(1S,2R,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acrylate (2c). To a solution of 2.5 g (10.8 mmol) of alcohol **2a**, 0.19 g (1.52 mmol) of 4-(dimethylamino)pyridine, and 2.19 g (21.6 mmol) of triethylamine in 100 mL of dichloromethane at 0 °C was slowly added 1.96 g (21.6 mmol) of acryloyl chloride. The mixture was stirred at 0 °C for 1.5 h and then 20 mL of saturated $NaHCO_3$ solution was added. The layers were separated and the aqueous layer was extracted with three 40-mL portions of dichloromethane. The organic layers were combined, dried (4-Å molecular sieves), and concentrated. The crude product was filtered through a short column of silica gel (Skelly-B–EtOAc, 50:1) to yield 2.80 g (91%) of acrylate: ^1H NMR ($CDCl_3$) 7.35–6.90 (m, 5 H, aromatic CH's), 6.27-5.40 (m, 3 H, $HC{=}CH_2$), 5.12 (dt, J = 9 Hz, J = 4 Hz, 1 H, CHO), 1.33 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 0.97 (d, J = 7.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) 164.8, 150.8, 129.4, 129.1, 127.9, 125.5, 125.1, 71.1, 50.9, 40.0, 38.3, 31.2, 27.4, 27.1, 26.0, 21.6, 18.6; IR (CH_2Cl_2) 1710 (C=O) cm^{-1}; mass spectrum, m/e calcd for $C_{19}H_{26}O_2$ 286.1933, obsd 286.1941.

(1S,2R,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Pyruvate (2d). To a solution of 1.62 g (6.99 mmole of epientphenmenthol (**2a**) in 60 mL of pyridine was slowly added 2.23 g (20.9 mmol) of freshly prepared pyruvyl chloride at −10 °C. The reaction mixture was stirred under nitrogen at room temperature for 16 h. The mixture was then diluted with 75 mL of dichloromethane and washed successively with 2 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried (4-Å molecular sieves) and concentrated to afford 2.48 g of a mixture of the acetate and pyruvate esters. The desired pyruvate was isolated by preparative HPLC (Skelly-B–EtOAc, 20:1) to give 1.08 g (51%): ^1H NMR ($CDCl_3$) 7.38–6.93 (m, 5 H, aromatic CH's), 5.17 (m, 1 H, CHO), 2.05 (s, 3 H, $CH_3C{=}O$), 1.32 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 0.95 (d, J = 7 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) 191.1, 159.3, 150.7, 128.1, 125.5, 73.7, 50.7, 39.9, 38.0, 31.0, 28.4, 27.3, 26.3, 24.5, 21.2, 18.6; IR ($CHCl_3$) 1740 (C=O), 1725 (C=O) cm^{-1}.

(1S,2R,5R,2'S)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl 2-Hydroxy-4-octenoate (2e). To a solution of 1.991 g (6.5 mmol) of the hydrate of in 30 mL of dichloromethane at −78 °C was added dropwise 2.87 g (11 mmol) of tin tetrachloride. The mixture was stirred at −78 °C (under N_2) for 10 min and the 1.64 g (19.5 mmol) of 1-hexene was then added. After a further 6 h at −78 °C, 1.01 g (10 mmol) of triethylamine was added. The mixture was washed with water, dried (4-Å molecular sieves), and concentrated to yield 6.68 g (88%) of crude ene adduct. Analysis of the crude product by HPLC and showed that it is at least 97% pure. The product was purified by prep HPLC to give 1.58 g of pure compound **2e**: yield 65%; ^1H NMR ($CDCl_3$, 200 MHz) 7.37–7.06 (m, 5 H, aromatic CH's), 5.53–5.17 (m, 2 H, CH=CH), 5.08 (dt, J = 10.5 Hz, J = 4.4 Hz, 1 H, $CHOC{=}O$), 3.37 (q, J = 6 Hz, 1 H, $CHC{=}O$), 2.62 (d, J = 6 Hz, 1 H, OH), 1.33 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 0.97 (d, J = 7.4 Hz, 3 H, CH_3), 0.87 (t, J = 7.4 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) 173.8, 151.0, 133.9, 128.0, 125.4, 124.2, 72.4, 69.8, 50.9, 39.7, 38.4, 37.2, 34.7, 31.2, 28.4, 27.4, 24.9, 22.5, 21.3, 18.6, 13.6; mass spectrum, m/e calcd for $C_{24}H_{36}O_3$ 372.2664, obsd 372.2671.

