about 50% between the 5′- and 6′-methine protons similar to that observed in NOE experiments on vancomycin and ristocetin.[3] Such a relationship was unequivocally demonstrated by the results of the X-ray analysis of vancomycin CDP-I.[2]

The stereochemistry of the glycosidic linkages is as indicated on the basis of a combination of anomeric proton couplings and $^1J(^{13}CH_1)$ values.[10] The glucosidic linkage is β ($J_{1,2}$ = 7.5 Hz) as in vancomycin and ristocetin. The rhamnose glycosidic linkage is α based on the rhamnose C_5 shift of 70.1 Hz and the $^1J(^{13}CH_1)$ of 171 Hz in the ^{13}C NMR of **12** [R = *O*-α-L-rhamnose (**9**)]. An α linkage is also indicated for the two ristosaminyl glycosidic bonds since both anomeric proton signals are broad singlets which preclude an $H_{1,2}$ axial–axial orientation. The mannose linkage can be discerned as α based on the $^1J(^{13}CH_1)$ of 170 Hz in the fully coupled spectrum of 5.

An important feature of the avoparcin chemistry is that aqueous solutions of α- and β-avoparcin lose antibacterial activity when they are heated at 80 °C for 16 h in the pH range 5–8. When monitored by analytical HPLC, an equilibrium mixture is observed consisting of ca. 30% of starting antibiotic and 70% of a diastereomer which we call epiavoparcin and which has a longer retention time in the HPLC profile. Equilibration of purified epi-β-avoparcin yields the same ratio of β-avoparcin and epi-β-avoparcin as observed above. It is especially noteworthy that epi-β-avoparcin is 10–100-fold less active against gram-positive bacteria than avoparcin. We believe this transformation is best explained by an epimerization at the α-methine (1′) of the N-terminal phenylsarcosine subunit. This could prevent effective binding to mucopeptide precursor molecules involved in bacterial cell wall biosynthesis, thus resulting in the greatly reduced activity.[11]

The structure of epi-β-avoparcin is based on the following chemical and spectral evidence. The isomeric nature of epi-β-avoparcin with β-avoparcin was shown by a molecular weight determination using ^{252}Cf-plasma desorption mass spectroscopy.[15] This gave a strong quasi-molecular ion $(M + Na)^+$ at 1965 ± 2 identical to that observed for β-avoparcin. The IR and UV spectra were also identical with those of β-avoparcin. The specific rotation, however, was slightly higher (−110°) compared to the original −94°. The 270-MHz ^1H NMR spectrum of epi-β-avoparcin is generally the same as for β but with some slight chemical shift differences in the aromatic and peptide methine patterns. Most significantly, proton C_6 now resonates on the downfield side of A_6 (δ 7.73 in both α and β) at δ 7.84 from 7.61 and undergoes an upfield shift on protonation. This is exactly opposite to the situation with α- and β-avoparcin and suggests a change in C_6's relationship to the *N*-methyl grouping. Although the chemical shift of methine 1′ (a sharp singlet at δ 4.09) was unchanged, that of methine 2′ was shifted downfield to δ 5.19 from 5.05. The resonance of the remaining peptide methine protons are unchanged from those in β, suggesting a difference only in the N-terminal side of the molecule. This is supported by the slight upfield shift (ca. 0.1 ppm) of the phenylsarcosine aromatic proton doublets $G_{3,5}$ and $G_{2,6}$ to δ 6.87 and 7.15, respectively. There were no changes in the α-CH–NH coupling constants of any of the peptide methine protons, thus ruling out any inversion of an α-CH adjacent to an NHCO grouping. The lability of the 1′-methine proton of avoparcin has been amply demonstrated by several experiments. By subjecting CDP-I avoparcin to a very mild first stage Edman reaction (pH 8.0, 1 h, room temperature, and no acid treatment) two optically inactive thiohydantoins of (*p*-hydroxyphenyl)sarcosine were isolated.[16] One was the normally expected product while the other contained a benzylic hydroxyl group instead of the α-methine proton.[4] In addition when pure β-avoparcin was epimerized in D_2O and the resultant two products isolated, the 270-MHz ^1H NMR spectrum of each lacked the 1′ signal at δ 4.08, confirming complete exchange with deuterium at this position. The partially deuterated β-avoparcin from this experiment exhibited normal optical and biological properties. No other peptide methine protons exchanged. There was some sharpening of the α-CH signals due to further exchange of amide NH's. The aromatic hydrogens on ring D exchanged completely and those ortho to phenolic hydroxyls on rings E and F only partially.

