Asymmetric Synthesis. Preparation of Chiral Methyl Chiral Lactic Acid by Catalytic Asymmetric Hydrogenation

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Abstract: Chiral methyl chiral lactic acid, a molecule which has a chiral methyl group because of the specific incorporation of the three isotopes of hydrogen, has been synthesized by a sequence of simple, convenient steps culminating in catalytic asymmetric hydrogenation. Moreover, the method allows for the preparation of all 12 possible isomers which arise from the permutation of the isotopes of hydrogen and of the two chiral centers. The absolute configuration of the chiral methyl group has been established. Chiral methyl chiral lactic acid is potentially a key molecule for biogenesis studies because numerous other specifically labeled substrates can be prepared from it by simple elaboration and degradation.

The remarkable stereospecificity of enzymatic reactions has been probed in a number of ingenious ways.[1] Most notable of these has been the use of substrates in which the isotopes of hydrogen have been introduced in a stereochemically determined manner. Thus the classic studies[2] on yeast alcohol dehydrogenase showed, by deuterium incorporation, that only the pro-*R* hydrogen atom of ethanol was abstracted and that only the re-face of the carbonyl group of acetaldehyde was attacked.

One of the more spectacular developments in the stereospecific hydrogen isotope labeling of substrates was the synthesis of chiral methyl acetic acid (CHDTCOOH) by Cornforth[3] and Arigoni;[4] the former used a purely chemical approach while the latter initially used a biological-chemical synthesis. It was then shown[3,4] that malate synthase converted chiral methyl acetic acid to *S*-malic acid with inversion of configuration based on the assumption of a normal isotope effect and on the known stereospecific abstraction of the pro-*R* hydrogen atom of malic acid in the fumarase transformation[5] (Figure 1).

The hidden chirality of the malate synthase reaction is but a simple example where the inherent asymmetry of enzymatic reactions is revealed by specific labeling; that there is hidden chirality in the numerous steps in the biosynthesis of cholesterol from acetate has been determined by these methods.[6,7] Such studies provide the crucial underpinning for an understanding of the stereochemical details of enzymatic reactions and are essential for a complete definition of mechanisms.

These elegant methods, however, depend on the availability of suitably labeled materials, many of which are only available in small quantities after exceedingly laborious preparations. It would therefore be of some importance to have a simple method of generating large quantities of a key labeled molecule from which other biologically important substrates could be derived by facile stereospecific elaboration. For this purpose we chose lactic acid.

This paper describes an asymmetric catalytic method which produces pure chiral methyl chiral lactic acid. The method is simple, it can give large amounts of lactic acid, and it is so designed that all of the possible permutations of the isotopes of hydrogen as well as the permutations of chirality can be produced. A total of 12 configurational isomers of lactic acid can be made using ^1H, ^2H, and ^3H. Moreover, the absolute configuration of the methyl group has been established.

I. Strategy

The rhodium(I) complexes of the bidentate phosphine ligands, (*S,S*)-chiraphos and (*R*)-prophos (Figure 2), act as efficient homogeneous asymmetric hydrogenation catalysts for a number of olefinic substrates.[8,9] These catalysts have a number of attractive features: first, with proper choice of the olefinic substrate high optical yields are obtained; second, the hydrogen addition to the olefin is stereospecific[8] and is believed to be cis.[10] In a previous report[9] we observed that the (*S,S*)-chiraphos catalyst reduced ethyl α-acetoxyacrylate (III in Figure 3) to (*R*)-ethyl *O*-acetyllactate (IV) in 84% optical purity whereas the analogous (*R*)-prophos catalyst gave the other enantiomer in 81% optical purity. Our strategy for generating chiral methyl chiral lactic acid using these catalysts is shown in Figure 3.

In order to carry through the scheme in Figure 3, we require a method of converting I to a single isomer of the enol acetate II and to find a method of replacing the bromine atom of II by an isotope of hydrogen (^iH) in a completely stereospecific way to produce III. At this stage we need to establish the configuration of III, preferably without recourse to assumptions about mechanism. Once the configuration of III is established, the cis-$^kH_2$ addition by the catalysts will produce a material (IV) whose optical purity at the α center is the same as that of the chiral methyl group, a result that is a consequence of the stereospecific hydrogen addition. Thus any method which affords VI or lactic acid in complete optical purity (at the α center) automatically purifies the chiral methyl group. Moreover, if the absolute configuration of the α center is known and the configuration of III is established, the absolute configuration of the chiral methyl group is known. It will be seen that the scheme in Figure 3 has considerable flexibility since the chirality of the α center and of the methyl group can be permuted by introducing the isotopes in different steps of the sequence and by changing the catalysts.

We note that, for biogenetic studies, it is not necessary to have complete ^3H incorporation; one ^3H in 10^4 molecules suffices if the products are assayed by radioactivity. It is important, however, to have nearly complete ^2H incorporation and those molecules which do have ^3H should be optically pure.

II. (*Z*)-Ethyl 2-Acetoxy-3-bromoacrylate (II)

Reaction of ethyl bromopyruvate (I) with acetic anhydride in the presence of an acid catalyst yields ethyl 2-acetoxy-3-bromoacrylate (II). The ^1H NMR spectrum of this material clearly establishes it to be a single isomer (Experimental Section). We show later that this is the *Z* isomer (Figure 3). The use of pyruvic acid derivatives is advantageous in that the methyl protons are readily exchanged. Pyruvic acid in D_2O, in the presence of 1 equiv of Na_2CO_3, exchanges its protons within 12 h at 25 °C. However, the conversion[11] of this labeled material to the ethyl bromopyruvate without concomitant isotope exchange is tedious and can be troublesome. We therefore devised a more direct and efficient method of label transfer. The base-sensitive ethyl bromopyruvate when dissolved in CF_3COOD containing a catalytic amount of

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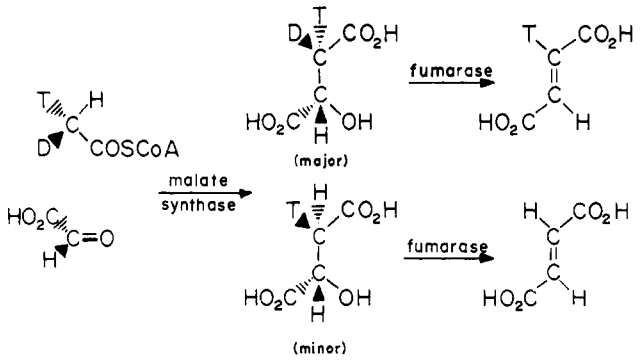

Figure 1. The stereochemical fate of a methyl group in chiral methyl acetic acid as shown by the malate synthase conversion to (*S*)-malic acid. The major and minor products arise because of the isotope effects due to protium and deuterium.

