4** were *trans*-stilbene oxide, *cis*-stilbene oxide, benzaldehyde, and deoxybenzoin, respectively.

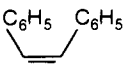
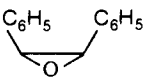
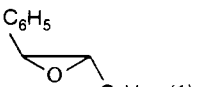
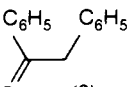
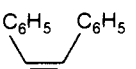
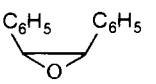
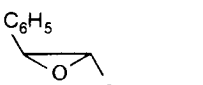
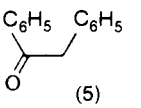
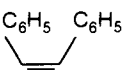
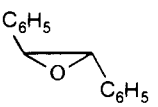
Scheme I. Possible Mechanism for Oxygen Transfer by Fe·BLM



Mechanism of Bleomycin-Mediated Oxidative Transformations. The mechanism of oxygen activation and transfer by bleomycin is of considerable interest, especially in view of the extent to which the chemistry of bleomycin parallels that of cytochrome P-450 and related model systems (cf. Tables I and II and ref 33). While no definitive evidence concerning the mechanism of oxygen transfer by bleomycin is available at present, both the facile O-exchange noted for the activated Fe·BLM complex in H_2O and the typical monooxygenase chemistry observed following activation of bleomycin with (mono)oxygen surrogates suggests that the active

(28) Oppenheimer, N. J.; Rodriguez, L. O.; Hecht, S. M. *Biochemistry* **1980**, *19*, 4096.
(29) Muraoka, Y., Suzuki, M.; Fujii, A.; Umezawa, Y.; Naganawa, H.; Takita, T.; Umezawa, H. *J. Antibiot. (Tokyo)* **1981**, *34*, 353.
(30) Bradner, W. T. In "Bleomycin: Current Status and New Developments"; Carter, S.; Umezawa, H.; Crooke, S. T., Eds.; Academic Press: New York, 1978; pp 333–342.
(31) Oppenheimer, N. J.; Chang, C.; Chang, L.-H.; Ehrenfeld, G.; Rodriguez, L. O.; Hecht, S. M. *J. Biol. Chem.* **1982**, *257*, 1606.
(32) Hecht, S. M., unpublished results.
(33) Ehrenfeld, G. M.; Murugesan, N.; Hecht, S. M. *Inorg. Chem.* **1984**, *23*, 1496.

Table II. *cis*-Stilbene Oxidation by Fe^{III}·TPP, Fe^{III}·BLM and Cu^{II}·BLM in Acetonitrile[a]

oxidant	substrate	products (yield)[b,c]			
Fe (III) • TPP (Cl) + C_6H_5IO		 (39)	 (1)	 (2)	C_6H_5CHO (1)
Fe (III) • BLM + C_6H_5IO		 (20)	 (8)	 (5)	C_6H_5CHO (5)
Cu (II) • BLM + C_6H_5IO		 (2)	C_6H_5CHO (1)		

[a] Oxidations with BLM were carried out in 10:1 CH_3CN–H_2O; oxidation of *cis*-stilbene with Fe·TPP was carried out in 1:1 CH_2Cl_2–CH_3CN. [b] Yields were determined by HPLC analysis. No significant amounts of products were observed in the absence of BLM (or TPP). [c] Yields are based on the amounts of added C_6H_5IO.

species so derived contains a single oxygen atom. The similarity of the behavior of this species and of cytochrome P-450 models in the presence of olefinic substrates prompts us to suggest that the activated intermediate derived from Fe·BLM may also involve a perferryl oxygen.[8b] The transfer of oxygen from this type of intermediate could be envisioned by either of two routes, as shown in Scheme I. Path "a" would involve the concerted transfer of oxygen with the regeneration of Fe^{III}·BLM, while path b would involve a stepwise electrophilic process. The latter possibility has the obvious virtue of providing access, in a mechanistic sense, to all of the characterized reaction products (cf. Tables I and II). Although not necessarily inconsistent with path b, the observed stereoselectivity during olefin oxidation would not be a consequence of this mechanism. Conceivably, stereoselectivity may derive from a solvent-cage effect that precludes isomerization of the short-lived radical intermediate.[10g,34]