The epimerization at the terminal methine center occurs under identical conditions for all the known avoparcin components. In other words, for each avoparcin component (total isolated to date is 5) there is a corresponding epiavoparcin. Details on all these minor components as well as their epimerized counterparts will be published in a full paper.

Acknowledgment. We thank Professor K. Nakanishi of Columbia University for helpful discussions and P. Demou of Yale University for the 270-MHz ^1H NMR spectral determinations. We also express our thanks to N. Kuck and associates for the microbiological assays.

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(15) Courtesy of Professor R. D. McFarlane of Texas A & M University.

(16) Using the identical Edman conditions, D(−)-(*p*-hydroxyphenyl)glycine gave an optically active thiohydantoin: $[\alpha]^{25}D$ −166° (*c* 0.89, MeOH). This result suggests that the *N*-methyl grouping exerts a labilizing effect on this center in avoparcin. At this point we are uncertain as to the effect of pH on the epimerization since below 5 and above 8 the complexity of the product mixture makes analysis difficult. Avoparcin CDP-I has been isolated from acid hydrolysis (0.14 N HCl) of avoparcin, and it is not epimerized. Of course, this does not rule out the formation of an epimer under these conditions but we have not isolated it.

Optically Active Radical Complexes, ESR–HPLC–OR Study of the Carbonyl(quinone)rhenium–(+)- and (−)-DIOP Radical Complexes

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Received June 1, 1981

For many years it has been a constant challenge to this laboratory to produce and isolate optically active radicals or radical complexes for ESR, optical, and chemical studies. Reactions which involve optically active radical intermediates have been of interest for many years. The configuration of an optically active radical intermediate is often inferred from the product analysis[1-4] or by observations of different optical rotation values for the solution containing both the presumed optically active radical and the parent optically active reactant.[5] With organic radicals, two factors contribute to the difficulty of direct detection of optical activity. The first one is the chemical reactivity of the radicals, and the second one is the probable loss of chirality in the derived carbon radicals due to the change in the tetrahedral symmetry. However, among many organometallic radical reactions induction of optical activity can occur in labile adducts of radical complexes, as compared to the well-known cases of induced optical activity in paramagnetic complexes.[6] Numerous paramagnetic metal

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complexes with natural optical activity are also known in literature.[6,7] Nevertheless, the paramagnetism in these complexes arises mainly from the metal d electrons, and therefore they are not usually considered as radicals or radical complexes. In a free radical system such as the photochemical reactions of rhenium carbonyls in the presence of phosphines, substituted rhenium carbonyl radicals ($Re(CO)_4PR_3\cdot$) and ($Re(CO)_3(PR_3)_2\cdot$) have been postulated as intermediates,[8] and indeed they can be trapped by *o*-quinones to yield some rather stable radical adducts.[9] *o*-Quinones have been extensively used as spin traps for organometallic radicals.[10,11] Now, if the phosphine present is optically active, it would certainly induce optical activity in the substituted rhenium carbonyl "radical". When reacted with quinones, this will in turn induce optical activity in the stable radical adduct. It should be emphasized that the spin adducts referred to here retain the "radical character" because the unpaired electron is mainly in the organic moiety, but delocalization of the electron onto the optically active ligand via the metal center also occurs.[9]

