tential was chemically irreversible (as judged by bulk electrolysis at −0.65 V), oxidation at +0.90 V generated a green solution of the ESR-active monocation $[\mathbf{3b}]^{+}$.[17] This redox behavior differs considerably from that reported for $Re_2Cl_6(PR_3)_2$ compounds,[7] for which two one-electron reductions both occur at potentials more negative than +0.1 V. The $^{31}P\{^1H\}$ NMR spectrum of **3b** (in $CDCl_3$) shows a singlet at δ −6.18 (vs. 85% aqueous H_3PO_4 with positive chemical shifts downfield) in accord with magnetically and chemically equivalent phosphine ligands. A clue to the structure of this Re_2^{6+} core complex was provided by an analysis of the 200-MHz ^1H NMR spectra of the phenyl rings of the PPh_3 ligands. There are two groups of resonances (intensity ratio 2:1), the upfield set of which (comprising two apparent triplets and an apparent quartet) can be attributed to a unique phenyl ring of each PPh_3 ligand.[18] A series of decoupling experiments showed that the ortho protons of these two sets of rings (δ +7.90 and +6.46) are coupled to two trans phosphorus nuclei. This implies that these compounds possess the unsymmetrical and entirely unexpected structure $(RO)_2Cl_2ReReCl_2(PPh_3)_2$, a conclusion that we have confirmed by an X-ray structure analysis on crystals of **3b**.

The structure of a single crystal of **3b** was determined[19] by following general procedures described elsewhere.[20,21] The compound crystallizes in the monoclinic space group $P2_1/c$, with one complete molecule in the crystallographic asymmetric unit. The molecule, shown in Figure 1, consists of a strongly bonded dirhenium unit with an unsymmetrical distribution of unidentate ligands on the metal centers. The effective C_2 axis lies along the Re(1)–Re(2) axis. The conformation of the molecule is essentially eclipsed and the Re(1)–Re(2) distance in **3b** is 2.231 (1) Å. The Re(1)–O distances, 1.892 (8) and 1.883 (8) Å, are short compared to the Re–O distance of 2.085 (14) Å observed[12] in $Re_2Cl_5(OEt)(dppm)_2$. The shortening of the Re–O bond lengths in **3b** could be due to extensive interaction of an oxygen pπ orbital perpendicular to the C–O–Re(1) plane and the Re(1) atom. The Re(1)–O–C angles are 120.7 (9)° and 120 (1)°. Although strong π-interaction normally tends to involve both oxygen lone pairs thus leading to M–O–C angles greater than the Re–O–C angles in **3b**, any increase of this angle is opposed by a repulsive interaction between the ethyl group of EtO and the phenyl groups of PPh_3. The Re(1)–Cl distances (average value of 2.358 [3] Å) in **3b** are slightly longer than the Re(2)–Cl bond lengths (average value of 2.334 [2] Å). This could be due to the presence of strong Re–O bonds. The Re(2)–P distances of 2.466 (3) and 2.487 (3) Å are normal.[9,12]

The X-ray structure of **3b** and other data suggest that molecules of type **3** are quadruply bonded, mixed-valence dirhenium compounds $(RO)_2Cl_2Re^{IV}Re^{II}Cl_2(PPh_3)_2$. The only known[22,23] dirhenium complex with an asymmetric arrangement of ligands is $Cl_4ReRe(dth)_2Cl$, dth = 2,5-dithiahexane, which has a staggered conformation of ligands around the Re_2 unit and a Re–Re bond order of 3. In **3b**, the electronic configurations of Re(1) and Re(2) are d^3 and d^5, respectively, and the ground electronic configuration of this eclipsed molecule can be written as $(\sigma)^2(\pi)^4(\delta)^2$. The quadruple bond, however, is different from those previously known in that one component is formally dative in character.

Acknowledgment. Support from the National Science Foundation (Grant CHE82-06117 to R.A.W. and Grant CHE8211407 to F.A.C.) is gratefully acknowledged.

Supplementary Material Available: Tables of crystallographic data and atomic positional parameters for $Re_2Cl_4(PPh_3)_2(OEt)_2$ (3 pages). Ordering information is given on any current masthead page.