At present, there is less experimental data available for the transfer of oxygen from activated bleomycin formed by admixture of Fe^{II}·BLM + O_2 + ascorbate. Nonetheless, the findings that this activated bleomycin can also mediate the formation of typical monooxygen products from olefins, effect the hydroxylation of aromatic substrates, and participate in the O-demethylation of *N,N*-dimethylaniline are consistent with the postulate that a perferryl ion may also be accessible by incubation of Fe^{II}·BLM with ascorbate in the presence of O_2[6b,32,33] (cf. Scheme I). Also consistent with the postulate were the observations that olefin epoxidation, substrate hydroxylation, and DNA strand scission by aerobically activated Fe^{II}·BLM were all dramatically accelerated by sources of e^-.[32,35]

While the chemistry mediated by activated Cu·BLM was generally quite similar to that of Fe·BLM following anaerobic activation with C_6H_5IO,[36] little direct evidence has been accumulated concerning the nature of relevant intermediates. Nonetheless, it is interesting to note that Valentine and coworkers[37] have recently described olefin epoxidations mediated by $Cu(NO_3)_2$ + C_6H_5IO.

Experimental Section

Bleomycin A_2 was obtained by fractionation of blenoxane, as described,[38] *N*-Acetylbleomycin A_2,[28] epibleomycin A_2,[39] isobleomycin A_2,[40] decarbamoylbleomycin A_2,[41] and deglycobleomycin A_2[13,31] were obtained by modification of bleomycin A_2. $Fe(ClO_4)_3$·$9H_2O$, $Fe(NH_4)_2(SO_4)_2$·$6H_2O$, and $CuCl_2$·$2H_2O$ were used to prepare the corresponding metal complexes of the bleomycins. The alkenes were commercially available and purified either by distillation or recrystallization prior to use. The *cis*- and *trans*-stilbenes were contaminated with ca. 3% and 1% of the other stereoisomer, respectively. The authentic epoxides of cyclohexene, norbornene, *cis*- and *trans*-stilbene, and styrene were prepared by treatment with 1.1 equiv of *m*-chloroperbenzoic acid in chloroform; the epoxides were isolated following extractive workup. Reagent grade methanol was degassed prior to use. Iodosobenzene was prepared from iodobenzene diacetate by the method of Saltzman and Sharefkin.[42]

^1H NMR spectra were obtained either on a Varian EM-390 (90 MHz) spectrometer or on a Nicolet NT-360 (360 MHz) spectrometer. For gas chromatography–mass spectrometry, a Varian 3700 gas chromatograph was coupled to a VG-Micromass 70/70 HS mass spectrometer. The oxidation products obtained using norbornene or cyclohexene as substrates were analyzed on a SP-1000 fused silica capillary column. Quantitation was effected by comparing the total ion current areas for identified components with the total ion current area of iodobenzene. Since the quantity of iodobenzene is known, the quantities of other identified components present were obtained as simple proportionalities. No corrections for differing molar response factors were made.

HPLC was performed using a Waters HPLC system equilibrated and run in 7:3 cyclohexane–chloroform (spectral grade) with an Alltech Associates (25 cm × 4.6 mm) analytical silica gel column. Compounds were detected by the absorbance at 254 nm, and quantitation was accomplished by comparison of peak areas with those of authentic samples.

Olefin Oxidation Using Fe^{III}·TPP(Cl) and Iodosobenzene. A solution containing 3.5 mg (5.0 μmol) of (chlorotetraphenylporphyrinato)iron(III) and 45 mg (0.25 mmol) of *cis*-stilbene in 5 mL of CH_2Cl_2 (or 5 mL of 1:1 CH_2Cl_2–CH_3CN) was treated with 25 mg (113 μmol) of solid iodosobenzene in portions over a period of 15 min. The combined solution was stirred under argon at 25 °C for 2 h then analyzed by HPLC as described above.

Olefin Oxidation Using Fe^{III}·BLM and Iodosobenzene. In a typical experiment, a solution containing 3.1 mg (2.1 μmol) of Fe^{III}·BLM A_2 (formed by admixture of equimolar BLM A_2 and $Fe(ClO_4)_3$·$9H_2O$ in 1.0 mL of 6:4 CH_3OH–H_2O) was combined under N_2 with a solution containing 80 mg (0.44 mmol) of *cis*-stilbene in 2.0 mL of methanol. A

