Ene Reaction Mechanisms. 3. Intermolecular and Intramolecular Kinetic Isotope Effects (KIE) for Some Ene Reactions of Hetero Enophiles[1]

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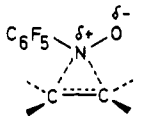
The KIE values for the ene reactions (i) of *N*-sulfinyl-*p*-toluenesulfonamide (**2**) and *N*-[(nonafluorobutyl)-sulfonyl]chloral imine (**4a**) with allyl benzene (**1**) (intra- as well as intermolecular effects) and (ii) of **2**, *N*-tosylchloral imine (**4b**), pentafluoronitrosobenzene (**5**) and *N*-phenyl-1,2,4-triazoline-3,5-dione (**6**) with 1-methyleneindan (**3**) (intermolecular effects) have been determined. Whereas **2** shows both intra- as well as intermolecular KIE's there is no observable intermolecular effect for **4**, **5**, and **6**. The results point to a nonconcerted, two-step ene reaction mechanism for the hetero enophiles investigated with different rate-determining steps for the two cases.

Some time ago[3] we determined the temperature dependence of the intramolecular hydrogen kinetic isotope effect (KIE) for the ene reaction of allyl benzene (**1**) with *N*-sulfinyl-*p*-toluenesulfonamide (**2**). From the observed values we concluded that the rate-determining step is the hydrogen transfer after a fast, reversible formation of a cyclic charge-transfer complex A. The transition state in this case has to be bent with the nitrogen atom in such a position as to allow its lone electron pair to coordinate with the allylic hydrogen. We called such a process a "pseudopericyclic reaction" (Scheme I).

On the other hand, Seymour and Greene recently reported KIE results on the reaction of pentafluoronitrosobenzene (**5**) with 2,3-dimethyl-2-butene.[4] As they pointed out, in their case the formation of an intermediate (possibly as three-membered ring B) should be rate determining while the subsequent hydrogen transfer had to be fast.



B

This seems to indicate the possible existence of at least two different (nonconcerted) mechanisms for ene reactions, their realization depending on the structures of the reactants involved. To examine this hypothesis we determined the KIE values for a number of ene reactions using enophiles with different heteroatoms forming the enophilic bond.

Results

The first series of experiments was done with **1**. We had determined earlier the intramolecular isotope effect for its reaction with **2** ($CHCl_3$, 20 °C)[3] (Scheme II),

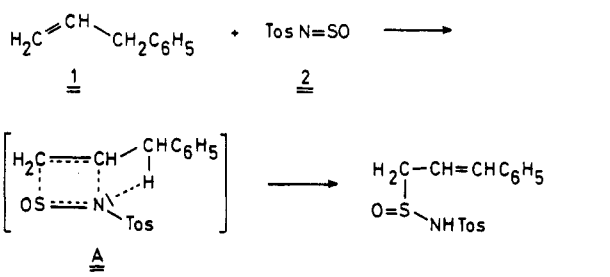
$$k_H/k_D \text{ (intra)} = 2.8651 \pm 0.0002$$

The value of the intermolecular effect now was found to be

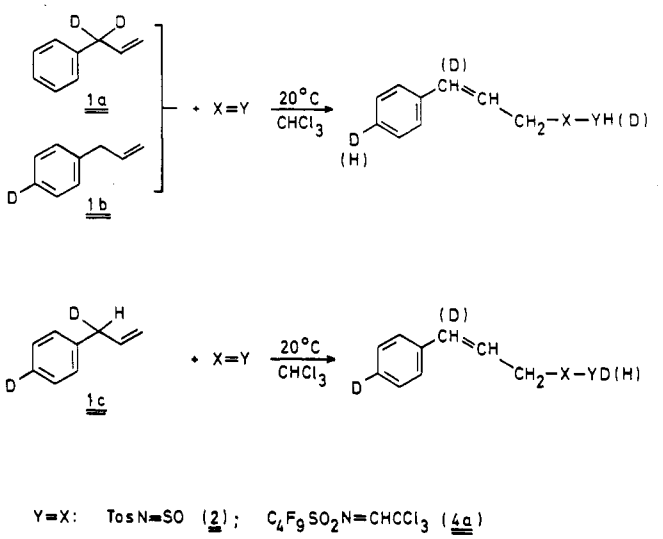
$$k_H/k_D \text{ (inter)} = 2.77 \pm 0.15$$

1 is only moderately reactive component in ene reactions.

