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A Convenient Synthesis of Chiral Succinic Acid-d_2 By Catalytic Asymmetric Reduction Using a Ruthenium BINAP Catalyst

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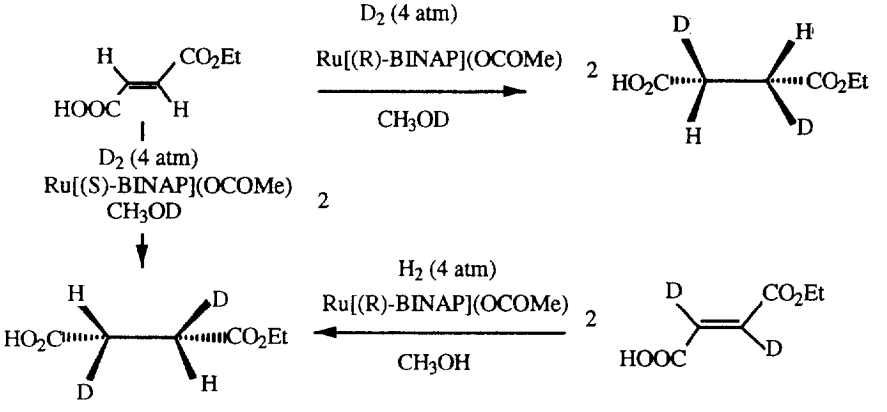
Abstract: The synthesis of (2R,3R) and (2S,3S) dideuteriosuccinic acid in 63 ± 10% enantiomeric excess by reduction of the half acid ester of ethyl fumarate from (R) and (S) BINAP ruthenium (II) diacetate complex, respectively, is reported. (2R,3R) and (2S,3S)-Dideuteriosuccinic acid has also been prepared from (R)-BINAP ruthenium (II) dicarboxylate complex directly in similar optical purity by reversing the sequence of introduction of the isotopic label.

2-Deuteriosuccinic and 2,3-dideuteriosuccinic acids have played a central role in the determination of configuration of molecules who owe their chirality to the presence of deuterium.[1] Both are available in high optical purities, easily modified chemically to a variety of other compounds[2] and have large specific rotations and CD spectra in the ultraviolet region. Chemical syntheses of (2R, 3R) and (2S,3S)-dideuteriosuccinic acids have been reported[3] as has an enzymatic preparation of the (2R,3R) enantiomer.[4] The chemical synthesis is hampered by the relatively low overall yield (3-5%) starting from commercially available 1,4-butynediol.

Noyori and coworkers[5,6] have reported that homogeneous hydrogenation of α,β or β,γ-unsaturated carboxylic acids in the presence of a catalytic amount of (R)- or (S)-[BINAP]Ru dicarboxylate complex affords the corresponding saturated products resulting from overall *cis* addition in high enantiomeric excess and quantitative chemical yields. A series of experiments are reported which indicate that methanol is the solvent of choice and that the degree of enantioselection is affected by the hydrogen pressure, type of substrate and double bond geometry. For α,β-unsaturated acids, hydrogen from dihydrogen was introduced into the α position and the second hydrogen incorporated into the β position originated from the solvent.[6,7]

We report here that catalytic reduction with deuterium of the half ethyl ester of fumaric acid-OD at 4 atm deuterium pressure in methanol-OD in the presence of Ru[(R)-BINAP]$(OCOCH_3)_2$, prepared according to the method of Noyori, Kitamura, and Tokunaga[8], proceeds in high chemical yield and affords the half ethyl ester of (2R,3R)-succinic-d_2 acid. Use of the air sensitive Ru catalyst prompted appropriate precautions in its handling. A solution of OD exchanged mono-ethyl fumarate in CH_3OD (25 mL) was prepared in a 200-mL Schlenk tube and added to solid Ru[(R)-BINAP]$(OCOCH_3)_2$ (112 mg, 0.121 mmol) in another 200-mL Schlenk tube under a flow of argon. The mixture was stirred until the ruthenium complex was completely dissolved. The resulting solution was then transferred to the glass bottle of the Parr hydrogenation apparatus with a cannula under

argon. The septum of the glass bottle was exchanged in a glove bag under Ar for a rubber stopper fitted with a steel valve. The glass reaction flask was then attached to a Parr hydrogenation apparatus by way of the steel valve and pressurized with deuterium to 4 atm. The solution was magnetically stirred at room temperature for 85 h. The solvent was removed under reduced pressure and mono-ethyl (2R,3R)-dideuteriosuccinate (2.2 g, 86.9% yield) was isolated by molecular distillation of the residue. The product was identified by ^{1}H and ^{13}C NMR spectra and by conversion to (2R,3R)-dideuteriosuccinic acid.[3] Using the (S)-[BINAP]Ru complex in this same procedure resulted in a mono-ethyl (2S,3S)-dideuteriosuccinate product as illustrated and characterized below.