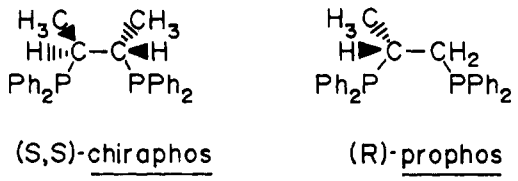

Figure 2. The structures and absolute configurations of the ligands (*S,S*)-chiraphos and (*R*)-prophos.

CF_3COOK exchanges its methylene protons in 40 h at 70 °C:

$$BrCH_2CO_2Et \xrightarrow{CF_3CO_2{}^jH/CF_3CO_2K} BrC{}^jH_2CO_2Et$$

The notable feature of this reaction is that no detectable decomposition occurs and the pure labeled product is easily obtained in almost quantitative yield. Conversion to ethyl 2-acetoxy-3-bromoacrylate (II) occurs without label exchange.

III. Stereospecific Debromination

Ethyl 2-acetoxy-3-bromopyruvate (II) contains very base-sensitive groups and hence the usual lithium reagents were not available to us for stereospecific debromination. Vinylic halides, however, can be reduced under mild neutral conditions using either Zn/Ag or Zn/Cu couples.[12,13] We have used both of these under a variety of conditions; in all cases clean debromination was induced but none gave a pure isomeric product using deuterium as a label. The highest selectivity was achieved using the Zn/Ag couple in THF/D_2O (3:2) at 25 °C. A combination of ^1H NMR and mass spectrometry showed that slightly more than 85% of the deuterium incorporation was stereospecific. These results, although useful in another context which we deal with presently, were not sufficient for our purposes.

It has been known for some time that low oxidation state metal complexes, notably those having d^8 and d^{10} configurations, undergo oxidative additions with vinylic halides to give σ-vinyl complexes.[14] Moreover, the bulk of the evidence suggests that these additions occur with complete retention of configuration.[15] These systems would be ideal for our purposes provided that we could find a mild method of stereospecifically inserting a proton into the σ-vinyl–metal bond. Cleavage of this kind has been reported[16] but the stereochemistry has not been established.

The zerovalent complexes $[Pt(PPh_3)_4]$[17] and $[Pd(PPh_3)_4]$[18] (PPh_3 = triphenylphosphine) when suspended in benzene readily react with the bromoacrylate II to give the corresponding σ-vinyl complexes in high yield. This oxidative addition for palladium is shown in Figure 4. Both of these complexes are robust and ^1H NMR shows them to be a single isomer; the oxidative addition is stereospecific.

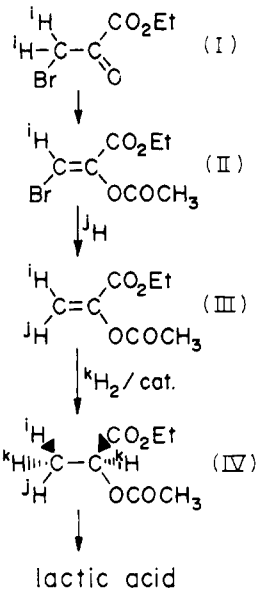

Figure 3. The strategy for the preparation of chiral methyl chiral lactic acid.

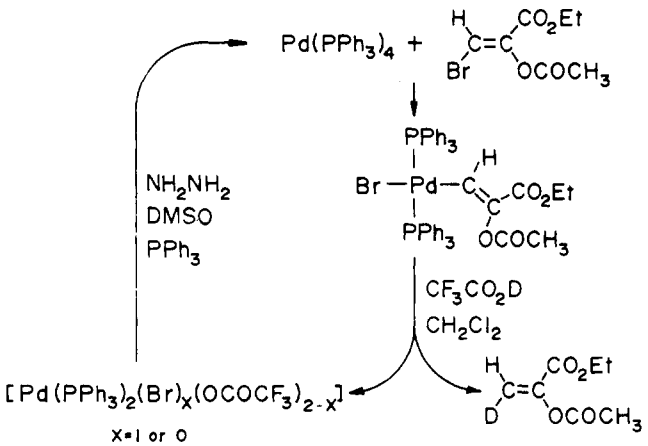

Figure 4. A scheme for obtaining the isomerically pure (*Z*)-ethyl 2-acetoxy-3-deuterioacrylate from the corresponding bromo compound. Also shown is the method of recycling the palladium.

A single-crystal X-ray structural determination[19] of the palladium complex shows it to have the structure illustrated in Figure 4; namely, the ethyl 2-acetoxy-3-palladoacrylate moiety has the *Z* configuration. The next step was to find a mild method of cleaving the metal–carbon bond stereospecifically to produce the labeled product (III).

As expected, the platinum derivative proved much more inert to metal–carbon bond cleavage than the palladium analogue. Reaction of the palladium complex in CH_2Cl_2 solution containing 15 equiv of CF_3COOD and a catalytic amount of trifluoroacetic anhydride resulted in the clean cleavage of the metal–vinyl bond and the production of the labeled product (III) in high yield. This reaction is also completely stereospecific.