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solution of iodosobenzene (15 mg, 68 μmol) in 1.5 mL of methanol was added dropwise over a period of 15 min, and the combined solution was stirred at room temperature for 1–2 h. Workup of the reaction mixture was accomplished by dilution with 25 mL of water and extraction with CH_2Cl_2 (3 × 15 mL). The resulting reaction product(s) was analyzed as indicated in the tables. Olefin oxidations carried out in aqueous acetonitrile typically employed 5.0 μmol of Fe^{III}·BLM A_2 in 400 μL of H_2O under N_2, which was treated with 45 mg (0.25 mmol) of *cis*-stilbene in 4.5 mL of CH_3CN. The combined solution was then treated with 20 mg (90 μmol) of C_6H_5IO, which was added as a solid in five portions over a period of 20 min. The reaction mixture was stirred at 25 °C for 1 h, then partitioned between $CHCl_3$ and water, and analyzed as indicated in the tables.

The oxidation of *cis*-stilbene with iodobenzene diacetate activated bleomycin was carried out in the same fashion in aqueous methanol, with the exception that the reaction was analyzed after 1.5 and 12 h. Attempted oxidations with Cu^{II}·BLM were run analogously, with the exception that 5 equiv of Cu(II) (relative to BLM) were employed in the case of Cu^{II}·BLM.

Olefin Oxidation Using Fe^{III}·BLM and Sodium Metaperiodate. A solution containing 3.1 mg (2.1 μmol) of Fe^{III}·BLM in 1.0 mL of 6:4 methanol–water was combined with a solution containing 80 mg (0.44 mmol) of *cis*-stilbene in 2.5 mL of methanol. A solution containing 15 mg (70.1 μmol) of sodium metaperiodate in 1.5 mL of 50% aqueous methanol was added dropwise over a period of 15 min, and the combined solution was stirred at room temperature for 1 h. Workup of the reaction mixture was carried out by dilution with 25 mL of water and extraction of the aqueous phase with $CHCl_3$ (3 × 5 mL).

Olefin Oxidation Using Fe^{III}·BLM and Ethyl Hydrogen Peroxide. An anaerobic solution containing 50 μg (0.096 μmol) of $Fe(ClO_4)_3 \cdot 9H_2O$ and 100 μg (0.07 μmol) of bleomycin A_2 in 45 μL of 65% aqueous methanol was treated with 2 mg (11.1 μmol) of *cis*-stilbene in 100 μL of methanol. Ethyl hydrogen peroxide (10% solution, 14 μL, 2.25 μmol) was then added dropwise in 50 μL of methanol over a period of 10 min. After an additional 1 h at 25 °C, the reaction mixture was concentrated and the products analyzed by HPLC.

***trans*-Cyclohexane-1,2-diol Monomethyl Ether.**[43] To a solution of 1.0 g (10.2 mmol) of cyclohexene oxide in 10 mL of methanol was added 50 μL of concentrated H_2SO_4. The solution was stirred overnight at 25 °C, then diluted with 30 mL of $CHCl_3$, and washed with three portions of saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated to afford *trans*-cyclohexane-1,2-diol monomethyl ether as a colorless liquid, yield 0.87 g (65%). The ^1H NMR spectrum ($CDCl_3$, $(CH_3)_4Si$) contained an OCH_3 resonance at δ 3.13; silica gel TLC (4:1 hexane–ethyl acetate) R_f 0.30.

***cis*-Cyclohexane-1,2-diol Monomethyl Ether.**[44] A solution of *trans*-cyclohexane-1,2-diol monomethyl ether (0.8 g, 6.15 mmol) in 3 mL of dry pyridine was cooled to 0 °C and then treated dropwise with 1.2 mL of methanesulfonyl chloride. After it was stirred for 3 h at 25 °C, the reaction mixture was treated with water (0.5 mL) and stirred for an additional 30 min. The reaction mixture was then poured into 50 mL of ice water and extracted with two 15-mL portions of $CHCl_3$. The chloroform extract was dried and concentrated and the residue was purified by vacuum distillation (bp 130 °C (0.1 mm)), affording 0.5 g (39%) of *trans*-2-(methoxycyclohexyl)methanesulfonate as a colorless liquid.

The mesylate was dissolved in 25 mL of dry dimethylformamide and the solution was heated at reflux for 6 h in the presence of 3 g of sodium benzoate. The cooled reaction mixture was diluted with water (25 mL) and extracted with 20 mL of $CHCl_3$. The chloroform extract was washed with aqueous $NaHCO_3$ (3 × 15 mL) and water (2 × 15 mL) and then dried (Na_2SO_4). Concentration of the $CHCl_3$ solution provided 0.6 g (100%) of *cis*-2-(methoxycyclohexyl)benzoate as a colorless liquid.