(16) CV's were measured at a Pt-bead electrode. For details of our experimental procedure, see: Zietlow, T. C.; Klendworth, D. D.; Nimry, T.; Salmon, D. J.; Walton, R. A. *Inorg. Chem.* **1981**, *20*, 947. For both couples, the separation between the coupled anodic and cathodic peaks (ΔE_p) was 105 mV at v = 200 mV/s, and the $i_{p,a}/i_{p,c}$ ratios were close to unity. Under these same experimental conditions, the ferricinium/ferrocene couple has an $E_{1/2}$ value of +0.47 V vs. Ag/AgCl.

(17) This solution possessed a CV with couples at $E_{1/2}$ = +0.79 and −0.59 V vs. Ag/AgCl, both of which correspond to one-electron reductions. The X-band ESR spectrum (CH_2Cl_2 solution at −160 °C) gave a broad complex signal between 2000 and 5500 G.

(18) The ^1H NMR spectrum of the phenyl resonances of **3b** (recorded in CD_2Cl_2) can be described as follows: δ +7.90 (q, 4 H) and ca. +7.50 (m, 6 H), +7.31 (t, 1 H), +7.12 (t, 2 H), +6.46 (q, 2 H).

(19) Crystal data for $Re_2Cl_4(PPh_3)_2(OEt)_2$: monoclinic, $P2_1/c$; a = 10.782 (3) Å, b = 14.330 (3) Å, c = 26.924 (7) Å, $\alpha = \gamma = 90°$, β = 96.98 (2) °, V = 4129 (3) Å^3, Z = 4, d_{calcd} = 1.816 g/cm^3; μ(Mo Kα) = 63.09 cm^{-1}. An automated diffractometer Enraf-Nonius CAD-4 was used to collect 4150 data with $F_o^2 > 3\sigma(F_o^2)$ by using ω-scan technique. An empirical absorption correction was based on azimuthal scans of nine reflections. The positions of two independent Re atoms in the crystallographic asymmetric unit were derived from a three-dimensional Patterson map and refined by least squares. The structure was refined to residuals of R = 0.040 and R_w = 0.048 and a quality of fit index of 1.166 with a largest shift/esd = 0.19.

(20) Bino, A.; Cotton, F. A.; Fanwick, P. E. *Inorg. Chem.* **1979**, *18*, 3358. Cotton, F. A.; Frenz, B. A.; Deganello, G.; Shaver, A. *J. Organomet. Chem.* **1973**, *50*, 227. North, A. C. T.; Phillips, D. C.; Mathews, F. A. *Acta Crystallogr., Sect. A., Cryst. Phys., Diffr., Theor. Gen. Crystallogr.* **1968**, *A24*, 351.

(21) Calculations were done on the VAX-11/780 computer at the Department of Chemistry, Texas A&M University, College Station, TX, with a VAX-SDP software package.

(22) Bennett, M. J.; Cotton, F. A.; Walton, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 3866.

(23) Bennett, M. J.; Cotton, F. A.; Walton, R. A. *Proc. R. Soc. London, Ser. A* **1968**, *303*, 175.

Norhalichondrin A: An Antitumor Polyether Macrolide from a Marine Sponge[1]

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In our continuing search for physiologically active substances from marine sources, we recently found several antitumor compounds from *Halichondria okadai* Kadota.[2] One of them, norhalichondrin A, is a new type macrolide; in this report, we describe the structure determination of norhalichondrin A, a major component in a series of halichondrins.[3]

Halichondria okadai Kadota is a common, widely distributed sponge in the Pacific coast of Japan. Prior studies by Scheuer

(1) This work was presented at the 50th Annual Meeting of the Chemical Society of Japan, Tokyo, Japan, April 1, 1985.

(2) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Engen, D. V.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469–2471.

(3) The name halichondrin B was given to the most potent antitumor constituent in this series. Bioactivity of halichondrin B was about 50 times that of norhalichondrin A. Actually, halichondrin B shows high T/C % against L-1210 leukemia, P-388 leukemia, and B-16 melanoma in vivo. These data involving the structure of halichondrin B will be published very soon by D. Uemura, K. Takahashi, T. Yamamoto, Y. Tsukitani, H. Kikuchi, and Y. Hirata.