Figure 5 shows the ^1H NMR spectrum of the (protonated) ethyl α-acetoxyacrylate in the vinylic proton regions. The other two spectra refer to the corresponding deuterated products from the Zn/Ag reduction and from the palladium cleavage reaction. It will be noted that the two deuterated products retain the low-field vinylic proton signal which establishes that both the Zn/Ag and the palladium cleavage reaction give predominantly the same deuterated isomer. In the next section

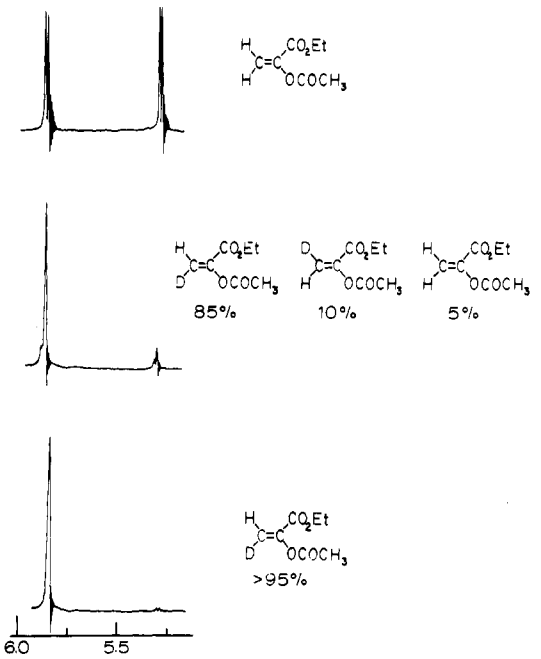

Figure 5. The ^1H NMR spectrum (in $CDCl_3$) of the vinylic proton signals of the enol acetates shown. The top spectrum refers to the fully protonated species, the middle spectrum shows the same spectrum after debromination of (*Z*)-ethyl 2-acetoxy-3-bromoacrylate using a Zn/Ag couple in the presence of deuterium, and the bottom spectrum refers to the species derived from the palladium reactions shown in Figure 6. The percent values for the species alongside the middle spectrum were obtained by a combination of ^1H NMR integration and mass spectrometry. The percent figure for the bottom spectrum merely reflects the sensitivity of the ^1H NMR method and is not meant to suggest that the product is not isomerically pure.

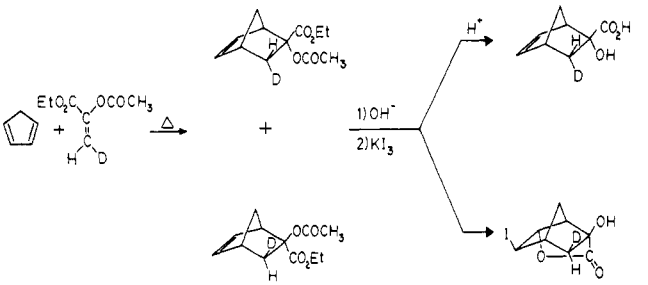

Figure 6. Outline of the scheme for the preparation of the two Diels-Alder adducts and the iodolactonization reaction.

we establish that the deuterated products have the *Z* configuration; that is, the deuterium is trans to the carboethoxy group.

With this information, together with the crystal structure, we are in a position to deduce the overall stereochemistry of the palladium cleavage reaction. The cleavage reaction proceeds with complete retention because the configurations of ethyl 2-acetoxy-3-palladoacrylate moiety and the derived deuterated product are the same. The Zn/Ag reduction can give either a completely scrambled product or one with a degree of configurational retention.[12,13] It thus follows that, because the major deuterated product has the *Z* configuration, the bromo progenitor also has the *Z* configuration. Hence the oxidative addition with palladium also proceeds with retention. To our knowledge, this is the first time that it has been established that the acid cleavage of the palladium-σ-vinyl bond proceeds with complete retention.

The products of the palladium acid cleavage reaction are the enol acetate III and a crystalline palladium(II) complex of indefinite stoichiometry; the latter, however, can be converted to *trans*-$[Pd(PPh_3)_2Br_2]$ by adding LiBr to a solution of the complex. The enol acetate polymerizes in the presence of trace amounts of palladium complexes at the temperatures required for distillation (~90 °C). Indeed, it polymerizes slowly as a neat liquid at 0 °C under N_2. The polymerization problem was circumvented by codistilling the enol acetate with triglyme, in which it is indefinitely stable. When required it can be recovered by dilution with water, followed by ether extraction.

There is one potential drawback to the use of palladium in this scheme: it is expensive. We have found, however, that the palladium complex, which is recovered almost quantitatively from the cleavage reaction, can be reduced back to the $[Pd(PPh_3)_4]$ complex. A full cycle involving oxidative addition, acid cleavage, and hydrazine reduction results in the recovery of about 85% of the palladium (Figure 4).

The remaining issue to be resolved with respect to the palladium cleavage reaction is the determination of the degree of transference of tritium from CF_3COOT to the enol acetate. We found that the D/H rate constant ratio was about 3 for the cleavage reaction. Since the acid is necessarily in excess—because otherwise the complex is not soluble in CH_2Cl_2—and only a fraction of the trifluoroacetic acid molecules contain tritium, the amount of tritium transferred will not only depend on the isotope effect but also on the isotope concentration. Tritiated trifluoroacetic acid is simply prepared by reaction of HTO with the anhydride.

To give an indication of the transference of tritium in the cleavage reaction we have performed a convenient low-level radioactive experiment. The use of CF_3COOT having 830 cpm/μmol gave the enol acetate having 14.2 cpm/μmol. The transference ratio is therefore about 1:58. Larger counts emanating from the enol acetate can, of course, be obtained by simply introducing hotter trifluoroacetic acid. Moreover, the radioactive transference ratio will depend on which step of our scheme we choose to introduce the tritium. For example, nearly complete tritiation would be effected if we were to use T_2 gas, which can be obtained nearly pure, in conjunction with the rhodium catalyst. The example we have explored above is probably the least efficient for tritium transference (vide infra).

