Table I. Reductive Deuteriation of Aryl Aldehydes and Ketones[a]

compound	principal product	conditions			isolated yield, %
		pressure, psi	temp, °C	time, h	
acetophenone	ethylbenzene-*1,1-d*$_2$	20	25	4	69
2-acetonaphthone	2-ethylnaphthalene-*1,1-d*$_2$	12	55	4	73[a]
benzophenone	diphenylmethane-*1,1-d*$_2$	25	55	4-5	82
9-fluorenone	fluorene-*9,9-d*$_2$	25	55	12	80
α-tetralone	1,2,3,4-tetrahydronaphthalene-*1,1,4,4-d*$_4$	25	55	3-4	76
1-naphthaldehyde	1-methylnaphthalene-*1,1-d*$_2$	12	25	5	72[a]

[a] Approximately 90% of the starting material was converted.

there were several methods for the conversion of carbonyl groups into methylene-d_2 fragments.[1] However, most of these methods required several steps or suffered from other drawbacks. For example, the reduction of a carbonyl group to an alcohol by lithium aluminum deuteride followed by formation of the tosylate and further reaction with lithium aluminum deuteride leads to alkenes as well as alkanes and the Clemmenson reduction suffers from the disadvantage that the hydrogen atoms on adjacent aliphatic and aromatic carbon atoms are exchanged simultaneously.[1-3]

We recently reported a selective method for the exchange of benzylic hydrogen atoms using a palladium catalyst in acetic acid-*d* under a dideuterium atmosphere.[4] Inasmuch as palladium catalyzes the conversion of carbonyl groups adjacent to aromatic rings into methylene or methyl groups,[5] we became interested in the prospect of using this method to provide compounds with benzylic methylene-d_2 groups selectively. The results for several aromatic carbonyl compounds are given in Table I.

When the aromatic carbonyl compounds were reacted with dideuterium in the presence of a 10% palladium on carbon catalyst in acetic acid-*d* at 25–55 °C, the carbonyl groups were readily reduced. The products were separated and purified by distillation. Generally, high yields of the hydrocarbons were obtained in the first attempts to carry out the reaction. Reduction of the aromatic ring appears to be the principal side reaction. The ^{1}H NMR spectra of the products were compared with the ^{1}H NMR spectra of unlabeled authentic samples and the extent of ^{2}H incorporation was determined by examination of the ^{2}H NMR spectra. In all cases, the products were very selectively deuteriated in the benzylic position.

The results for the reduction of α-tetralone and the other aryl alkyl ketones underscore the high selectivity of the reaction. The catalytic method gave products with less than 5%, if any, deuterium on the adjacent carbon atom and none in the aromatic ring. In contrast, the Clemmenson reduction gave products that were labeled not only at the former carbonyl carbon atom but also at the ring positions and at the adjacent aliphatic carbon atoms.[2] The spectroscopic evidence also revealed that the carbonyl group in α-tetralone was reduced and that the benzylic hydrogen atoms at the 4 position were selectively exchanged. This observation is consonant with earlier observations.[4]

Catalytic reductions of this kind have been postulated to proceed in two steps in which the starting material is first converted to the benzyl alcohol and then hydrogenolysis (deuteriolysis) occurs to yield the hydrocarbon.[5] The high degree of selectivity observed in the palladium-catalyzed reactions precludes dehydration of the benzylic alcohol to an alkene as an intermediate step. Specifically, we did not obtain 1,2,3,4-tetrahydronaphthalene-*1,1,2,4,4-d*$_5$. Moreover, when the reactions of fluorenone and α-tetralone were stopped after the consumption of 1 mol of dideuterium, the intermediate secondary alcohols were isolated. These observations support the formulation of the reaction as a two-step process.[5,6]

Experimental Section

All the compounds examined in this study were obtained commercially. The physical and spectroscopic properties recorded for these materials were consistent with information in the literature and they were not purified. The catalyst (10% Pd/C) was obtained from Ventron, Alfa Division, and the dideuterium (99.7% isotopic purity) was provided by Cambridge Isotope Laboratories.