The recent development of the combined ESR–HPLC technique has enabled us to isolate some stable organometallic *radical* complexes such as the carbonyl(quinone)rhenium radical for a full spectroscopic characterization.[12] As it has been established that lability of the CO ligands is a characteristic of the 17-electron metal carbonyl species,[13] we have taken advantage of this fact and produced numerous heterobinuclear and -trinuclear metal organic radical complexes by allowing the thermal or photochemical ligand exchange reactions to proceed between the CO ligands and other organometals.[9,14] It follows that when the organometal ligand or the quinone spin trap is optically active, the daughter radical (or the spin adduct) complex would exhibit *induced* chirality. We wish to report here the preparation and isolation of some of these novel optically active *radical* complexes, [(+)- or (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane)carbonyl(3,5-di-*tert*-butyl-*o*-quinone)-rhenium radical (Q·-$Re(CO)_3$(+)/(−)-DIOP). Although DIOP is usually considered as a bidentate ligand, in this particular radical complex system only one of the two P atoms is directly coordinated to the Re, as indicated by the ESR analysis.[9] This preliminary report on the ESR–HPLC–OR study of the first of a series of optically active organometallic radical complexes is hoped to arouse general interest in the physics and chemistry of stable optically active organic radical adducts.

The physical instrumentation for ESR–HPLC study has been previously described,[12] and the chemical procedures for the photochemical preparation of both the parent carbonyl(quinone)rhenium complexes[12] and the daughter (quinone)rhenium organometal radicals[9] were given elsewhere. Typical ESR measurements were carried out in the second-derivative mode on a Bruker 420 X-band spectrometer by using a Hewlett Packard 5342 frequency counter and a Bruker NMR oscillator for *g*-factor determinations. Optical rotation measurements were made by using a Perkin Elmer 141 polarimeter. Decacarbonyldirhenium was supplied by Strem Chemicals, and the optically active phosphine ligands, (+)- and (−)-DIOP, were obtained from Alfa.

The parent Q·-$Re(CO)_4$ radical was prepared photochemically and separated by ESR–HPLC. To the red benzene solution containing this parent radical was added the corresponding optically active DIOP. The solution was then warmed to 60 °C for 5 min with the color changing from red to dark blue while the ESR spectrum changed from that of the parent radical (Figure 1a) to that of the daughter radical complex (Figure 1b) according to the following ligand exchange reactions: ESR–HPLC was then used to separate the daughter radicals from the parent radical and the uncreacted optically active DIOP and any other secondary products. Chloroform was used as the eluant, and at a typical flow rate of 2.0 mL/min through a Partisil-10 column, the retention times are 115 s for the parent Q·-$Re(CO)_4$ radical, 490 s for the daughter Q·-$Re(CO)_3$DIOP radical complex, and 150 s for the DIOP. Obviously, the different optically active substances are not separated by HPLC, and therefore pure (+)- or (−)-DIOP must be used to produce the corresponding optically active daughter radicals. Evaporation of the eluant containing the daughter radicals leaves only a paramagnetic solid which when redissolved in benzene gives the characteristic ESR spectrum (Figure 1b) and the corresponding optical rotation (Table I).

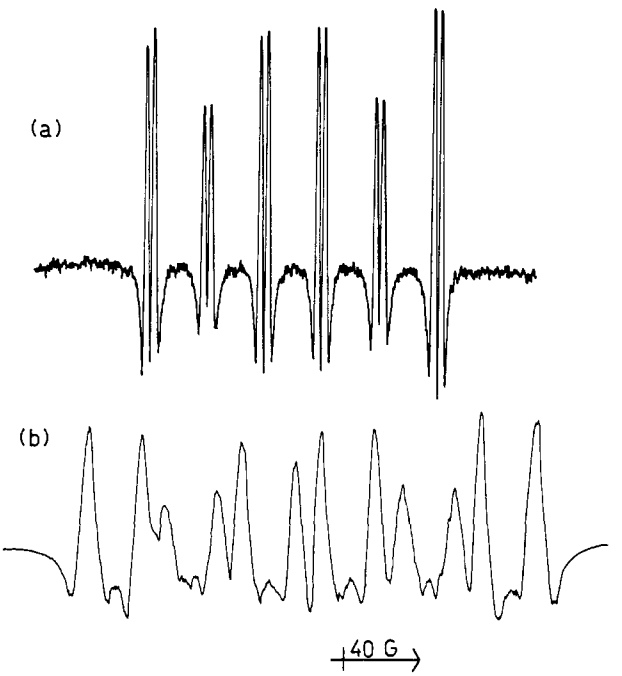
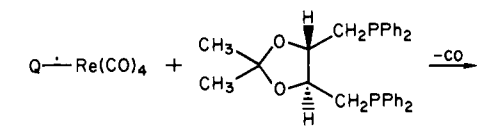


Figure 1. Second-derivative ESR spectra of (a) Q·-$Re(CO)_4$ and (b) Q·-$Re(CO)_3$-(±)-DIOP in benzene at room temperature.