Scheme I



Scheme II



Y=X: Tos N=SO (**2**); $C_4F_9SO_2N{=}CHCCl_3$ (**4a**)

Therefore, we could use only one other, highly reactive enophile for measuring KIE values, namely, *N*[(nonafluorobutyl)sulfonyl]chloral imine (**4a**), a compound we had prepared earlier[5] and found to be the most reactive enophile with a C=N bond known. The KIE values for its reaction with **1** are ($CHCl_3$, 20 °C)

$$k_H/k_D \text{ (intra)} = 2.65 \pm 0.6$$

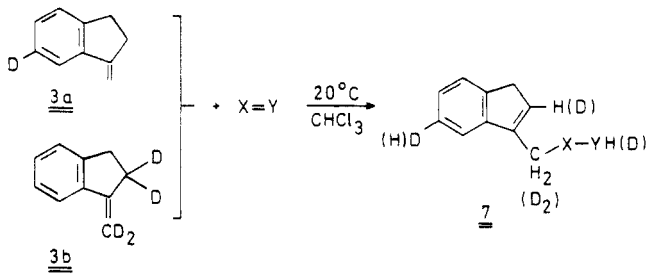
$$k_H/k_D \text{ (inter)} = 1.12 \pm 0.15$$

In the second series of experiments, we wanted to examine the behavior of as many different types of hetero enophiles as possible in their reactions with the same alkene (Scheme III). The large differences in reactivity of the various educts rendered the choice of this alkene somewhat difficult. We synthesized a number of compounds but found most of them unsuitable due to lack of reactivity, side reactions, or severe difficulties in the syn-

(1) Part 2: Münsterer, H.; Kresze, G.; Lamm, V.; Gieren, A. *J. Org. Chem.* **1983**, *48*, 2833.
(2) Present address: Department of Chemistry, University of Pittsubrgh, Pittsburgh, Pennsylvania 15260.
(3) Münsterer, H.; Kresze, G.; Brechbiel, M.; Kwart, H. *J. Org. Chem.* **1982**, *47*, 2677.
(4) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5227. Analogous result have been reported for ene reactions of **6**: Seymour, C. A.; Greene, F. D. *J. Am. Chem. Soc.* **1980**, *102*, 6384.
(5) Braxmeier, H.; Kresze, G., *Synthesis* **1985**, 683.

0022-3263/86/1951-0037$01.50/0

Scheme III



Y = X : TosN=SO (2), product 7a

Y = X : TosN=CHCCl$_3$ (4b), product 7b

Y = X : O=NC$_6$F$_5$ (5), product 7c

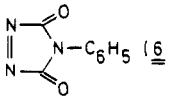
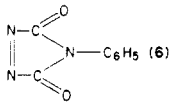
Y = X :  (6) product 7d

Table I. Intermolecular Kinetic Isotope Effects in the Methyleneindan (3) System at 20 °C ($CHCl_3$)

enophile	KIE
TosN=SO (2)	2.45 ± 0.5
C_6F_5N=O (5)	1.03 ± 0.1
 (6)	1.02 ± 0.1[a]
TosN=CHCCl$_3$ (4b)	1.05 ± 0.1

[a] In CH_2Cl_2.

thesis of the pure deuterated derivatives. Only methyleneindan (3) gave satisfactory yields of ene products with all four enophiles investigated. But even in this case we could not achieve the synthesis of the 2-monodeuterio nor the 2,2-dideuterio derivatives in a pure state (see Experimental Section). Therefore, we used 1-(dideuteriomethylene)-2,2-dideuterioindan (**3b**) for the experiments. In this case, there are contributions of the primary and the secondary KIE to the observed values. However, the latter may be safely assumed to be not larger than 0.3;[6] any real effect to be evaluated as a primary KIE, then, should have a value >1.3. Our experimental results are summarized in Table I: Only **2** shows a finite intermolecular KIE in its reaction with **3**.

Discussion

The ene reactions of **5** and **6** with other alkenes are known to proceed with finite intramolecular KIE values; we ourselves have found that this is true also for the reaction of **4a** (with **1c**, see above). Generalizing, we may state the following. There is a striking difference in behavior of the various types of hetero enophiles. Whereas only an intramolecular isotope effect but no intermolecular KIE is observable for the nitroso compound **5**, the azo compound **6**, and the imines **4**, the *N*-sulfinyl compound **2** shows intra- as well as intermolecular KIE's in ene reactions. In all cases investigated here the process should not be concerted but proceed in two steps, viz., complexation and hydrogen transfer with bond switching. In the case of **2**, the hydrogen transfer has to be rate-determining; in the other cases, this step should be fast, the slower one being the preceding complexation.

The reactivity of **2** in these ene reactions is considerably higher than that of **4**, **5**, or **6**. The atom to which the hydrogen is transferred is the same in **2**, **4**, and **6** and, moreover, is similarly acceptor substituted. The ability to accept the hydrogen, therefore, should not be very different in the three compounds. We conclude from this that the observed change in the rate-determining step is caused by the different relative ease of complexation between the alkene and the enophile. It is tempting to hypothesize that this difference is due to the formation of differently structured complexes in **2** and **4**, **5**, or **6**, respectively. But, of course, the structure of these complexes cannot be deduced from the data given here. We have determined the regiochemistry in various ene reactions of **2** and **4a**. The data allow some conclusions in the aforementioned respect; we shall report them in near future.