(1S,2R,5R,2'S)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl *endo*-2-Bicyclo[2.2.1]heptanecarboxylate (2f). To a solution of 0.916 g (3.2 mmol) of acrylate **2c** in 50 mL of dichloromethane at 0 °C was added 0.911 g (4.8 mmol) of titanium tetrachloride followed after 45 min by 1.06 g (16 mmol) of freshly distilled cyclopentadiene. After 4 h the reaction was quenched by the addition of 10 mL of water. The aqueous layer was separated and washed with three 25-mL portions of ether. The organic layers were dried and concentrated to afford 1.10 g of crude adducts. The endo diastereomer **2f** was isolated by preparative HPLC in 81% yield: ^1H NMR ($CDCl_3$, 200 MHz) 7.40–7.08 (m, 5 H, aromatic), 6.13 (d of d, J = 3.2 Hz, 1 H, C=CH), 5.94 (d of d, J = 6.0, 3.2 Hz, 1 H, CH=C), 5.02 (d of t, J = 8.4, 5.0 Hz, 1 H, CH), 3.11 (br s, 1 H, CHCH=C), 2.83 (br s, 1 H, CHC=C), 2.56 (d of t, J = 9.5, 4.2 Hz, 1 H, $CHC{=}O$), 0.93 (d, J = 7.4 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) 173.8, 150.7, 132.7, 132.1, 127.9, 125.7, 125.3, 71.3, 50.4, 49.5, 45.5, 43.7, 42.5, 40.2, 38.1, 31.1, 29.5, 27.4, 27.2, 27.0, 26.4, 21.7, 19.1; IR ($CHCl_3$) 1720 (C=O) cm^{-1}.

(1S,2R,5R,2'S)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl 2-Phenyl-2-hydroxypropionate (2g). To a solution of 0.977 g (3.3 mmol) of the pyruvate **2d** in 20 mL of dry ether at −78 °C was added 1.2 mL of a 3.0 M (3.6 mmol) solution of phenylmagnesium bromide in ether. After the reaction mixture had been stirred under nitrogen at −78 °C for 6 h, it was quenched with 8 mL of saturated NH_4Cl solution. The ethereal layer was separated and the aqueous layer was extracted with three 50-mL portions of ether. The organic layers were combined, dried (4-Å molecular sieves), and concentrated to give 1.19 g of crude material. The Grignard addition products were isolated by preparative HPLC to afford 0.974 g (78%) of a mixture of two diastereoisomers differing in configuration at C2' in a ratio of 86:14.

For the major isomer 2'*R*: ^{13}C NMR ($CDCl_3$) 174.5, 150.0, 143.0, 128.1, 128.0, 127.5, 125.6, 125.5, 125.4, 125.2, 75.6, 74.4, 49.9, 40.1, 37.1, 30.7, 27.3, 26.5, 26.2, 21.5, 19.1.

(2S)- and (2R)-1,2-Dihydroxy-*trans*-4-hexene (3). To a solution of 2.56 g (6.88 mmol) of **1e** in 70 mL of THF at −78 °C was slowly added 27 mL a 1.0 M (27 mmol) hexane solution of diisobutylaluminum hydride. The mixture was allowed to slowly warm up to room temperature over a period of 16 h. The mixture was then cooled to 0 °C and 15 mL of methanol was added to destroy any excess amount of diisobutylaluminum hydride. After 15 mL of water was added, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and extracted with three 50-mL portions of ether. The ethereal extracts were combined and washed with saturated sodium chloride solution. The organic layer was separated, dried (4-Å molecular sieves), and concentrated to give 2.20 g of crude product. The desired *S* diol was separated from 8-phenylmenthol by preparative HPLC (Skelly-B/EtOAc = 1:1) to yield 0.415 g (52%) of **3(2S)** that was further purified by simple vacuum distillation: ^1H NMR ($CDCl_3$, 200 MHz) 5.64–5.30 (m, 2 H, CH=CH), 3.80–3.58 (m, 2 H, CH_2O), 3.55–3.37 (m, 1 H, CHO), 3.18 (br s, 2 H, OH), 2.18 (t, J = 6.3 Hz, 2 H, CH_2), 2.0 (q, J = 7.4 Hz, 2 H, CH_2), 1.50–1.28 (m, 2 H, CH_2), 0.9 (t, J = 6.9 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) 134.4, 125.4, 71.9, 66.3, 36.8, 34.8, 22.6, 13.7; IR (CH_2Cl_2) 3040–3695 (OH) cm^{-1}; $[\alpha]_D$ −11.5° (EtOH).

The enantiomer, **3(2R)**, was obtained in an analogous fashion from 0.914 g of **2e** in 52% yield with ^1H NMR, ^{13}C NMR, and infrared spectra identical with those for **3(2S)**: $[\alpha]_D$ +11.1° (EtOH).

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A Study of the Catalytic Deuteration of Maleic and Fumaric Acids and Derivatives with Palladium on Carbon

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Catalytic deuteration of maleic and fumaric acids and of the corresponding esters with Pd/C is an important and useful method for the stereospecific incorporation of vicinal deuterium.[1-11] Reduction of fumaric and maleic acids and