The apparatus and the procedure have been described previously.[4] Typically, acetophenone (3.0 g) in acetic acid-*d* (30 mL) was sealed in a reaction bottle with 10% palladium on carbon catalyst (150 mg, 5% w/w of substrate) and connected to a dideuterium reservoir at an initial pressure of 20 psi. The bottle was vigorously shaken at room temperature for 4 h after which the reaction mixture was diluted with water and the product extracted into pentane. The extract was washed with water and then dried over anhydrous magnesium sulfate. The pentane was removed and the product was purified by distillation. The results are summarized in Table I.

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Decomplexation Studies of $Mo(CO)_5L$ Coordination Compounds Containing Organophosphorus Ligands. Determination of the Absolute Configuration of the [(-)-Me(EtO)(HO)P]$Mo(CO)_5$ Complex[1]

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The resolution and some reactions of a $Mo(CO)_5L$ coordination complex (**1a**) having a chiral P^{III} ligand were recently reported.[2] Ligand decomplexation of **1a** and of

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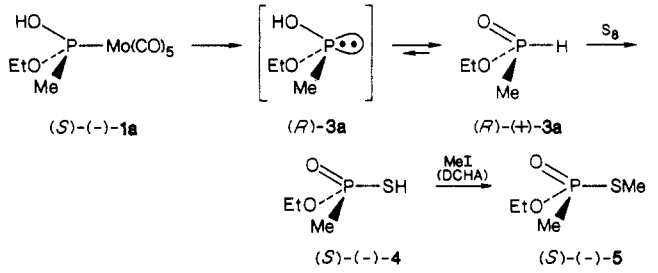
Scheme I



one chiral (**1b**) and one nonchiral (meso) derivative (**1c**) have now been carried out. While decomplexations of chiral P^{III} ligands from resolved platinum,[3] copper,[4] and boron[5] coordination complexes have been published, no such prior study in the more strongly complexed group VIB (6)[17] transition-metal series (Cr, Mo, W) is known to us.

In this study, the meso **1c** complex was used for the initial experimentation, because it was more readily available than its chiral **1b** analogue. After a series of experiments, displacement of the **3c** ligand was best achieved by treatment of **1c** with 2 mol equiv of triphenylphosphine at from 120 to 165 °C. The reaction was run under reduced pressure, in order to remove the displaced ligand from the reaction mixture, insofar as possible immediately as it was formed. The decomplexation apparently occurs by an initial displacement of CO at 120 °C to give an equilibrium mixture of *cis*- and *trans*-$Mo(CO)_4LL'$ species **2**, followed by displacement of **3c** (as might be expected[6]) by the second mole of triphenylphosphine (L') at up to 165 °C. Here, the *cis*- and *trans*-**2c** species were observed and assigned by ^{31}P NMR,[7] and these assignments were corroborated by independent synthesis of the pure cis isomer.

$$Mo(CO)_5L \xrightarrow{Ph_3P} Mo(CO)_4(PPh_3)L \xrightarrow{Ph_3P}$$

2

1a, L = MeP(OEt)(OH)
b, L = MeP(OEt)(OMe)
c, L = $MeP(OEt)_2$

$$MeP(OEt)(OR) + Mo(CO)_4(PPh_3)_2$$

3a, R = H
b, R = Me
c, R = Et

When the method was applied to racemic **1b**, however, an equilibrated mixture of P^{III} products was obtained, which consisted of a 2/1/1 mole ratio of the unsymmetrical **3b** and the two symmetrical methylphosphonites $MeP(OMe)_2$ and **3c**, respectively. In view of this result, it was apparent that if the resolved **1b** complex had been used, optically active **3b** product, if not thermally racemized, would have been chemically racemized via the redistribution reaction[8] that occurred under these conditions.