IV. Configuration of the Labeled Enol Acetate

The configuration of the labeled enol acetate was established as follows. The thermal Diels-Alder reaction of cyclopentadiene and the monodeuterated enol acetate III gives approximately a 60:40 mixture of the exo and endo isomers of the adduct (Figure 6). In order to proceed, we require separation and identification of the stereochemistry of these two adducts. This was achieved, first, by aqueous alkaline hydrolysis of both the ester and acetate groups followed by an iodolactonization reaction[20] which, for steric reasons, can only occur when the carboxylate group occupies an endo disposition. The neutral iodolactone was then extracted with CH_2Cl_2 from the basic aqueous solution which thereafter, upon acidification, released the exo acid for similar extraction. In this way the two isomers of the Diels-Alder adduct were separated and their configurations established (Figure 6).

Figure 7 shows the ^1H NMR spectra of the undeuterated and deuterated exo acid in D_2O solution. We now need to determine whether the deuterium is exo or endo in this isomer, for it follows that, when this is established, the geometry of the label in the starting enol acetate is also established because of the retentive stereochemistry of the thermal Diels-Alder reaction.

The resonances of H_1 and H_2 (Figure 7) are separated by their chemical shifts and are split by geminal coupling ($J_{1,2}$ = 11.0 Hz). Further splitting occurs through vicinal coupling of H_3 and H_1 ($J_{1,3}$ = 4.0 Hz), but, because of their geometric

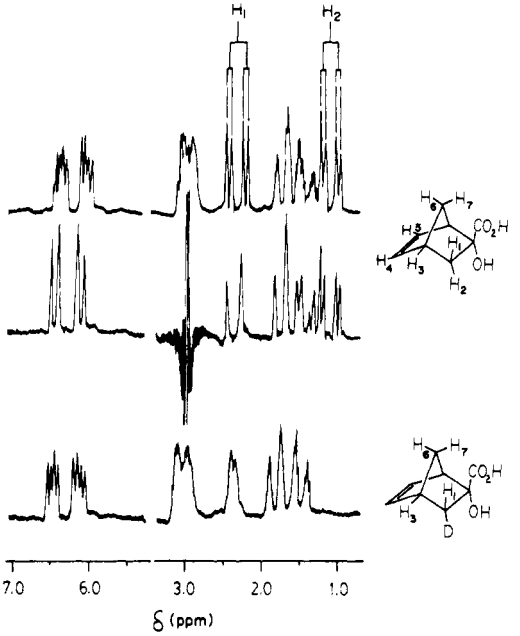

Figure 7. The ^1H NMR spectra of the two molecules shown in D_2O. The middle spectrum is observed after decoupling of the bridgehead protons of the upper molecule. The bottom spectrum refers to the deuterated molecule.

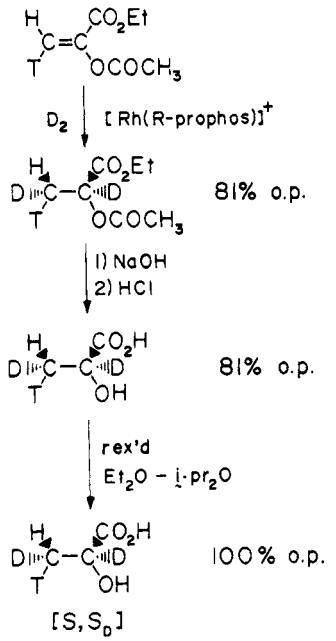

Figure 8. Outline of the method for obtaining an optically pure chiral methyl chiral lactic acid.

dispositions, the coupling of H_3 with H_2 is negligible.[21] However, the particular rigid geometry of this bicyclo[2.2.1] system allows for W coupling[21] of H_6 and H_2 ($J_{2,6}$ = 3.5 Hz). Since $J_{1,3}$ and $J_{2,6}$ are similar coupling constants, resonances due to H_1 and H_2 cannot be assigned convincingly on this basis and further information is required. This is provided by the results of the spin decoupling of the bridgehead protons shown in the middle spectrum of Figure 7.

It will be noted that the multiplicity of the vinylic proton resonances (δ 6–7) is resolved into a pair of doublets. This, and other features, establishes that bridgehead protons were indeed decoupled. More significantly, the original quartet centered at δ 2.43 collapses into a doublet but the high-field quartet centered at δ 1.15 is retained upon decoupling. Therefore, the

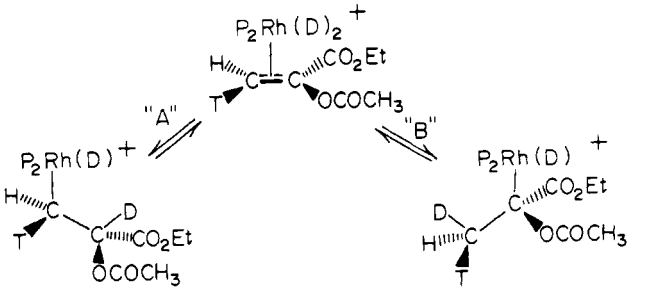

Figure 9. The two intermediates which might occur during hydrogenation. The one derived from path B could lead to some scrambling of the chiral methyl group if the reverse (β-elimination) reaction were significant. Moreover, under particular circumstances (see text), equilibration via B could lead to the appearance of the hydrogen isotopes attached to the methyl at the α-carbon atom of the hydrogenated product.

δ 2.43 centered quartet of the top spectrum arises from H_1 and the one centered at δ 1.15 is associated with H_2.

The bottom spectrum in Figure 7 refers to the monodeuterated species. It is obvious that the deuterium is in the endo disposition. The broadness of the doublet assigned to H_1 is probably due to geminal deuterium coupling which is not fully resolved. Thus the original deuterated enol acetate has the *Z* configuration and the acid-cleavage reaction proceeded with retention.