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(3) Chickos, J. S.; Alul, R.; Baush, M. *J. Org. Chem.* **1981**, *46*, 3559. Annamalai, A.; Keiderling, T. A.; Chickos, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 6254.
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Table I. Reduction of Diethyl Fumarate and Diethyl Maleate with Deuterium. Analysis of the Corresponding Dideuteriosuccinic Anhydride

expt[a]	conditions	parent ion	relative intensity[b]	deuterium analysis	
				MS	NMR[c]
	Diethyl Fumarate				
1	5% Pd/C, ethyl acetate, room temp, ~1.5 atm D_2	d_0	0.01		
		d_1	0.10	1.9 ± 0.04	1.9 ± 0.06
		d_2	1.0		
		d_3	0.01		
5	5% Pt/C, ethyl acetate, room temp, ~1.5 atm D_2	d_0	0.2		
		d_1	0.39	1.57 ± 0.04	1.56 ± 0.04
		d_2	1.0		
		d_3	0.04		
		d_4	0.02		
	Diethyl Maleate				
6	5% Pd/C, ethyl acetate, room temp, ~1.5 atm D_2	d_0	0.04		
		d_1	0.16	1.89 ± 0.04	1.92 ± 0.06
		d_2	1.0		
		d_3	0.08		
		d_4	0.01		
10	5% Pt/C, ethyl acetate, room temp, ~1.5 atm D_2	d_0	0.89		
		d_1	0.97	1.10 ± 0.04	1.12 ± 0.06
		d_2	1.0		
		d_3	0.09		
		d_4	0.01		

[a] Experiments are numbered to correspond with experimental data available in the supplementary material. [b] Corrected for background and ^{13}C contributions. [c] NMR analysis on the corresponding ethyl esters.

their simple esters has been shown unequivocally to proceed by cis addition of deuterium with a high degree of stereoselectivity by infrared,[1] NMR,[4] and structural studies.[2,3]

Yet despite the interest in and importance of this reduction in providing isotopically substituted stereochemical handles, a systematic study of the extent of deuteration of these substrates over the variety of experimental conditions that have been used by different laboratories has not been reported. The fact that dialkyl succinates do not exhibit a parent ion region when studied by electron impact mass spectroscopy is likely one reason for this. Some unusual deuterium substitution patterns we observed in cyclobutane-d_2 derived from these materials, prompted us to systematically investigate the catalytic reduction of maleic and fumaric acids and the corresponding diethyl esters. We have examined the effects of solvent, temperature, and, to a limited extent, catalyst on the reduction. The results of these studies are summarized in this report.

Results

Analysis of the extent of deuteration in diethyl succinate-d_2 derived from diethyl maleate and diethyl fumarate was achieved by both proton NMR integration of the corresponding diethyl succinates and by mass spectrometric analysis of the parent ion region of the corresponding succinic-d_2 anhydrides derived from them. All other reductions were analyzed by mass spectroscopy on the resulting succinic-d_2 anhydrides. The results of these investigations are summarized in Tables I and II and in the supplementary material available (see paragraph at the end of paper). The data listed in Tables I and II has been corrected for background and natural abundance ^{13}C. Details about these corrections are available in the Experimental Section.

Examination of the results in Tables I and II indicates that factors such as solvent, temperature, catalyst, and substrate are important variables in controlling the extent of deuterium incorporated in these reductions. In reduction of diethyl fumarate and diethyl maleate, comparisons of the amount of deuterium incorporated in experiments 1 and 5 clearly demonstrate the superiority of Pd/C over Pt/C in these reductions. These results are in sharp contrast to the results obtained in the reduction of unsaturated hydrocarbons.[12] Temperature also appears to be an important variable in affecting the extent of deuteration in these reductions. Elevated temperatures, similar to conditions used previously for reduction of maleic and fumaric acids appears to decrease the amount of label incorporated but without loss in stereochemistry of the d_2 species.[4]

Reduction is clearly less sensitive to solvent. Results obtained for reactions of neat liquids, in ethyl acetate, ethanol, acetic acid, water, and D_2O are quite similar. The solvent, however, does appear to be a major source of the hydrogen which becomes incorporated in the molecule. This is clearly evident by comparison of results obtained for reductions of maleic and fumaric acids in ethyl acetate and D_2O (experiments 15, 18, 19, and 22).

A comparison of the results obtained for reduction of the esters to the corresponding carboxylic acids clearly indicate that the esters give the best overall incorporation of deuterium. A careful examination of the isotopic distribution within each parent ion series also reveals one other interesting feature. In addition to a d_1 peak, which is observed in each succinic-d_2 anhydride regardless of origin, *meso*-succinic-d_2 anhydride derived either from maleic acid or the corresponding ethyl and methyl esters also contains a significant d_3 peak of approximately 10%. This ion is completely absent in the results obtained from reduction of the corresponding fumarates. It was in fact the presence of a significant d_3 peak in *cis*-dideuteriocyclobutane derived from the reduction of diethyl maleate (and the absence of such a peak in *trans*-1,2-dideuteriocyclobutane) which prompted us to investigate the factors which affect this reduction. The discussion which follows

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Table II. Reduction of Fumaric and Maleic Acids and Maleic Anhydride with Deuterium. Analysis of the Corresponding Dideuteriosuccinic Anhydrides