Table I. Optical Rotation Measurements for (±)-DIOP Ligands and Q–$Re(CO)_3$-(±)-DIOP Radical Complexes in Benzene at Room Temperature with Light at 436 nm

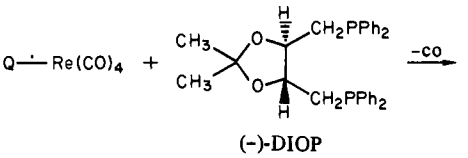
system	*c*, mg/mL	α, deg	$[\alpha]^{22}_{436}$, deg
(+)DIOP	12.2 ± 0.5	0.022 ± 0.002	18.0 ± 1.0
(−)-DIOP	13.7 ± 0.5	−0.025 ± 0.002	−18.0 ± 1.0[a]
Q–$Re(CO)_3$-(+)-DIOP	1.40 ± 0.10	0.010 ± 0.002	7.0 ± 1.0
Q–$Re(CO)_3$-(−)-DIOP	0.86 ± 0.10	−0.006 ± 0.002	−7.0 ± 1.0

[a] Compared with the literature value of $[\alpha]^{22}_D = -12.3$ (*c* 4.57).



(+)-DIOP

Q—Re(CO)$_3$—·(+)-DIOP (1)



(−)-DIOP

Q—Re(CO)$_3$—·(−)-DIOP (2)

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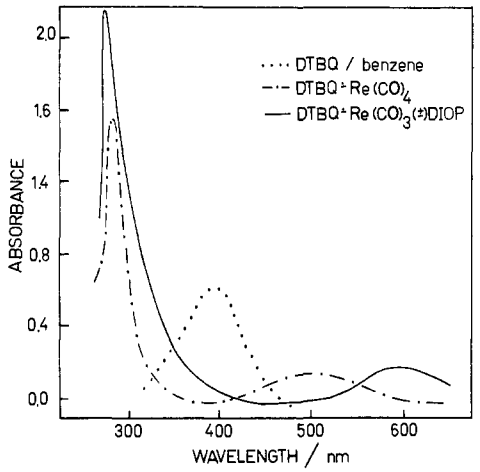

Figure 2. UV-visible absorption spectra of Q, Q·Re(CO)$_4$, and Q·Re(CO)$_3$-(±)-DIOP in benzene.

The assignment of the ESR parameters of the daughter radical Q·Re(CO)$_3$DIOP is consistent with those reported for monosubstitution.[9] The g factor is 2.0010; A_{Re} = 37.4 and A_P = 26.5 G. Again, as expected, the two optically active daughter radicals, Q·Re(CO)$_3$-(+)-DIOP and Q·Re(CO)$_3$-(−)-DIOP, have the same ESR parameters as well as similar UV absorption spectra (Figure 2). In Figure 2 the visible band of the quinone (λ_{max} = 395 nm) is shifted upon complexation to lower energy (λ_{max} = 505 nm) which is shifted again (λ_{max} = 600 nm) after ligand exchange with DIOP. These shifts are consistent with the explanation that the quinone π electrons are being delocalized onto the rhenium upon complexation and again onto the DIOP moiety upon exchange.