V. Catalytic Hydrogenation

The final step in the production of chiral methyl chiral lactic acid is the catalytic hydrogenation of the labeled enol acetate. Using either the (*S,S*)-chiraphos or (*R*)-prophos catalysts gives enantiomeric products which are slightly more than 80% optically pure and we require a simple method for obtaining the lactic acid optically pure. Figure 8 outlines our procedure for achieving this. Aqueous alkaline hydrolysis of *O*-acetyl ethyllactate followed by neutralization and removal of the solvent gives the optically impure lactic acid as an oil. This oil dissolves in approximately equal volume of a boiling 1:1 solution of diethyl ether/diisopropyl ether. On standing at 5 °C, this solution deposits large, colorless, very weakly hygroscopic crystals of optically pure chiral methyl chiral lactic acid in a remarkable 60% yield. Provided that the catalytic hydrogenation is stereospecific then the chiral methyl group and the lactic acid are simultaneously resolved.

A key assumption in our strategy is that the catalytic hydrogenation step occurs stereospecifically cis. The current view is that the hydrogen transfer, in these rhodium catalysts, is a two-step process involving hydrogen transfer to give initially a σ-alkyl intermediate followed by hydrogen insertion into the incipiently formed σ-alkyl rhodium bond.

Figure 9 shows two possible σ-alkyl intermediates for our system. The question that pertains to the stereospecific cis addition is whether the σ-bonded intermediate is sufficiently long lived to undergo the reverse process, namely, β-elimination. If the reaction proceeds only along path A, then whether β-elimination occurs or not will be inconsequential since β-elimination will lead to an olefin whose face is bonded to the rhodium atom in the same chirality as the one that existed before the first hydrogen was transferred. This is also true of path B, but, if the incipiently formed chiral methyl group of the intermediate were to freely rotate, then β-elimination would lead to a degree of scrambling of the hydrogen isotopes.

The bulk of the evidence suggests that, with these soluble rhodium catalysts, scrambling does not occur. For example, the early study[10] on the deuteration of maleic and fumaric acids showed that stereospecific cis deuteration had occurred. Since the maleic and fumaric acids would give a common σ-alkyl intermediate, β-elimination would be expected to lead

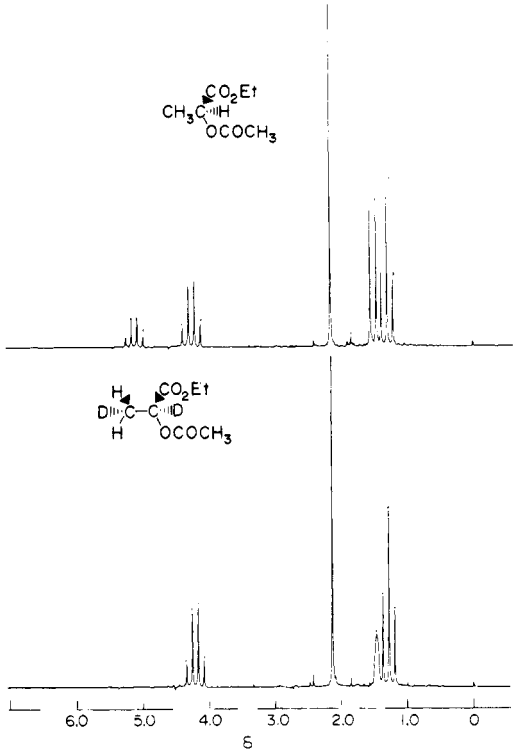

Figure 10. The ^1H NMR spectra (in $CDCl_3$) of the two products derived from catalytic reduction using the rhodium-(*R*)-prophos catalyst. The top spectrum refers to hydrogenation; the bottom spectrum refers to deuteration.

to a degree of scrambling. Moreover, tetrasubstituted olefins are much more difficult to reduce than the less substituted homologues, which suggests that the σ-alkyl intermediate is more readily formed by the less substituted carbon atom of the olefin (see path A in Figure 9). Both of these arguments would support the assumption that no scrambling occurs with the present enol acetate substrate.

In order to check this assertion, we have taken our unlabeled enol acetate and reduced it with both hydrogen and deuterium using the prophos catalyst. The ^1H NMR spectra in $CDCl_3$ solution are shown in Figure 10. It will be noted that the quartet centered at δ 5.05, due to the resonance of the proton at the α center, is absent in the deuterated product. This supports the view that no scrambling occurs in our system, at least at the level of detectability of the ^1H NMR experiment. It, however, does not prove it, for if during deuteration (a) the reaction went via path B (Figure 9) and if (b) β-elimination occurred to form a hydridodeuteriorhodium-olefin species and if then (c) the hydride and deuterioligands did not have time to undergo fluxional interchange before addition to the olefin occurred again, then it is possible that no deuterium would appear at the α center despite isotopic scrambling of the methyl group. We consider these circumstances highly unlikely but they remain a logical proviso. The matter could ultimately be settled by a biological assay of the chiral methyl acetic acid that can be made from our lactic acid (vide infra).

VI. Discussion

The scheme we have outlined for the preparation of chiral methyl chiral lactic acid is in principle completely flexible. Using the (*R*)-prophos and (*S,S*)-chiraphos catalysts and using different sequences for the addition of the isotopic labels, all 12 possible permutations of labels and chirality can be prepared. Figure 11 outlines a scheme for the production of six of these species when the (*R*)-prophos catalyst is used. Each of the six chiral methyl chiral lactic acids in Figure 11 has an

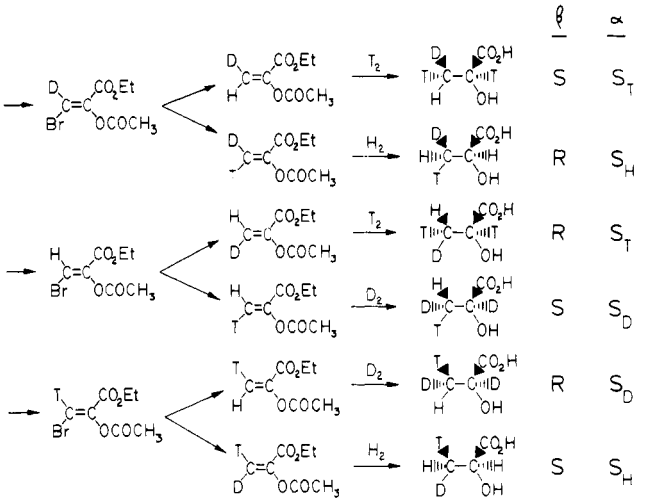

Figure 11. An outline of a scheme for generating six isomers of chiral methyl chiral lactic acid using the (*R*)-prophos catalyst. The are six more (mirror image) isomers which can be obtained using the (*S,S*)-chiraphos catalyst. The isomers arise from permutation of the isotopes of hydrogen and of the chirality of the methyl group (β) and the carbon center (α).