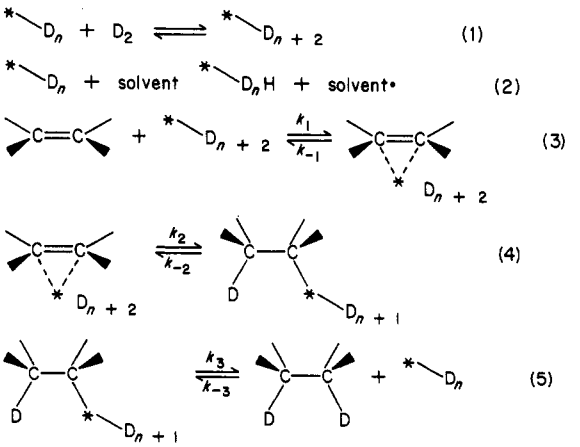
expt[a]	conditions	parent ion	relative intensities[b]	deuterium analysis MS
		Fumaric Acid		
15	5% Pd/C, ethyl acetate, room temp, ~1.5 atm D_2	d_0	0.01	
		d_1	0.13	1.86 ± 0.04
		d_2	1.0	
		d_3	0	
		d_4	0	
16	5% Pd/C, ethyl acetate, 70 °C, ~1.5 am D_2	d_0	0.20	
		d_1	0.34	1.54 ± 0.04
		d_2	1.0	
		d_3	0.03	
		d_4	0	
18	5% Pd/C, D_2O, room temp ~1.5 atm D_3	d_0	0	
		d_1	0.01	
		d_2	1.0	2.05 ± 0.04
		d_3	0.02	
		d_4	0.02	
		Maleic Acid		
19	5% Pd/C, ethyl acetate, room temp, ~1.5 atm D_2	d_0	0.07	
		d_1	0.17	1.8 ± 0.04
		d_2	1.0	
		d_3	0.05	
		d_4	0	
20	5% Pd/C, ethyl acetate, 70 °C, ~1.5 atm D_2	d_0	0.12	
		d_1	0.35	1.8 ± 0.04
		d_2	1.0	
		d_3	0.03	
		d_4	0.02	
22	5% Pd/C, D_2O, room temp, ~1.5 atm D_2	d_0	0.03	
		d_1	0.04	2.0 ± 0.04
		d_2	1.0	
		d_3	0.05	
		d_4	0.02	
		Maleic Anhydride		
23	5% Pd/C, ethyl acetate, room temp, ~1.5 atm D_2	d_0	0.01	
		d_1	0.04	1.95 ± 0.04
		d_2	1.0	
		d_3	0.01	
		d_4	0	
26	5% Pt/C, ethyl acetate	*c*	*c*	*c*

[a] Experiments are numbered to correspond with experimental data available in the supplementary material. [b] Correctedfor background and ^{13}C contributions. [c] No absorption of D_2.

focuses on a hypothesis which was invoked to explain the formation of this species and the experiments which we devised to test this hypothesis.

The generally accepted mechanism for reduction of olefins is outlined in Scheme I.[12-15] The asterisk in this

Scheme I



scheme refers to the catalyst which is of unknown composition. Reversibility in each of these steps depends upon experimental conditions. The high degree of stereoelectivity observed in the reduction of this system however requires k_{-1}, k_{-2}, and k_{-3} in steps 3–5 to be either small or

(12) Augustine, R. L.; Yaghmaie, F.; Van Peppen, J. F. *J. Org. Chem.* **1984**, *49*, 1865. Mitsui, S.; Shoinoya, M.; Gohke, K.; Watanabe, F.; Imaizumi, S.; Senda, Y. *J. Catal.* **1975**, *40*, 372. Mitsui, S.; Imaizumi, S.; Nanbu, A.; Senda, Y. *Ibid.* **1975**, *36*, 333. Mitsui, S.; Gohke, K.; Saito, H.; Nanbu, A.; Senda, Y. *Tetrahedron* **1973**, *29*, 1523. Mitsui, S.; Senda, Y.; Suzuki, H.; Sekiguchi, S.; Kumayai, Y. *Ibid.* **1973**, *29*, 3341. Nishimura, S.; Sakamoto, H.; Ozawa, T. *Chem. Lett.* **1973**, 855.