With the racemic **1a** complex, ligand decomplexation occurred at a lower temperature (120 °C), and ethyl methylphosphinate (**3a**) was produced. When (−)-**1a** (98% ee) was used, (+)-**3a** (6% ee) was obtained. The optical purity and absolute configuration of this product and the absolute configuration of its parent (−)-**1a** complex were established by the chemistry that is summarized in Scheme I.

As shown in the scheme, the (+)-**3a** product was converted into the known (*S*)-(−)-**4** thioic acid that was characterized as its known methyl ester, (*S*)-(−)-**5**, because the ester has a much larger specific rotation than the acid in this series.[9] Since the stereochemistry at the phosphorus is not affected by this alkylation reaction, the known stereochemistry (retention[10]) of the sulfur addition reaction establishes the configuration of the free ligand to be (*R*)-(+)-**3a**, a result which also establishes the *R* configuration for its corresponding P^{III} tautomer. Because the ligand must be displaced from the complex as the P^{III} tautomer with its dative electron-pair bond (hence with retention of configuration at phosphorus), the absolute configuration of phosphorus in the complex may be assigned as (*S*)-(−)-**1a**, as shown. Of course, the stereochemistry of the displacement reaction from the standpoint of the Mo atom cannot be established on the basis of these results.

Since the sulfur addition is known to occur with essentially total stereospecificity,[10] the low optical purity obtained for (−)-**5** must correspond to that originally present in the (+)-**3a** product. Therefore, the decomplexation reaction must have been accompanied by over 90% thermal racemization of either the reaction intermediate or the product, due to the elevated temperature required by the procedure. Thus, while these results establish the previously unknown configuration of the (*S*)-(−)-**1a** complex (and its (*S*)-(+)-**1b** derivative known[2] to be of the same configuration), the method did not prove to be useful as a new synthesis route to optically active (uncomplexed) organophosphorus species via this system.

Experimental Section

General Data. The instrumentation and general experimental details that were used were previously reported.[2] The NMR spectral results are given as mol % composition, unless otherwise stated.[11]

(+)-Ethyl Methylphosphinate (3a) by Decomplexation of (−)-(Ethyl hydrogen methylphosphonite)pentacarbonylmolybdenum (1a). A 1.15-g sample of the (−)-ephedrine salt of (−)-**1a** [(−)-eph·(−)-**1a**],[2] $[\alpha]^{25}_D$ −23.9° (*c* 1.79, methanol), was used. By ^{31}P NMR, it was 96.4 mol % pure and 97.5% ee [94% (−)-eph·(−)-**1a**, δ 158.8, and 2.4% (−)-eph·(+)-**1a**, δ 159.6]. It was dissolved in a mixture of 20 mL of methanol and 2 mL of water and then acidified to pH 1.5 with 2.2 mL of 1 N HCl. A blue solution was obtained. The methanol was removed under reduced pressure without heating, and the residual water layer was extracted several times with a total of 50 mL of ether. The latter was dried ($MgSO_4$) and then was concentrated under reduced pressure (protected from light) to give 0.75 g (2.2 mmol) of (−)-**1a** as a light blue oil (97% of theory). This product was combined with 1.14 g (4.4 mmol) of freshly sublimed triphenylphosphine and was evacuated to 0.5 mm under an argon atmosphere. The mixture was slowly heated until a reaction was observed (bubbling)

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(11) ^{31}P NMR spectra were acquired by using pulse widths of less than 40° with a 2.5-s delay between pulses and an acquisition time of 0.5–1.0 s. As run in our NMR laboratory (no attempt to exclude oxygen), most P^{III} and P^{V} compounds have T_1's of less than 12 s. Integrated peak areas obtained in this way have provided data good to ±3–4% when compared to GC results, notwithstanding the warning given in a reference cited by a referee: Shortt, A. B.; Durham, L. J.; Mosher, H. S. *J. Org. Chem.* **1983**, *48*, 3125.