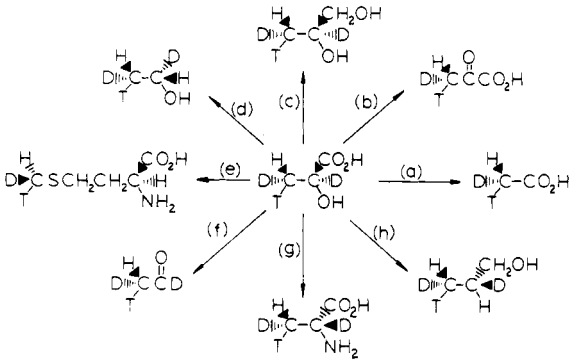

Figure 12. A selection of the possible specifically labeled products that may be derived from elaboration and degradation of chiral methyl chiral lactic acid.

enantiomer which can be prepared simply by switching the (*S,S*)-chiraphos catalyst.

In addition, these chiral methyl chiral lactic acids provide excellent synthons for the preparation of other specifically labeled chiral molecules. To give an indication of the potential usefulness, we outline some of the possible products which can be derived (Figure 12). Reactions (a),[22] (c),[9] and (e)[23] have been described in detail. The other derivatives should be available by straightforward synthetic methods. There are, of course, numerous other derivatives that can be conceived as a result of elaboration or degradation of these labeled lactic acids. The simplicity, flexibility, and general tidiness of the present method should provide a facile entry into areas of biogenesis which hitherto have been restrained by the sometimes tedious and cumbersome methods required for the generation of labeled precursors.

VII. Experimental Section

(*Z*)-Ethyl 2-Acetoxy-3-bromoacrylate. Freshly distilled ethyl bromopyruvate[24] (72 g, 0.37 mol) was taken up in acetic anhydride (88 mL, 0.93 mol) and the solution was refluxed for 24 h under N_2 in the presence of *p*-toluenesulfonic acid (1 g). The resulting dark brown reaction mixture was then fractionally distilled through a 25-cm vacuum-jacketed column filled with glass helices. The product came over as a slightly yellow, clear liquid (61.1 g, 70%, bp 99.5 °C, 10 mm) which is indefinitely stable at 25 °C under N_2: ^1H NMR δ 7.33 (1 H, s), 4.25 (2 H, q, J = 7 Hz), 2.28 (3 H, s), 1.3 (3 H, t, J = 7 Hz) ($CDCl_3$/Me_4Si).

Anal. Calcd for $C_7H_9BrO_4$: C, 35.5; H, 3.8; Br, 33.7. Found: C, 35.7; H, 4.0; Br, 33.9.

Zn–Ag Couple. Zinc dust (22 g) was suspended in 10% aqueous HCl (110 mL) and the mixture was stirred at 25 °C under N_2 for 20 min. Acetone (50 mL) was then added and the solvent was decanted from the zinc. The gray slurry was washed by decantation with six 50-mL portions of acetone and then silver acetate in boiling acetic acid (125 mL) was added to the zinc residue. The mixture was rapidly stirred for 5 min without further heating. The liquid was decanted and the resulting black, granular solid was washed with acetic acid (2 × 60 mL), then with acetone (2 × 50 mL), and finally with dry THF (2 × 50 mL). Finally, the residue was stirred with D_2O (5 mL) in dry THF (50 mL) for 15 min; after decantation, this procedure was repeated a second time and then the solid was washed with dry THF (50 mL). This elaborate procedure reduces the amount of proton incorporation in the next step.

Debromination. The moist couple was suspended in dry THF (20 mL) in D_2O (20 mL) and to it was added (*Z*)-ethyl 2-acetoxy-3-bromoacrylate (10 g, 0.042 mol) in dry THF (10 mL). The mixture was stirred at 25 °C under N_2 for 24 h. The gray slurry was filtered and washed with THF (3 × 25 mL) and the THF in the filtrate was removed on a rotary evaporator. To the aqueous residue was added CH_2Cl_2 and the product was extracted. The organic phase was dried and upon removal of the solvent the pure deuterated olefin remained (5.2 g, 77%). It can be distilled in vacuo.[9]

***trans*-[Pd(PPh$_3$)$_2$Br(CH=C(OCOCH$_3$)COOEt)]·CH$_2$Cl$_2$.** To a suspension of $[Pd(PPh_3)_4]$[18] (15.0 g, 0.013 mol) in degassed benzene (60 mL) was added a solution of (*Z*)-ethyl 2-acetoxy-3-bromoacrylate (3.5 g, 0.015 mol) in benzene (12 mL) over a period of 10 min. The yellow slurry was stirred and heated at 65 °C under N_2 for 2 h to give a yellowish-gray precipitate and an olive-brown supernatant solution. The reaction mixture was cooled and diluted with ether (80 mL) and the resulting precipitate was filtered and washed with ether. The solid was taken up in CH_2Cl_2 (300 mL), the solution was passed through a 4 × 1 cm Florisil column to remove the metal, and the now clear yellow solution was diluted with ether (500 mL) and then with cyclohexane (1 *L*). After standing at 25 °C for 8 h, the solution deposited yellow prisms of the product (10.6 g, 85%). The CH_2Cl_2 solvate was detected by ^1H NMR.

Anal. Calcd for $C_{44}H_{41}BrCl_2O_4P_2Pd$: C, 55.5; H, 4.3; Br, 8.4; Cl, 7.4; P, 6.5. Found: C, 55.7; H, 4.2; Br, 8.2; Cl, 7.7; P, 6.2.