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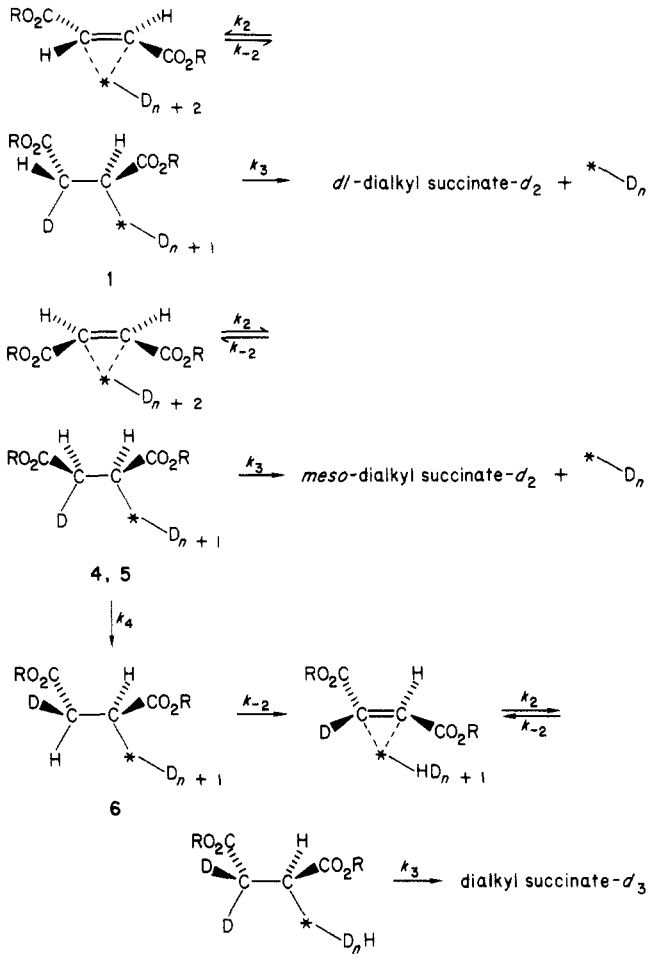
(14) Horuite, I.; Polanyi, M. *Trans. Faraday Soc.* **1934**, *30*, 1164.

(15) Burwell, R. L. *Catal. Rev.* **1972**, *7*, 25.

(16) It is possible that only certain sites on the catalyst are capable promoting the reverse process associated with k_{-2}. For a discussion of how the nature of the catalyst may affect reversibility and how solvents may affect this role, see: Augustine, R. L.; Warner, R. W.; Melnick, M. J. *J. Org. Chem.* **1984**, *49*, 4853 and references cited.

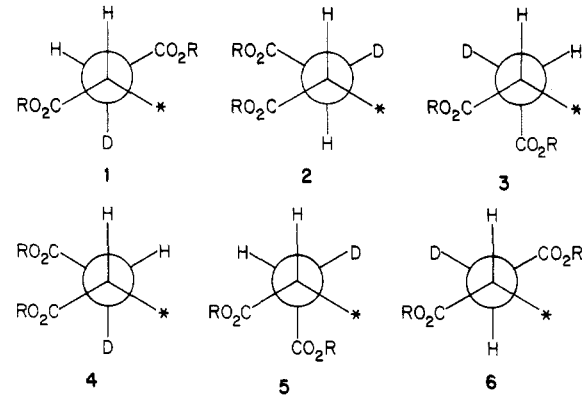
Scheme II



highly stereoelective. Failure to incorporate deuterium into diethyl succinate under the reaction conditions requires the deadsorption of product from the catalyst to be irreversible. The presence of small amounts of succinate-d_1 in reduction of both acids and esters in excess of the isotopic purity of the deuterium used, requires the presence of a competitive source of hydrogen. The results in Tables I and II suggest the presence of a step such as 2 as the proton source. It is likely that this is the process which shows the most sensitivity to temperature.

A possible explanation that can explain why only maleates consistently form small amounts of d_3 species while fumaric acid and derivatives do not, can be rationalized by postulating that step 4 is reversible. Scheme II follows the course of reduction of fumarates and maleates according to the steps outlined in Scheme I in detail beginning with step 4. Insertion of deuterium into the Pd–olefin complex in the fumarate series produces a substituted alkylpalladium intermediate. If we assume that conformation interconversion is fast and that of all conformations possible (1–3 Scheme III) **1** is most stable, reversibility in step 4, associated with k_{-2}, will regenerate the original olefin–metal complex. Alternatively, insertion of deuterium into palladium carbon bond produces *dl*-succinate-d_2. In the maleate series, a similar series of steps initially produces an intermediate in step 4, **4** or **5**, which is both structurally and conformationally different from **1**. Allowing this conformation to relax to the most stable form, produces **6**, which neglecting isotopic substitution, is conformationally identical with **1**. Reversibility associated with k_{-2} in this conformation is now suited for removal of hydrogen rather than deuterium. To the extent that k_4k_{-2} is competitive with k_3, it is possible to explain why production of succinate-d_3 occurs is only the maleate series.[15] The hydrogen which is removed as a result of reversal (k_{-2}) enters the pool and may ultimately become incorporated into another maleate molecule, thereby also increasing the relative amounts of succinate-d_1 formed in the reduction of maleates. Subtraction of the intensity of the d_3 species from the d_1 species in Tables I and II gives a resulting intensity for the d_1 species which compares well with the amount of d_1 species obtained in the fumarate series.

Scheme III



To test the usefulness of this hypothesis, the reduction of a maleate derivative that could not undergo bond rotation in step 4 was chosen. Reduction of maleic anhydride appeared to be a good test case. The results of these investigations are reported in Table III. Over the variety of conditions tested, the isotopic distributions obtained in this reduction reproduced the results obtained in the fumarate series better than those of the corresponding maleates. We conclude from these results that this model adequately explains the dependence of isotopic substitution on stereochemistry. Differences in the total amount of isotope introduced in maleic anhydride and the other maleates are likely a reflection of differences in the rates of reduction relative to rates of hydrogen transfer occurring with solvent.