The measurement of the optical rotation for the optically active daughter radicals was carried out at 436 nm, since their absorption (Figure 2) in the 589-nm region (sodium line) would make it impossible to use the sodium line. The optical rotations as well as the specific rotation of the (±)-DIOP ligands were therefore also carried out at 436 nm and compared with those of the radicals (Table I). The results clearly establish the optical activity of the two daughter radicals. According to the Condon[15] formulation, the final result leading to the angle of rotation per unit length for dilute systems where the mean index of refraction is near unity is

$$\frac{\phi(k)}{l} = \frac{4\pi N\alpha k^2}{3mc}\sum_{n''}\frac{\mathrm{Im}(\langle g|\hat{R}|n'\rangle\langle n'|\hat{L}|g\rangle)}{k_{n''g}^2 - k^2} \qquad (3)$$

Here, N is the number of molecules per unit volume, α = 1/137, the fine structure constant, m, the electron mass, c, the velocity of light, and $k_{n''g}$ is related to the energy difference between an excited-state $|n''\rangle$ and the ground-state $|g\rangle$ by $E_{n''} - E_g = hck_{n''g}$. $\hat{R}$ and $\hat{L}$ are, respectively, the coordinate and orbital angular momentum operators for the molecule. It is expected that the energy difference between the excited and ground states for the radical systems is smaller than that of the DIOP ligand itself. The smaller specific rotation for the radical complexes would seem to suggest that the term $(\langle g|\hat{R}|n''\rangle\langle n''|\hat{L}|g\rangle)$ for the radical is also smaller than the corresponding term for the pure ligand. A further combined ESR, UV, OR, and ORD (optical rotary dispersion) study of stable optically active radicals should open up a new area for theoretical and physical examinations of the structure of these radical adducts. Currently, we have prepared some optically active quinones, such as d- or l-camphorquinone and used them as optically active spin traps for organometallic radicals. Some of these optically active quinone–organometallic radical adducts also exhibit interesting CIDEP (chemically induced dynamic electron polarization) phenomenon. A full account of further physical and chemical aspects of these unique optically active radical complexes will be published in the near future.

Acknowledgment. This research is supported by the National Sciences and Engineering Research Council of Canada and Queen's University. Delightful discussions with other members of our group, particularly Drs. Hutchinson and Depew and D. Weir, are cheerfully acknowledged.

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Total Synthesis of (±)-Pentalenolactone E Methyl Ester

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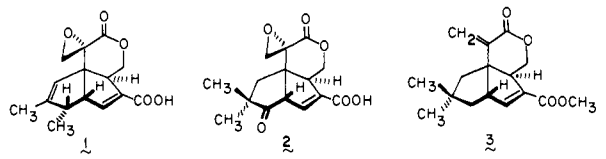
Received July 10, 1981

Following the discovery that various strains of *Streptomyces* produce pentalenolactone (**1**), an acidic lipophilic sesquiterpene possessing antibiotic properties,[1,2] have come a number of reports describing the isolation and characterization of several structurally related biosynthetic intermediates or shunt metabolites.[3,4] In contrast to **1**, however, these substances, e.g., pentalenolactone G (**2**), carry a *gem*-dimethyl moiety indicating that Wagner–Meerwein rearrangement has not yet been enzymatically implemented. During the course of recent biosynthetic experiments,



1 2 3

Cane and Rossi treated the acidic fraction of an ether extract from *Streptomyces* UC5319 with diazomethane and obtained a new substance which they named pentalenolactone E methyl ester (**3**).[4a] Structural assignment to **3**, which is excreted (in acid form) into the fermentation broth during the early stages of growth prior to full production of **1**, was based on spectroscopic data. We now describe an expedient approach to this interesting tricyclic substance which confirms the original structural formulation.

In a previous report[5] the basic principles of a new protocol for stereocontrolled lactone annulation was described. This scheme was used to transform the readily available keto ester **4** by controlled diisobutylaluminum hydride reduction and Claisen rearrangement to **5**. Following deketalization, chemospecific nucleophilic attack by methoxide ion at the aldehydo carbonyl can be achieved in methanol solution at room temperature. Intramolecular Michael addition of the alkoxide center within this intermediate to the proximal enone system delivers a single stereoisomer of **6**.

Our next concern was homologation of the carbonyl group in **6** to an α,β-unsaturated ester. During the course of initial experiments, it became clear that **6** was quite prone to retrograde (Grob) fragmentation in the presence of reasonably basic reagents

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