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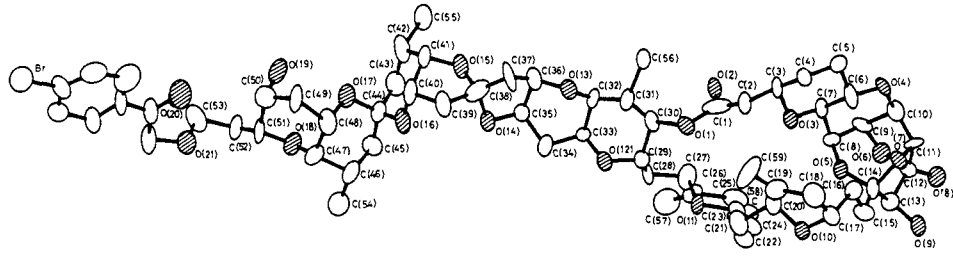
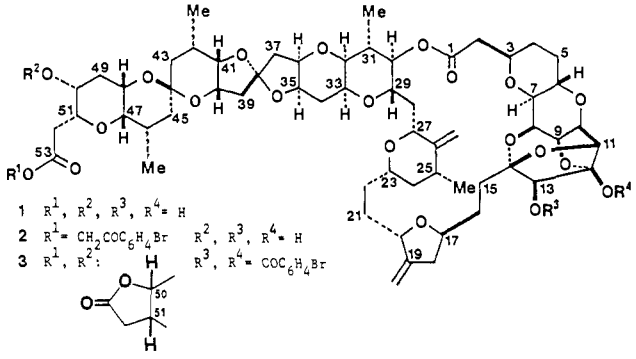


Figure 1. Computer-generated perspective drawing of the final X-ray model of the *p*-bromophenacyl ester **2**.

and Tsukitani resulted in the identification of okadaic acid[2] as a cytotoxic constituent of this animal. However, our interest in the same animal focused on the fact that sponge extracts exhibited remarkable in vivo antitumor activity.[3] Bioassay against B-16 melanoma cells guided the isolation of halichondrins in low yield, including norhalichondrin A (**1**):[4] amorphous solid [(5×10^{-6})% yield from wet animals]; $[\alpha]_D$ −47.8° (MeOH, *c* 1.13).



1 R^1, R^2, R^3, R^4 = H
2 R^1 = $CH_2COC_6H_4Br$ R^2, R^3, R^4 = H
3 R^1, R^2: H R^3, R^4 = COC_6H_4Br

The SIMS spectrum showed the highest mass peak at *m/z* 1127 (M + 1) corresponding to the final molecular formula $C_{59}H_{82}O_{21}$. The IR spectrum (KBr) indicated the presence of hydroxyls (3450 cm^{-1}), lactone larger than five-membered ring or ester (1740 cm^{-1}), and carboxylate (1580 cm^{-1}). The ^1H and ^{13}C NMR spectra were not so fruitful for structural elucidation because of their complexity. However, two sets of exomethylene (^1H NMR δ 4.81, 4.87, 5.02, 5.06, 1 H each; ^{13}C NMR δ 104.81, 105.76, 153.17, 153.32), four carbon atoms bearing two oxygen atoms (^{13}C NMR δ 98.51, 112.86, 113.38, and 114.87), four secondary methyl groups (^1H NMR δ 0.96, 0.97, 1.06, 1.09, 3 H each as a doublet; ^{13}C NMR δ 15.88, 17.47, 18.13, 18.42), and then carbonyl group(s) (^{13}C NMR δ 172.81) were recognized by the NMR spectra in CD_3OD.

Norhalichondrin A (**1**) was treated with *p*-bromophenacyl bromide and triethylamine in DMF at 50 °C. After separation by preparative TLC, the desired crystalline *p*-bromophenacyl ester **2** [IR ($CHCl_3$) 1735, 1705, 1590 (weak) cm^{-1}] was recrystallized from acetone–methanol, furnishing well-formed, monoclinic crystals: mp 173.5–175.0 °C. Its structure has been unambiguously determined as follows. The space group is $P2_1$ and lattice constants are a = 44.654 Å, b = 9.264 Å, c = 9.494 Å, and β = 93.72°. The structure was solved by the Monte-Carlo direct method[5] with the aid of MULTAN 78 program system[6] using 3080 unique reflections [$|F_o| \geq 3\sigma(F_o)$].[7] Full-matrix least-square refinement with anisotropic temperature factors for the non-hydrogen atoms and anomalous dispersion corrections have converged to a standard crystallographic residual of 0.1092 for the structure