Finally, we return to the assumptions regarding the most stable palladium alkyl conformation in the series **1–3** and **4–6** (Scheme III). Clearly the experimental results can only be explained if **1** and **6** are most stable. Isotopic distributions predicted from reversibility (associated with k_{-2}) originating from conformations **3** and **5** (produced from fumarates and maleates, respectively) are reversed from those experimentally observed, while no differentiation between fumarate and maleates is predicted from reversibility associated with complexes **2** and **4**. In view of the anticipated length of the carbon–palladium bond,[17] assignment of structures **1** and **6** as the most stable conformations is a reasonable assumption.

Experimental Section

Infrared Spectra were recorded on a PE 780 spectrometer equipped with a data station. Liquid samples were recorded as thin films, and solids were run as Nujol mulls. NMR spectra were recorded on a Varian T-60 NMR spectrometer as neat liquids. Mass spectra were recorded on a Picker AEI MS-12 mass spectrometer.

Materials. Commercially available samples (reagent grade when available) were used without further purification. Ethyl acetate was dried and distilled before use. Catalysts were obtained

(17) The carbon–palladium bond length in Pd(II) complexes is roughly 2 Å. Wells, A. F. "Structural Inorganic Chemistry", 5th Ed.; Clarendon Press: Oxford, 1984. Brown, I. D.; Brown, M. C.; Hawthorne, F. C. "BIDICS", Institute for Materials Research, McMaster University: Hamilton, Canada, 1981; p 23.

from Matheson Colemen and Bell (5% Pd/C) and Engelhard Industries (5% Pt/C). Deuterium was obtained from Matheson (99.5% isotopic purity).

Catalytic Reduction. The following procedure is illustrative of the manner in which reduction by deuterium was carried out. A lecture bottle of deuterium gas was connected to a manifold which in turn was connected to a vacuum line, a mercury manometer, and the reaction vessel. The reduction vessel consisted of an Erlenmeyer flask equipped with a standard taper inner connector (24/40). Stirring was achieved magnetically. For reactions above ambient, a water-cooled condenser was inserted between the manifold and the reaction flask. A positive pressure of deuterium was achieved by adjusting the mercury level in a mercury manometer (an inverted buret attached to a leveling bulb by means of Tygon tubing). Typically, sample, solvent, and catalyst were combined and evacuated several times, and then the sample was reduced. Reduction was continued until uptake of deuterium ceased. Reductions at positive pressures and at room temperature were generally complete within an hour. Longer reaction times were encountered in reduction of insoluble samples or at pressures below 1 atm of pressure.

Reduction of Dialkyl Butenedioates. Typically, ester (1.5 g), solvent (10 mL), and catalyst (80 mg) were reduced. All alkyl succinates were first isolated by filtration and evaporation of the solvent and then purified by vacuum distillation. Yields exceeded 80%. No other products were indicated by NMR analysis of the neat liquids. Hydrolysis of the alkyl succinates were achieved by stirring with KOH at room temperature. Ester (80 mg), water (5 mL), and KOH (1.1 g) were stirred at room temperature. When only one phase remained (reaction time, 1 h) the solution was acidified with 6 M HCl and repeatedly extracted with ether (6 × 50 mL). The acids isolated upon evaporation were recrystallized from ethyl acetate (0.3 g recovered).

Reduction of Butenedioic Acids. Reduction of the butenedioic acids (typically 600 mg, 10 mL of solvent, 80 mg of catalyst) was achieved as described above with the exception that both reactants and products were only slightly soluble in the solvents used. Reductions were generally slower and were allowed to proceed until absorption of deuterium ceased. Products were isolated by filtration followed by recrystallization in ethyl acetate (typically, 300 mg recovered, mp 188–190 °C). Hot filtration removed the catalyst.

Conversion to Succinic-d_2 Anhydride. Succinic-d_2 acid was converted to the anhydride be refluxing in excess acetyl chloride. Typically succinic acid (80 mg) was refluxed in acetyl chloride (1–2 mL) until all the acid dissolved (approximately 2 h). The resulting solution was transferred to the bottom portion of a small sublimer and the solution allowed to evaporate overnight in a hood. The residual succinic anhydride was sublimed [60 °C, (1 Pa)] and the parent ion region was analyzed by mass spectroscopy.

Reduction of Maleic Anhydride. Maleic anhydride was reduced in a similar manner to that previously described. Unlike previous reductions however, some unreacted maleic anhydride was usually detected in the isolated succinic anhydride. Recrystallization of the recovered succinic anhydride from ethyl acetate was not very effective in removing the maleic anhydride. This suggests why in large-scale reductions (25–50 g) absorption of deuterium ceased before complete reduction was achieved. It is likely that maleic anhydride become incorporated in the solid succinic anhydride and effectively removed from solution during reduction. In small-scale reductions (maleic anhydride, 2.6 g; 5% Pd/C, 400 mg; ethyl acetate, 10 mL), reduction was near complete, and the succinic-d_2 anhydride was isolated by filtration of the suspended solid followed by recrystallization from ethyl acetate (recovered 1.7 g; mp 117–120 °C; authentic sample, mp 118–120 °C). The catalyst was removed by hot filtration. The parent ion region was identical with that of succinic anhydride prepared from succinic-d_2 acid with the exception that a small peak could be observed from maleic anhydride at m/e 98. No evidence of deuterium incorporation into the maleic anhydride was ever observed, even when the peaks at m/e 98 were amplified. Samples of succinic-d_2 anhydride which were not recrystallized before mass spectral analysis indicated the presence of trace amounts of other materials. Investigation of these materials was not pursued.