***trans*-[Pt(PPh$_3$)$_2$Br(CH=C(OCOCH$_3$)CO$_2$Et)]·CH$_2$Cl$_2$.** To a suspension of $[Pt(PPh_3)_4]$[17] (7.0 g, 5.63 mmol) in degassed benzene (25 mL) was added a solution of (*Z*)-ethyl 2-acetoxy-3-bromoacrylate (2.0 g, 8.44 mmol) in benzene (5 mL). The mixture gradually cleared to give an olive-brown solution which was then heated at 60 °C for 6 h under N_2. A gray precipitate formed. The product was purified by the method described for the palladium analogue and formed colorless prisms (4.8 g, 82%).

Anal. Calcd for $C_{44}H_{41}BrCl_2O_4P_2Pt$: C, 50.7; H, 4.0; Br, 7.7; Cl, 6.8; P, 6.0. Found: C, 50.8; H, 4.0; Br, 7.9; Cl, 6.9; P, 6.1.

Cleavage Reaction Using [$^2H_1$]Trifluoroacetic Acid (CF$_3$COOD). Trifluoroacetic anhydride (33.6 g, 0.16 mol) was cooled to −4 °C and to it was added D_2O (2.9 g, 0.145 mL, 99.8% d_2) very slowly. The initial reaction is extremely vigorous. When the addition was complete, the mixture was allowed to stand at 25 °C for 12 h. It was distilled at normal pressure under N_2, discarding the first 5 mL.

(*Z*)-CH(D)=C(OCOCH$_3$)CO$_2$Et. A solution of the palladium–vinyl complex (4.8 g, 5 mmol) in dry $(CaH_2)CH_2Cl_2$ (50 mL), containing $(CF_3CO)_2O$ (0.71 mL, 5 mmol) and CF_3COOD (5.6 mL, 75 mmol) was refluxed under dry N_2 for 24 h. The resulting orange solution was diluted with CCl_4 (50 mL) and the solvents were removed on a rotary evaporator. A further 50 mL of CCl_4 was added to the residue and the solvent was removed again, which gave an initial red oil which slowly began to deposit bright yellow crystals of a palladium complex. The crystals were slurried in CCl_4 (25 mL) and ether (50 mL) was added, whereupon the initial solid dissolved and lemon-yellow crystals immediately began to precipitate. This mixture was cooled at 5 °C for 12 h and the crystals were collected and washed with ether (2 × 25 mL). The filtrate was pumped to a yellow oil which yielded more lemon-yellow crystals. These were slurried with ether (5 mL) and collected and the solvent was removed to give a yellow oil. The last traces of the palladium complexes were removed by taking up the oil in ether and washing the ethereal solution with aqueous 0.1 M thiourea solution (5 × 25 mL) and once with water. The ethereal solution was dried (Na_2SO_4) and then was pumped down to an oil. (It is necessary to remove as much of the palladium complex as possible; otherwise the olefin polymerizes when distillation is attempted.)

Addition of triglyme (1 mL) to the residual oil and distillation under high vacuum (0.1 mm) directly into a dry ice–acetone cooled receiving flask gave a clear, colorless liquid consisting only of the required d_1 olefin and triglyme. If kept in this solution at 5 °C under N_2 the olefin is indefinitely stable and has no tendency to polymerize. The pure d_1 olefin can be recovered in 90% overall yield by washing an ethereal solution of the distillate with water (2 × 25 mL). After the ethereal extract is dried with Na_2SO_4, the pure olefin is obtained upon removal of the solvent and should be hydrogenated within a few days; otherwise the neat olefin may polymerize.

Cleavage Reaction Using [$^3H_1$]Trifluoroacetic Acid (CF$_3$CO$_2$T). Trifluoroacetic anhydride (25 g, 0.12 mol) was cooled to −4 °C and to it was added, very slowly, HTO (0.5 mL, 0.022 mol, 1 mCi/g) followed by H_2O (1.5 mL, 0.089 mol). The solution was stirred at 25 °C for 10 h and used without distillation in the next step.

(*Z*)-CH(T)=C(OCOCH$_3$)CO$_2$Et. The same procedure as previously described for the cleavage of the palladium–vinyl bond using deuterium was followed. Thus, the palladium–vinyl complex (9.53 g, 0.01 mol) was taken up in a solution of 12 mL (0.15 mol) of CF_3COOT as prepared above and $(CF_3CO)O$ (1 mL) in dry CH_2Cl_2 (95 mL). The mixture was refluxed for 18 h. After distillation and removal of the triglyme, there was obtained 1.4 g (83%) of the labeled olefin.

Radioactivity Measurements. An 8-μL aliquot of the labeled CF_3COOT as prepared above was dissolved in 20.00 mL of scintillation cocktail (toluene–PPO–POPOP) containing 8 μL of unlabeled olefin. This solution had an average activity of 830 cpm/μmol.

An 8-μL aliquot of the neat labeled olefin from the cleavage reaction above was dissolved in the scintillation cocktail together with an 8-μL aliquot of unlabeled CF_3COOH. The average activity of this solution was 14.2 cpm/μmol.

Asymmetric Catalytic Deuteration of (*Z*)-CH(T)=C(OCOCH$_3$)COOEt. The procedure was similar to that previously described.[8,9] To a solution of [Rh((*R*)-prophos)(NBD)]ClO_4·½CH_2Cl_2 (0.15 g) in dry, freshly distilled ($LiAlH_4$), and degassed THF under an atmosphere of D_2 was injected the labeled olefin, (*Z*)-CH(T)=C(OCOCH$_3$)COOEt (1.1 g), in THF (5 mL). The solution was stirred at 25 °C under 1 atm of D_2 for 12 h. The reaction mixture was worked up in the usual way[8,9] and the product, CH(D)(T)C(D)(OCOCH$_3$)COOEt (1.1 g), was isolated by molecular distillation.