at 100 °C. This temperature was maintained about 1.5 h and then raised to 120 °C while the pressure was lowered to 0.2 mm. A distillate of 72.2 mg was obtained, which was diluted to 1.00 mL with dry benzene, and a rotation of +0.056° (1 dcm) at 589 nm was observed. The ^{31}P NMR spectrum showed only a single peak at δ 33.4 (consistent for **3a**), but the ^{1}H NMR spectrum revealed the sample contained 55 mol % ethanol. Therefore, the distillate actually contained only 47.5 mg (20% yield) of partially resolved (+)-**3a**, $[\alpha]_D$ +1.18° (*c* 4.75, benzene), when corrected for its observed purity. From the following results, this product should be 6% ee, hence the specific rotation of 100% ee **3a** would be 19.6°.

(−)-*O*-Ethyl *S*-Methyl Methylphosphonothiolate (5). The benzene solution of (+)-**3a** (47.5 mg, 0.439 mmol) from above was treated with 14.1 mg (0.439 mmol) of sulfur and 79.6 mg (0.439 mmol) of dicyclohexylamine (DCHA). The sulfur dissolved completely after stirring overnight at ca. 25 °C. The product [DCHA salt of (−)-4] was not isolated, but the benzene solution was directly treated with an excess of methyl iodide (225 mg, 1.6 mmol) in 1 mL of dry benzene. The reaction mixture was warmed to 50 °C and then was cooled to room temperature. The DCHA·HI that was obtained after standing overnight was filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up in petroleum ether, refiltered, and then reconcentrated to yield 58.6 mg of an oil, **5**, α_{obsd} −0.264° (1 dcm) in 1.00 mL of dry chloroform. The ^{31}P NMR spectrum of this solution showed a single peak at δ 55.9. The ^{1}H NMR revealed a mixture of 63.9 mol % **5**, 9.7 mol % ethanol, and 26.5 mol % water, which corresponds to 91.4 wt % of **5**. Therefore, the isolated product actually contained 53.5 mg (80% yield) of (−)-**5**, $[\alpha]^{25}_D$ −4.93° (*c* 5.4, chloroform), when corrected for its observed purity, 6% ee, based upon $[\alpha]_D$ +83° reported for 100% ee (*R*)-(+)-**5**.[9a]

Reaction of (Ethyl methyl methylphosphonite)pentacarbonylmolybdenum (1b) with Two Equivalents of Triphenylphosphine. Compound **1b**, bp 53–56 °C (3 μm), was prepared from the reaction of diazomethane with racemic **1a** (obtained from its dicyclohexylamine salt[2]), as described for that of (+)-**1a** obtained from its ephedrine salt.[2] The ester (1.91 g, 5.30 mmol) was mixed with an excess over 2 equiv of freshly sublimed triphenylphosphine (3.06 g, 11.7 mmol) in a distillation apparatus. The system was evacuated to 0.5 mm under dry nitrogen while the apparatus was flame-dried, and the mixture was heated to 120 °C. The temperature was then raised during 1 h to 165 °C at 0.5 mm, and these conditions were maintained for 1 h, while the receiver was cooled in a dry ice/acetone bath. The vacuum was removed, the receiver was warmed to room temperature, and the distillate (0.36 g) was taken up in 2 mL of dry benzene. The ^{31}P NMR spectrum revealed a mixture of MeP(OEt)(OMe) (**3b**; δ 180.6; 47%), $MeP(OMe)_2$ (δ 183.5; 24%), $MeP(OEt)_2$ (**3c**; δ 177.9; 22%), species at δ 34.3 (2%) and 31.6 (3%), assigned as MeP(O)(H)(OMe) and MeP(O)(H)(OEt) (**3a**), respectively, and seven trace components, 2% total. The P^{III} species were assigned from comparison of these data to those which had been earlier recorded for these species, from other studies.[12,13]