The stereochemistry of reduction of maleic anhydride was confirmed to proceed by way of cis addition of deuterium by first conversion to *meso*-diethyl succinate-d_2[18] and then to *cis*-1,2-dideuteriocyclobutane.[2] The reduction of maleic anhydride appears the best way of preparing *meso*-succinate-d_2 derivatives.

Control Experiments. The following control experiments were performed to evaluate the reliability of these experiments. First, succinic acid and ester were shown not to incorporate deuterium under the reaction conditions.

Hydrolysis of succinic anhydride-d_2 with water afforded succinic-d_2 acid. This was recrystallized in ethyl acetate and recyclized with acetyl chloride as described above. The recovered succinic anhydride-d_2 indicated the absence of any exchange processes which could lead to the loss of deuterium and stereochemistry in the purification and cyclization of succinic-d_2 acid.

Corrections and Calculations. The corrected data reported in Tables I and II differ from the raw data in so far as they have been corrected for background and ^{13}C contributions to the parent ion region. A typical background correction was obtained in the mass region of interest, m/e 101–104, by noting that similar backgrounds were observed in the region m/e 98–108, regardless of whether succinic anhydride or succinic-d_2 anhydride was used, provided that both were prepared by similar routes. Commercial samples of succinic anhydride did not exhibit P − 1 and P − 2 peaks. Therefore, to simulate a typical background characteristic of this system, succinic acid was cyclized with acetyl chloride and the parent ion region examined. The relative intensities observed in this spectrum were used (relative to the intensity of the m/e 105 peak observed) to proportionately correct for background contributions at each mass in the region m/e 101–104. Corrections for background in this mass range (relative to an intensity of 0.07 at m/e 105 and after subtraction of appropriate ^{13}C contributions (0.045) for each respective P + 1 peak), resulted in corrections of the following: m/e 101, 0.015; 102, 0.04; 103, 0.03; 104, 0.04. Peaks at m/e 100 were not corrected. Observed peaks at this mass were generally small. Corrected data in Tables I and II have been rounded off to the nearest hundredth and the average deviation of each entry (duplicate runs) were ±0.01. Corrections for the isotopic purity of the deuterium used (0.995) were ignored.

The amount of deuterium incorporated, the last column in each table, was calculated by the following relationships:

analysis by mass spectroscopy

succinic anhydride-d_2

$$\text{deuterium incorporation} = \sum_{\substack{n=1 \\ j=P-1}}^{\substack{j=P+2 \\ n=4}} nI_j \Big/ \sum_{j=P-2}^{j=P+2} I_j$$

analysis by NMR

diethyl succinate-d_2

$$\text{deuterium incorporation} = 2\left[1 - \frac{2M - OM}{OM}\right]$$

dimethyl succinate-d_2

$$\text{deuterium incorporation} = 2\left[1 - \frac{3M - OM}{OM}\right]$$

In the analysis by mass spectroscopy, n_i refers to the number of deuterium present in each corresponding parent ion in question, P − 1, P, ..., and I_j refers to the relative intensity following background corrections of each respective parent ion. For analysis by NMR, M and OM refer to the integrated intensities of the methylene hydrogens adjacent to the carboxyl and oxygen respectively.

Acknowledgment. I would like to thank Karim Al-Nawwar for the synthesis of *cis*-dideuteriocyclobutane from maleic anhydride and the National Science Foundation (CHE-8405386) for partial support.

(18) *meso*-Diethyl succinate-d_2 was prepared from *meso*-succinic-d_2 anhydride by refluxing in ethyl alcohol in the presence of benzene and sulfuric acid. Vogel, A. I. "A Textbook of Practical Organic Chemistry", 3rd ed.; Wiley: New York, 1966; p 386.

Registry No. Maleic acid, 110-16-7; fumaric acid, 110-17-8; diethyl maleate, 141-05-9; diethyl fumarate, 623-91-6; maleic anhydride, 108-31-6; succinic-d_2 acid, 91314-17-9; *cis*-succinic-d_2 anhydride, 80655-74-9; Pd, 7440-05-3; Pt, 7440-06-4.

Supplementary Material Available: Tables containing raw and corrected data for reduction of maleic and fumaric acids and derivatives over a variety of different experimental conditions are available (7 pages). Ordering information is given on any current masthead page.

Trimethylsilyl-Substituted Optically Active β-Lactams

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Introduction of funtionalized units at the C-3 position of β-lactams has become an increasingly interesting and worked over reaction. As part of a program devoted to the synthesis of β-lactams which would provide access to a variety of functionalized carbon units at the C-3 position by exchange of a feasible substituent, we turned our attention to the synthesis of β-lactams silylated at the C-3 carbon atom.