The benzoate (0.6 g) was added to a mixture of 10 mL of CH_3OH, 10 mL of H_2O, and 1.0 g of NaOH. The resulting cloudy solution was clarified by the addition of another 6 mL of CH_3OH and was then heated at reflux for 2 h. The cooled reaction mixture was partitioned between H_2O (100 mL) and $CHCl_3$ (25 mL). The organic layer was dried (Na_2SO_4) and concentrated to afford 0.35 g of a yellow liquid, which was purified by chromatography on a silica gel column. *cis*-Cyclohexane-1,2-diol monomethyl ether was isolated as a light amber liquid, yield 0.3 g (96%): ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 3.18 (s, 3, OCH_3); silica gel TLC (4:1 hexane–ethyl acetate) R_f 0.35.

Oxidation of *cis*-Stilbene in the Presence of Fe^{II}·BLM, Ascorbate and Dioxygen. A solution containing 3.0 mg (2.07 μmol) of BLM A_2 in 100 μL of H_2O was treated with 20 mg (0.11 mmol) of *cis*-stilbene in 3 mL of methanol and then with 0.85 mg (2.16 μmol) of ferrous ammonium sulfate in 0.2 mL of 50% aqueous methanol. The resulting brownish combined solution was treated with solid sodium ascorbate (20 mg, 0.10 mmol), and the resulting solution was stirred in the presence of air for 1 h. The reaction mixture was treated with $CHCl_3$ (20 mL) and partitioned against H_2O (2 × 20 mL). The dried organic phase was concentrated and analyzed by HPLC as described above.

Oxidation of *cis*-Stilbene in the Presence of ^{18}O-Labeled C_5H_6IO and H_2O. A solution consisting of 1.0 mg (0.68 μmol) of Fe^{III}·BLM A_2 in 25 μL of $H_2{}^{16}O$ and 200 μL of anhydrous methanol was maintained under N_2 and treated dropwise with a solution of 6 mg (27 μmol) of $C_6H_5I^{18}O$ (prepared as described by Groves et al.[15]) in 200 μL of CH_3OH over a period of 10 min. The combined solution was maintained at 25 °C for 1 h and then concentrated to dryness. The residue was applied to a silica gel TLC plate; development with 7% ethyl acetate in hexane permitted isolation of pure *cis*-stilbene oxide, which was analyzed for isotope content by mass spectrometry.

In a complementary experiment, *cis*-stilbene was oxidized in the presence of $C_6H_5I^{16}O$ and $H_2{}^{18}O$.

Oxidation of *cis*-Stilbene in the Presence of Fe^{III}·BLM and (Tosyliminolodo)benzene. A solution containing 3.1 mg (2.1 μmol) of Fe^{III}·BLM A_2 in 1.0 mL of 6:4 CH_3OH–H_2O was added to 80 mg (0.44 mmol) of *cis*-stilbene in 3.0 mL of methanol. A solution containing 25 mg (67 μmol) of (*p*-tosyliminoiodo)benzene in 1.0 mL of CH_3OH was then added dropwise over a period of 10 min. The combined solution was stirred under N_2 at 25 °C for 1 h, then diluted with $CHCl_3$, and washed with water. The dried organic layer was concentrated, and the liquid residue (72 mg) was fractionated on a preparative silica gel TLC plate; development was with 7% ethyl acetate in hexane. The products isolated from the reaction included *cis*-stilbene oxide (2.7 mg, 21%), deoxybenzoin (0.85 mg, 7%), and unreacted *cis*-stilbene.

Determination of Optical Purity of Styrene Oxide. Styrene oxide (3 mg, 25 μmol), obtained by the oxidation of styrene using Fe^{III}·BLM + iodosobenzene in the same fashion as reported above for *cis*-stilbene, was dissolved in $CDCl_3$ (0.3 mL) and solid portions of the chiral NMR lanthanide shift reagent tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) ($Eu(hfc)_3$) were added incrementally and a series of ^1H NMR spectra were obtained. A desired separation of enantiomeric α and β protons of styrene epoxide was obtained at a 0.035 mM concentration of shift reagent. The pertinent shift data obtained are ΔΔδ (α-H) 0.18, (trans-β-H) 0.40, and (cis-β-H) 0.2. Integration of the fully separated enantiomeric peaks showed the presence of equal amounts of *R* and *S* epoxides.