Optically Pure Chiral Methyl Chiral Lactic Acid. The (*S*)-ethyl *O*-acetyllactate derived from the above asymmetric deuteration reaction was 81% optically pure.[9] The lactic acid derived from it was prepared and purified as follows. The labeled (*S*)-ethyl *O*-acetyllactate (3.0 g) from the reduction above was stirred with 2.5 equiv of a 10% NaOH solution at 25 °C for 2 h. The now clear solution was acidified to pH 4 using 12 M HCl and the water was removed under reduced pressure to give an oil and solid NaCl. Dry ether was added to the residue and the NaCl was collected and washed with ether. The ether extract was pumped down to give a colorless oil which was again taken up in ether and filtered to remove the last traces of NaCl. The ether was removed and the oily residue was pumped at 0.1 mm at 40–45 °C to remove the last traces of solvent and the acetic acid.

The resulting viscous oil was dissolved at 30 °C in 1.4 ml of a 1:1 (by volume) solution of diethyl ether/diisopropyl ether; both ethers were freshly distilled from $LiAlH_4$. The solution was held at 5 °C until colorless needles of the lactic acid formed. (Crystallization may be induced by seeding the solution with pure lactic acid.) The optically pure lactic acid (1 g, 60%) was collected and washed with cold 1:1 diethyl ether/diisopropyl ether (2 mL) and was dried in vacuo. This material is very weakly hygroscopic and further crystallization does not change either its specific rotation or its melting point. The values of the rotations and melting points given below are compared with those of a recrystallized sample of lactic acid obtained from Sigma (given in parentheses): mp 53 °C (53 °C), $[\alpha]_D$ 1.39° (1.35°), $[\alpha]_{578}$ 1.51° (1.47°), $[\alpha]_{546}$ 1.93° (1.87°), $[\alpha]_{476}$ 5.69° (5.69°) (*c* 0.801, H_2O, 25 °C).

Determination of the Stereochemistry of the Labeled Olefins. Diels–Alder Reaction. Ethyl 2-acetoxyacrylate (20.8 g) and excess freshly cracked cyclopentadiene (11 g) were mixed and heated at 100 °C for 4 h under N_2 in a flask equipped with a dry ice condenser. The solution was cooled to 25 °C and stirred for 12 h. The reaction mixture was then distilled under reduced pressure giving the exo and endo Diels–Alder adducts as a colorless liquid (15.3 g, 52%, bp 110–116 °C 10 mm).

Hydrolysis of the Diels–Alder Adducts. The mixture of Diels–Alder adducts (7.1 g, 0.032 mol) was suspended in 20% NaOH solution (20 mL, 3 equiv) and the mixture was heated at 60 °C for 3.5 h under N_2. A brown-red solution resulted which was acidified to Congo red with 6 N HCl and then was continuously extracted with CH_2Cl_2 for 18 h. The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a slightly yellow crystalline solid which was dried in vacuo for 4 h. There was thus obtained 4.5 g (92%) of a mixture of endo and exo stereoisomers of the hydroxy acid.

Iodolactonization Reaction. The mixture of hydroxy acids (4.5 g, 0.029 mol) as prepared above was dissolved in hot water (30 mL), Norite (1 g) was added, and the mixture was warmed on a steam bath for 10 min and then filtered. A clear, slightly yellow solution resulted, which was neutralized with a 20% NaOH solution (6.0 mL, 1 equiv) and then diluted with a 5% $NaHCO_3$ solution (50 mL). A solution of KI_3 (5 g of I_2, 10 g of KI, and 30 mL of H_2O) was added dropwise to a stirred solution of the neutralized acids at 25 °C until the brown color persisted. This resulting solution was then continuously extracted with CH_2Cl_2 for 8 h. The aqueous layer was set aside. The pink-brown organic layer was mixed with $MgSO_4$ and solid $Na_2S_2O_3$ to give a clear, colorless solution. After filtration, the CH_2Cl_2 was removed to give the white, crystalline iodolactone. This material was recrystallized from CH_2Cl_2/hexane giving colorless plates (3.4 g), mp 121.5 °C.

Anal. Calcd for $C_8H_9O_3I$: C, 34.3; H, 3.2; I. 45.3. Found: C, 34.2; H, 3.0; I. 45.2.

The aqueous layer obtained after extraction of the iodo lactone was acidified to Congo red using 6 N HCl and then was extracted continuously with CH_2Cl_2 for 12 h. The organic phase was stirred with $MgSO_4$ and solid $Na_2S_2O_3$. Removal of the solvent gave the exo hydroxy acid as white crystals which were recrystallized from CH_2Cl_2/hexane to give colorless prisms (2.0 g), mp 113–114 °C.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.3; H, 6.5. Found: C, 62.1; H, 6.4.

Regeneration of $[Pd(PPh_3)_4]$. The yellow complex obtained from the palladium cleavage reaction, $[Pd(PPh_3)_2(Br)_x(OCOCF_3)_{2-x}]$ (15.2 g), and triphenylphosphine (19 g) were taken up in Me_2SO (150 mL) at 150 °C under N_2. A deep red solution resulted. The oil bath was removed and $NH_2NH_2{\cdot}H_2O$ (3.0 g) was added dropwise to the stirred hot solution. Stirring was continued as the mixture was allowed to cool to 25 °C. The yellow crystals of $[Pd(PPh_3)_4]$ were filtered under N_2 and were washed with ethanol (3 × 50 mL) and then with ether (2 × 50 mL). The crystals (19 g, ~91%) were dried in vacuo and then were stored at 5 °C under N_2.

Proton Exchange of $BrCH_2OCOOEt$. A solution of CF_3COOD (12.9 g) and ethyl bromopyruvate (1.1 g) was treated with K_2CO_3 (0.05 g) and the resulting solution was kept at 70–75 °C under nitrogen for 40 h. The CF_3COOD was removed at 15 mm and the deuterated product, $CD_2BrCOCOOEt$ (1.0 g), was collected by bulb-to-bulb transfer under 0.1 mm at 55–65 °C.

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