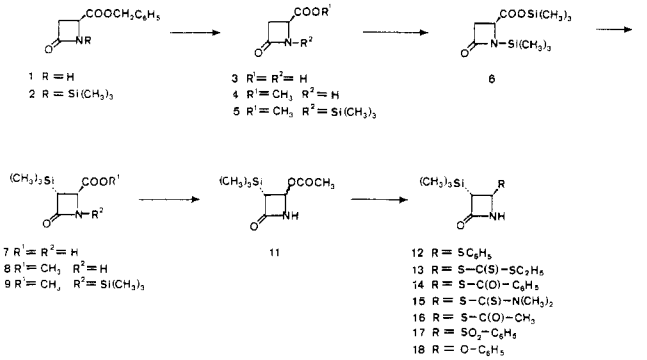
The evolution of the synthetic strategy employed for the approach was based on the following considerations: (1) the desire to develop a chiral stereocontrolled synthesis with regard to the C-3–C-4 substituents, (2) elaboration of a suitable C-4-substituted azetidinone derivative from the readily available azetidinone carboxylic acid benzyl ester which has already the correct absolute configuration at C-4, and (3) formation of a C-3–silicon bond with the hope of allowing preparation of analogues involving facile replacement of the trimethylsilyl unit.[1] Consequently, the general synthetic approach was outlined as depicted in Scheme I.

The synthesis of the benzyl ester **1** was executed essentially analogous to the report of Salzmann et al.[2] in which the chirality at C-4 was derived from L-aspartic acid. The debenzylation of **1** with hydrogen in the presence of palladium-on-carbon furnished the crystalline carboxylic acid.[2a-c] Racemization does not occur under those conditions.[2]

N-Silylation of β-lactam derivatives with chlorotrimethylsilane has been performed previously in the presence of base,[3] and furthermore a C-3 trimethylsilyl derivative has been found a useful precursor for the synthesis of 3-alkylidenazetidinones.[1] Application of hexamethyldisilazane (HMDS) in the presence of 2–5 mol % of saccharin as a catalyst[4] in refluxing chloroform caused clean formation (84–88%) of the *N*,*O*-bis(trimethylsilyl) derivative of the β-lactam carboxylic acid **6**.

The yield of **6** dropped to 48% without saccharin even after a reaction time of 4 h. The product was separated from excess of HMDS by distillation. Its extreme sensitivity toward moisture made working under an atmosphere of argon mandatory. The analytical and spectral data supported structure **6**.

Scheme I



Similarly, catalyzed N-silylation of the benzyl (**1**) and the methyl ester (**4**) respectively provided the corresponding N-silylated products **2** and **5** in yields of 78% and 86%. A lower yield (44%) of **2** was obtained starting from **1** and by using chlorotrimethylsilane in the presence of triethylamine. Here again, the superior effect of saccharin as catalyst was noted: no formation of product was observed after 2 h without saccharin, and a yield of only 57% was realized in the presence of catalytic amounts of ammonium sulfate.[4] Small samples of **2** could be sublimed, while the product from larger runs was more conveniently purified by short-path distillation yielding white crystals.

Quite in contrast to the air sensitivity of **6**, the compounds **2** and **5** respectively proved surprisingly stable on exposure to air and may be stored without special protection for several weeks. The good solubility of **2** in ligroin and subsequent workup permit ready separation from any hydrolyzed product while **5** was purified by distillation.

Treatment of **6** with 1 equiv of lithium diisopropylamide in tetrahydrofuran at −75 °C generated the azetidinone enolate of **6** in situ, which underwent a 1,4-silyl shift from the carboxylic acid oxygen to the C-3 carbon atom, providing the carboxylic acid **7** in 78% yield. The trimethylsilyl group attached to nitrogen presumably was lost during the hydrolytic workup. Inspection of the NMR spectrum of the crude acid indicated that it consisted of at least 98% of the trans stereoisomer on the basis of the coupling constant[5] $J_{3,4}$ = 2.5 Hz in the ^{1}H NMR spectrum. Recrystallization from methanol yielded samples of the pure trans acid **7**.

The somewhat surprising silyl shift yielding exclusively *trans*-**7** requires some further explanation. None of the N-silylated β-lactam carboxylic acid esters (**2**, **5**) showed any indication of a migration of the trimethylsilyl group from the nitrogen to C-3. This was taken, at least in the case of the methyl ester **5**, as indicative that preference is given to a 1,4-silyl shift from oxygen to the C-3 carbon atom rather than a 1,3-shift from nitrogen to C-3. Anionic 1,4-silyl shifts are commonly observed when a silylated compound is treated with strong base. Several cases of 1,4-silyl group shifts from carbon to oxygen have been reported,[6] and the reverse migration has also been noted.[7,8] The details of the mechanism by which **7** is formed remain still open to question, but it may be presumed that **7** could arise from a 1,4-silyl shift from oxygen to the C-3 carbon

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