The far-UVCD spectra of the succinic acids isolated from the (R)-BINAP ruthenium complex with the d_0-fumaric acid and from (2S,3S)(-)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol are shown in Figure 1 as spectra C and D, respectively. Since both have the same CD sign, the absolute configurations of the dominant product are likewise identical. The absolute configuration and sign of (2R,3R)-(-)-dideuteriosuccinic acid was previously assigned by Portsmouth *et al.*[4] and is consistent with the stereochemistry obtained from lithium aluminum hydride reduction of (2S,3S)(-)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol assuming inversion of configuration at each carbon. The predominant formation of the 2R,3R enantiomer requires preferential reduction of the *re-re* face of the fumarate. This is in contrast to the observed stereochemistry in the reduction of many other α, β-unsaturated carboxylic acids with[(R)-BINAP]Ru complex. For example, reduction of tiglic acid with [(R)-BINAP]Ru and D_2 in methanol-OD results in formation of (2R,3R)-2,3-dideuterio-2-methylbutanoic acid, reduction of the *si-si* face of the olefin. The substituent in the α- position appears to be very influential in affecting the stereochemistry of the reduction.

The optical purity of the succinic acid was determined by the magnitude of the CD spectra obtained from each respective source, the rotation of the (2S,3S)(-)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol precursor used, and the isotopic purity of the resulting dideuteriosuccinic acid as determined by integration of the H NMR spectrum of the half ester of the ethyl succinic acid and mass spectral analysis of the succinic anhydride derived from both sources.[10] The isotopic purities in the two samples derived from the two different sources were similar (deuterium incorporation approximately 90 %). An enantiomeric excess (e.e.) of 63 ± 10 % was obtained by correcting the CD at 210 nm for D for its e.e. and then ratioing it to the CD at 210 nm for compound C in Figure 1. The uncertainty reported was generated by using reasonable errors in the evaluation of the optical and isotopic purities.

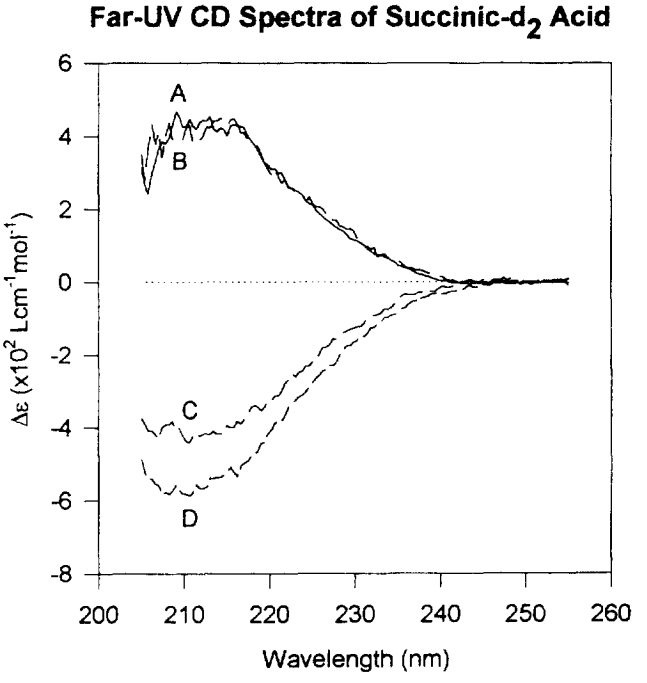


Figure 1. Far-UV CD spectra (in differential molar extinction units) for: A, succinic-d_2 acid (2.5 mg in 5 mL ethanol) prepared from monoethyl fumarate-d_2 and [(R)-BINAP]Ru complex; B: succinic-d_2 acid (1.25 mg in 5 mL ethanol) prepared from monoethyl fumarate-d_0 and [(S)-BINAP] Ru complex; C: succinic-d_2 acid (1.59 mg in 5 mL ethanol) prepared from monoethyl fumarate-d_0 and [(R)-BINAP]Ru complex; D: succinic-d_2 acid (1.41 mg in 5 mL ethanol) prepared from (2S,3S)(-)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol.

To eliminate the possibility that the observed UV CD spectra is an artifact resulting from the chiral BINAP catalyst, a series of experiments were conducted using [(R)-BINAP]Ru complex in which the sequence of introduction of the isotopic label was reversed. The mono-ethyl ester of fumaric-d_2 acid, prepared by reduction of diethyl acetylene dicarboxylate with Lindlar's catalyst, isomerization of the diethyl maleate-d_2 to diethyl fumarate-d_2 with I_2 and controlled saponification of the ester, afforded ethyl fumaric-d_2 acid, contaminated with a small amount of mono-ethyl succinate-d_4 (11 %). The mono ethyl (2R,3R)-dideuteriosuccinate isolated was converted to (2R,3R)-dideuteriosuccinic acid by treatment with sodium hydroxide. The CD spectrum of the succinic acid which was isolated (spectrum A) is of opposite sign to the spectrum of the sample prepared from mono-ethyl fumarate with D_2 in methanol-OD and the [(R)-BINAP]Ru complex (spectrum C), but similar to that prepared from the [(S)-BINAP]Ru complex (spectrum B). In addition, the optical purity determined from the UV CD spectrum and corrected for the chemical and isotopic purity of the precursor was identical, within the experimental uncertainty, to the value obtained above. This suggests the absence of a substantial isotope effect in the step leading to the asymmetric reduction.

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