When the experiment was repeated with authentic racemic styrene oxide using similar concentrations of oxide and shift reagent, comparable results were obtained.

Oxidation of *p*-Deuterioanisole with Fe(II)–Bleomycin and Ascorbate. A solution of 3.0 mg (2.1 μmol) of BLM A_2 in 100 μL of H_2O was combined with a 3.0-mL methanolic solution of *p*-deuterioanisole[10g] (12 mg, 0.11 mmol). Ferrous ammonium sulfate (0.85 mg, 2.16 μmol) in 0.2 mL of 50% aqueous methanol was added, and the resulting brown solution was treated with solid sodium ascorbate (20 mg, 0.10 mmol). The reaction mixture was stirred at 25 °C in the presence of air for 1 h, then diluted with 10 mL of ether, extracted with water (2 × 15 mL), and dried ($MgSO_4$). The solution was analyzed both by gas chromatography–mass spectrometry and also by chromatographic isolation on silica gel, followed by electron impact mass spectrometry.

Oxidation of Naphthalene with Fe(II)–Bleomycin and Ascorbate. A solution of 3.0 mg (2.1 μmol) of BLM A_2 in 100 μL of H_2O was treated with a solution containing 15 mg (0.12 mmol) of naphthalene in 3.0 mL of methanol. Ferrous ammonium sulfate (0.85 mg, 2.16 μmol) in 0.2 mL of 50% aqueous methanol was added, and the combined solution was treated with solid sodium ascorbate (20 mg, 0.10 mmol) to initiate the oxidation. The reaction mixture was stirred in the presence of air for 1 h, then treated with 20 mL of $CHCl_3$, and washed with portions of H_2O. The dried organic layer was concentrated, and the residue was purified by silica gel TLC, development with $CHCl_3$. Elution of the appropriate band (R_f 0.33) provided α-naphthol, identified by chemical ionization mass spectrometry (m/z, 145 $(M + H)^+$) and comparison with an authentic sample by TLC, yield 0.5 mg (172%, based on bleomycin A_2).

N-Demethylation of *N*,*N*-Dimethylaniline. A solution containing 7.3 mg (4.96 μmol) of Fe^{III}·BLM in 200 μL of H_2O was combined with a solution containing 80 mg (0.66 mmol) of freshly distilled *N*,*N*-dimethylaniline in 5 mL of methanol. The combined solution was treated dropwise under N_2 with 1 mL of CH_3OH containing 30 mg (136 μmol) of iodosobenzene; addition of the oxidant was completed within 10 min. The resulting solution was stirred at 25 °C for 1 h, then diluted with 20 mL of $CHCl_3$, and washed with two portions of H_2O. The organic layer was dried (Na_2SO_4) and concentrated to afford a brown liquid residue

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which was analyzed by HPLC and found to consist of a mixture of *N*-methylaniline (identical chromatographically with an authentic sample) and unreacted starting material. The yield of *N*-methylaniline was 40%, based on added C_6H_5IO (1100% yield, based on added BLM).

The demethylation of *N,N*-dimethylaniline was also effected by using Fe^{II}·BLM in the presence of ascorbate and O_2. A solution containing 3.0 mg (2.1 μmol) of BLM A_2 in 100 μL of H_2O was combined with a 3.0-mL methanolic solution containing 15 mg (0.12 mmol) of freshly distilled *N,N*-dimethylaniline in 2 mL of methanol. Ferrous ammonium sulfate (0.85 mg, 2.16 μmol) in 0.2 mL of 50% aqueous CH_3OH was added, followed by solid sodium ascorbate (20 mg, 0.10 mmol). The reaction mixture was stirred in the presence of air for 1 h, then treated with 20 mL of $CHCl_3$ and extracted with water (2 × 20 mL). The dried organic layer was analyzed by HPLC and found to contain a mixture of *N*-methylaniline (yield 140%, based on bleomycin) and unreacted *N,N*-dimethylaniline.