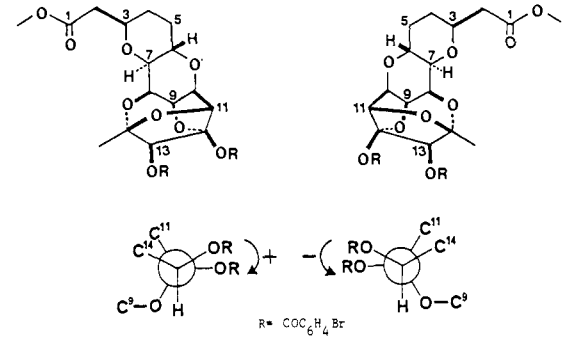


Figure 2. Exciton chirality of the 12,13-bis(*p*-bromobenzoate) system in **3**.

and 0.1102 for the enantiomer. The computer-generated perspective drawings[8] of a molecule of **2** is shown in Figure 1, including its absolute configuration.

Application of the nonempirical dibenzoate chirality method[9] was also consistent with the X-ray crystallographic result. Treatment of **1** with *p*-bromobenzoyl chloride in pyridine at 80 °C yielded product **3** with the γ-lactone [IR ($CHCl_3$) 1775 cm^{-1}]; **3** contains two *p*-bromobenzoyl groups judging from the ^1H NMR spectrum [C_6D_6, δ 6.9–7.8 (8 H, m), 5.89 (1 H, s, H13)]. This reaction seems to proceed by reasonable C13→C12 acyl migration,[10] followed by ordinary acylation of the secondary alcohol. The bis(*p*-bromobenzoate) **3** possessing the 1,2-dibenzoate system showed a typical positive split CD; EtOH 241 (Δε −19.3) and 257 nm (Δε 22.1).[11] This observation confirmed the chirality of the C13–$OCOC_6H_4Br$/C12–$OCOC_6H_4Br$ as shown in Figure 2. The novel 2,6,9-trioxatricyclo[3,3,2,$0^{3,7}$]decane system in **1–3** was proven by the full analysis with homonuclear correlated spectroscopy (COSY).[12] As expected, this moiety was not labile in basic media whereas acid solution caused obvious decomposition.

Norhalichondrin A (**1**) consists of a polyoxygenated C_{53} carboxylic acid which may act in an important role in the extension mechanism of naturally occurring long-straight carbon chains such as palytoxin.[13] Biosynthetic studies on **1** as well as brevetoxin[14] may lead us to a general concept. Our studies on the biological origin of **1** and its congeners are currently under way.

(4) Norhalichondrin A inhibited growth of B-16 melanoma cells in vitro at 5 ng/mL IC_{50}.

(5) Furusaki, A. *Acta Crystallogr., Sect. A* **1969**, *A35*, 220–224.

(6) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN 78, a system of computer programs for the automatic solution of crystal structure from X-ray diffraction data, University of York, York, England, 1978.

(7) An automated four-circle diffractometer Rigaku AFC-5R was used throughout this work.

(8) ORTEP crystallographic illustration program: Johnson, C. K. Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN.

(9) Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1969**, *91*, 3989–3991.

(10) See, for example: "Molecular Rearrangements, Part Two"; de Mayo, Ed.; Interscience Publishers: New York, 1964; pp 763–769, 1121–1127.

(11) The UV spectrum of **3** is as follows: λ_{max} (EtOH) 247 nm (ε 38 000).

(12) Nagayama, K.; Anil, K.; Wuthrich, K.; Ernst, R. R. *J. Magn. Reson.* **1980**, *40*, 321–334. Assignments of each proton signal in **1** have been attempted on the basis of the structure **2**. Each carbon signal has been also assigned by INEPT and 2D (^1H–^{13}C chemical shift correlation) experiments.

(13) (a) Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369–7371. (b) Moore, R. E.; Bartolini, G.; Barchi, J.; Bothner-By, A. A.; Dadok, J.; Ford, J. *J. Am. Chem. Soc.* **1982**, *104*, 3776–3779.

(14) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Engen, D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773–6775.

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Supplementary Material Available: 1D and 2D spectra of **1–3**, the ^{13}C NMR spectrum (75.4 MHz) of **1**, table of ^{1}H and ^{13}C NMR data of **1**, and table of atomic coordinates, temperature factors, and bond lengths and angles of **2** (23 pages). Ordering information is given on any current masthead page.