(Diethyl methylphosphonite)pentacarbonylmolybdenum (1c). A mixture of diethyl methylphosphonite[14] (**3c**) (42.2 g, 0.309 mol), molybdenum hexacarbonyl (81.8 g, 0.310 mol), and 300 mL of dry toluene was vigorously stirred at ca. 90 °C for 23 h in a 1-L flask under nitrogen. After the mixture was cooled to room temperature, 300 mL of petroleum ether (bp 30–60 °C) was added to precipitate unreacted molybdenum hexacarbonyl. The mixture was filtered under nitrogen, and the filtrate was concentrated on a rotary evaporator while the vacuum was slowly taken down to 0.5 mm. The residue was twice distilled on a McCarter molecular still at 50–60 °C (10 μm) to give 84 g (73%) of **1c**: ^{31}P NMR (neat) δ 183.0 (lit.[2] δ 182.9); ^{1}H NMR (neat) δ 1.67 (d, J_{PH} = 3 Hz, 3 H, CH_3P), 1.3 (t, J_{HH} = 7 Hz, 6 H, CH_3CH_2OP), 3.91 (m, J_{HH} = 7 Hz, $J_{PH} \sim$ 7 Hz, 4 H, CH_3CH_2OP).

Reaction of 1c with One Equivalent of Triphenylphosphine. A mixture of **1c** (3.41 g, 9.16 mmol) and triphenylphosphine (2.40 g, 9.16 mmol) was heated at 115 °C for 80 min to give a yellow oil. ^{31}P NMR: *cis*-**2**, δ 185 (d) and 39 (d, J = 31 Hz for both), 39% of integrated area; *trans*-**2**, δ 193 (d) and 49 (d, J = 78 Hz for both), 18%; **1c**, δ 183, 14%; triphenylphosphine, δ −5.0, 15%; eight other phosphorus compound signals, 14%. An additional 20 mol % of triphenylphosphine (0.48 g) was then added, and the heating was continued for another 90 min. At this point, a ^{31}P NMR spectrum revealed that the unreacted **1c** had been reduced from 28% to 6% of that originally taken, accompanied by a corresponding increase in the *cis*- and *trans*-**2** isomer content (2/1, respectively).

***cis*-(Diethyl methylphosphonite)(triphenylphosphine)-pentacarbonylmolybdenum (2).**[15] A solution of *cis*-$(C_5H_{10}NH)[(C_6H_5)_3P]Mo(CO)_4$[16] (3.00 g, 5.40 mmol) and **3c** (1.10 g, 8.08 mmol) in 20 mL of dichloromethane was refluxed for 30 min and then concentrated at 0.5 mm to a yellow residue. The latter crystallized from chloroform/methanol to give 1.76 g of *cis*-**2**, which was recrystallized to give a light beige product, mp 104–105 °C, >95% pure by ^{31}P NMR: δ 185 (d) and 39 (d, J = 30.8 Hz for both) for the two ligands, respectively. In an attempt to isomerize *cis*-**2** to the pure *trans*-**2** isomer, it was heated in toluene at 110 °C for 1 h. However, the ^{31}P NMR spectrum revealed a mixture of 39% *cis*-**2** and 40% *trans*-**2** isomers, 10% of (apparently) triphenylphosphine oxide (δ 25.7), 4% **1c** (δ 184), and three unidentified products. Heating this sample for an additional 2 h gave no significant change.

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An Efficient Enantioselective Synthesis of the (−)-*N*-(Ethoxycarbonyl)methyl Geissman-Waiss Lactone: A Practical Synthetic Route to (+)-Retronecine

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Pyrrolizidine alkaloids having retronecine (1) as the necine base are known to exhibit potent hepatotoxicity and, in certain cases, antitumor activity and carcinogenicity.[1] The challenging structures and the varied range of biological activities of pyrrolizidine alkaloids have made them attractive synthetic targets. The first synthesis of (+)-retronecine (1) was reported in 1962 by Geissman and Waiss.[2] While many synthetic routes to racemic retro-

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