Oxidation of Olefins with Fe^{III}·BLM Analogues and Iodosobenzene. In a typical experiment, an anaerobic solution containing 50 μg (0.096 μmol) of $Fe(ClO_4)_3 \cdot 9H_2O$ and 100 μg (0.09 μmol) of deglycobleomycin A_2 in 45 μL of 65% aqueous methanol was treated with 2 mg (11.1 μmol) of *cis*-stilbene in 100 μL of methanol. Iodosobenzene (0.5 mg, 2.3 μmol) was then added dropwise via a microsyringe from a 20-μL methanol solution over a period of 10–15 min. After 1 h at room temperature, the reaction mixture was concentrated and the products were analyzed by HPLC vs. authentic samples and by ^1H NMR spectroscopy at 360 MHz.

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Communications to the Editor

Control of Ring Junction Stereochemistry via Radical Cyclization

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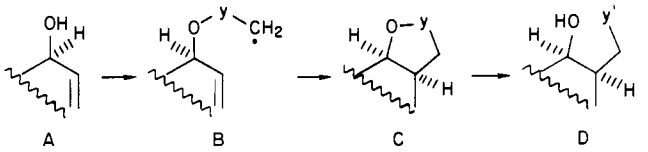
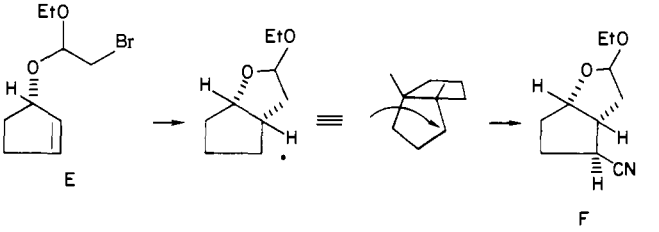
Continuation of our work on the use of free radical reactions in the control of the stereochemistry of carbon–carbon bonds[1-3] has now led us to a new method which appears promising for the control of ring junction stereochemistry.

We have reported[1-3] that it is possible to use an allylic hydroxyl to introduce a functional alkyl chain such that the new carbon–carbon bond not only has defined (hydroxyl vicinal) *regio*chemistry but also, when starting with cyclic allylic alcohols, totally determined stereochemistry (cis to the original hydroxyl). The formal scheme is illustrated.



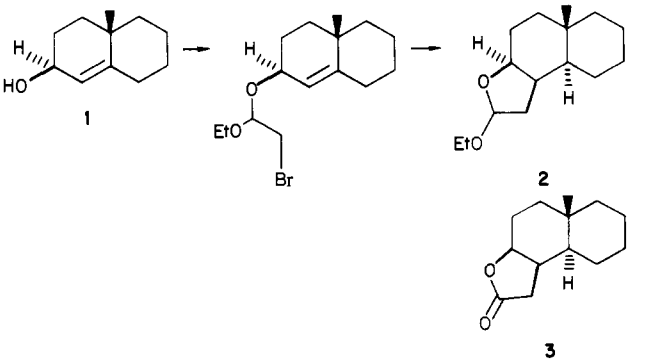
The success of this scheme depended (1) on finding means of achieving an easily removed connection of a two-atom chain terminating in a carbon-centered radical and (2) on the fact that the transition-state geometry for addition of the radical center (B → C) can only lead to the cis fusion of the new five-membered ring. A special virtue of this general process is that, after the necessary allylic hydroxyl has served its stereochemical control function, it can, in principle, be either inverted or removed.

Stereo- and regiochemical control at the near end of the allylic double bond is not the only control that can be derived from the original allylic hydroxyl. The newly formed cis-fused five-membered ring imposes a cup shape on the resulting bicyclic system, so that, in the absence of overriding competing steric hindrance, access to the radical resulting from the initial closure should be largely restricted to the convex side. This is well illustrated, using a mixed-acetal function to achieve a temporary link to the allylic hydroxyl, by the highly stereoselective transfer of a cyano group (E to F).[4]



It is the ability of this type of radical cyclization process to control stereochemistry at the far end of the double bond of a cyclic allylic alcohol that makes possible the control of ring junction stereochemistry.

Consider the allylic alcohol **1** (from sodium borohydride reduction of the corresponding octalone). Reaction of its mixed bromoacetal with tributylstannane leads to a cyclic acetal **2** in which the newly formed decalin fusion is trans: The lactone **3**



derived from Jones oxidation has a singlet methyl at δ 1.06, a position that strongly suggests the trans ring junction which would result from the approach of tributylstannane from the convex side. Confirmation of this stereochemical conclusion was easily obtained from the 1,3-glycol derived from the use of a silyl ether[5] rather

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