Simple ^{31}P NMR Method for the Determination of Enantiomeric Purity of Alcohols Not Requiring Chiral Auxiliary Compounds

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Essential to stereochemical analyses of asymmetric processes and chemical conversions of chiral compounds are facile methods for the determination of enantiomeric purities. NMR and chromatographic methods based on the formation of diastereomeric complexes or derivatives are widely used.[1] All these methods rely on chiral auxiliary compounds. Horeau[2] was the first to recognize the potential of using the intrinsic differences in chirality of an enantiomerically pure and (partly) racemic substance for enantiomeric excess (ee) determinations. The method depends on coupling of enantiomers (*R*,*S*) via achiral agent A resulting in diastereoisomers *R*-A-*R* (*S*-A-*S*) (a *d*,*l*-pair) and *R*-A-*S* (*S*-A-*R*) (a meso compound) (eq 1).

$$\underset{\text{R,S}}{\text{R,S}} + \text{A} \longrightarrow \underset{\text{(S-A-S)}}{\text{R-A-R}} + \underset{\text{(S-A-R)}}{\text{R-A-S}} \qquad (1)$$

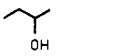
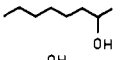
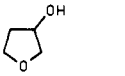
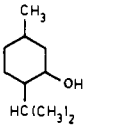
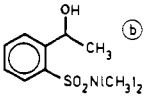
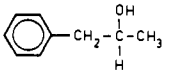
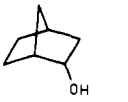
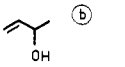
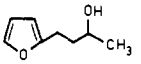
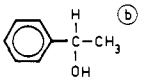
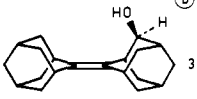
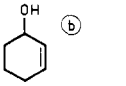
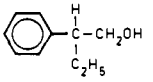
A few applications of this coupling reaction for ee determinations have been demonstrated.[2] The differences in properties between the diastereoisomers (eq 1) can be used in a new and practical method for ee determination if coupling via agent A proceeds in quantitative yield; A contains an unique atom that makes analysis of each diastereoisomer via a *single* NMR absorption possible; no deviation from statistical ratio's of coupled products via "chiral self-recognition"[3] occurs, and chemical shift differences are large enough for accurate integration. On the basis of these considerations and with the knowledge that ^{31}P NMR shows great advantages in ee determinations using chiral derivatizing agents,[4] we have developed a method for ee determination that requires no chiral auxiliary substance. Using PCl_3 as a dimerization agent, alcohols are converted into phosphonates in a fast and quantitative reaction (Scheme I).[5,6]

Application of this reaction for the determination of ee's of alcohols is illustrated for 2-octanol (Scheme I). Racemic **1** should

Table I. Determination of ee's of Optically Active Alcohols[8,9]

alcohol	% ee by weight	% ee by rotation	% ee by ^{31}P NMR
d-2-octanol		100	100
d-2-octanol	49.5	51	51
d-2-octanol	76	76	78
l-menthol		100	100
l-*N*,*N*-dimethylmandelicamide		48	48
l-ethyl lactate	39		41

Table II. ^{31}P NMR Data of Phosphonates from Racemic Alcohols and PCl_3[a,8]

alcohol	δmeso/Hz	δmeso/Hz	δd,l-pair/Hz	ratio meso : d,l
	454	387	425	49.5 : 50.5
	432	365	401	49.2 : 50.8
	481	447	464	49.1 : 50.9
	459	309	413	49.4 : 50.6
	368	329	346	50.0 : 50.0
	471	362	449	50.0 : 50.0
	525	515	518	(a)
	393	349	369	50.6 : 49.4
	449	395	433	50.4 : 49.6
	416	344	370	50.0 : 50.0
	337	291	330	50.0 : 50.0
	450	416	432	50.0 : 50.0
	652	590	623	50.0 : 50.0

[a] (a) approximately 50:50 (no base-line separation); (b) 3 equiv of pyridine added prior to addition of PCl_3.

(1) Chiral shift reagents: Sullivan, G. R. In "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1978, p 287. Chiral solvents: Pirkle, W. H.; Hoover, D. J. "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1982; p 263. Diastereomeric derivatives: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

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(3) Wynberg, H.; Feringa, B. L. *Tetrahedron* **1976**, *32*, 2831.

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(6) To prevent byproduct formation, decomposition, and/or racemization equimolar quantities of pyridine were added in the case of acid-sensitive alcohols, e.g., allylic and benzylic alcohols. Excess pyridine or pyridine salts do not influence the ^{31}P NMR determination.

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