Experimental Section

All solvents were dried according to standard procedures, distilled and stored over molecular sieves (400 pm, activated). Melting points are uncorrected. IR spectra were taken with a Perkin-Elmer 257 spectrometer, ^1H NMR spectra were recorded on a Varian A 60 (60 MHz) or a Bruker WP 200 (200 MHz) spectrometer with Me_4Si as an internal standard, ^{13}C NMR spectra were measured either on a Jeol JNM-FX 60 (15.0 MHz) or on a Jeol JNM-FX 90 (22.6 MHz) spectrometer, of which the latter was also used for measuring the ^2H NMR spectra, and ^{19}F NMR spectra were recorded on a Jeol C-60 HL (56.45 MHz) spectrometer with CF_3CO_2H as an internal standard. Reactions requiring dried, deoxygenated conditions (especially the kinetic measurements) were conducted under dried, oxygen-free nitrogen.

Preparations. Allyl benzene (**1**) was purchased from Fluka; 1-methyleneindan (**3**) was prepared from 1-indanone (Merck) by Wittig reaction;[7] **2**,[8] **4a**,[5] **4b**,[9] **5**,[10] and **6**[11] were obtained by known procedures.

3-Phenylpropene-*3,3-d*$_2$ (**1a**) was prepared by the procedure of W. T. Hendrix and J. L. von Rosenberg.[12]

3-(4-Deuteriophenyl)-1-propene (**1b**) was prepared analogously to the method described for the synthesis of the undeuterated compound.[14]

Allyl bromide (14.4 g, 118 mmol) was added dropwise to a solution of the Grignard reagent from 9.4 g (59.5 mmol) of 4-deuteriobromobenzene[13] and 1.6 g (66 mmol) of magnesium turnings in 50 mL of diethyl ether. The mixture was refluxed for 3 h. After the mixture was cooled, 10 mL of water was added. The ethereal phase was separated, dried over anhydrous $MgSO_4$, and distilled in vacuo, yielding 5.8 g (82%) of **1b**: bp 50 °C (12 mm); ^1H NMR ($CDCl_3$) δ 3.30 (d, 2 H, J = 7 Hz, CH_2), 4.90 and 5.12 (m, 1 H, and m, 1 H, =CH_2), 5.57–6.30 (m, 1 H, CH_2CH=), 7.13 (s, 4 H, Ar protons).

3-(4-Deuteriophenyl)propene-*3-d* (1c). The ene product of **1b** and **2** was preparaed analogously to the general procedure for the preparation for the preparation of **7** (see below): To 12.0 g (0.10 mol of **1b** in 80 mL of $CHCl_3$ was added 21.9 g (0.10 mol) of **2** in 50 ml of $CHCl_3$; reaction time, 20 h; yield, 29.6 g (88%) of the ene product; mp 145–148 °C dec (from EtOH).

This product (25.0 g, 74.3 mmol) was dissolved[3,15] in a mixture of 70 mL of 1,2-dimethoxyethane and 20.0 g (1.0 mol) of D_2O.

(6) Drenth, W.; Kwart, H. "Kinetics Applied to Organic Reactions"; Marcel Dekker: New York, 1980; p 133.

(7) Sadler, I. H., *J. Chem. Soc. B* **1969**, 1024.
(8) Kresze, G.; Wucherpfennig, W. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 149.
(9) Albrecht, R.; Kresze, G.; Mlakar, B. *Chem. Ber.* **1964**, 97, 483.
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(11) Wamhoff, H.; Wald, K. *Org. Prep. Proced. Int.* **1975**, *7*, 251.
(12) Hendrix, W. T.; von Rosenberg, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 4850.
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(14) Hershberg, E. B. *Helv. Chim. Acta* **1934**, 17, 351.
(15) Hori, T.; Singer, S. P. Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1456.

This solution was refluxed for 12 h. After the mixture was cooled, *p*-toluenesulfonamide was precipitated by pouring the reaction mixture into a mixture of water and pentane. The precipitate was filtered off and washed several times with pentane. The organic layers were collected, washed with water, and dried over anhydrous $MgSO_4$. The pentane was distilled off; the residue was distilled in vacuo to yield 5.8 g (65%) of **1c**; bp 50 °C (12 mm); ^{1}H NMR ($CDCl_3$) δ 3.33 (m, 1 H, CHD), 4.92 and 5.15 (m, 1 H, and m, 1 H, $=CH_2$), 5.60–6.35 (m, 1 H, CH=), 7.20 (s, 4 H, Ar protons).

6-Deuterio-1-methyleneindan (3a). 4-Deuteriocinnamic Acid. A mixture of 50 g (0.47 mol) of 4-deuteriobenzaldehyde, 48.6 g (0.47 mol) of malonic acid, 80 g of pyridine, and 0.5 g of piperidine as catalyst were stirred for 3 h at 100 °C. Thereafter, 300 mL of water was added, and the mixture was neutralized with concentrated HCl. The remaining 4-deuteriobenzaldehyde was removed by steam distillation. The acid crystallized in high purity: yield, 57.4 g (82%); mp 132 °C; ^{1}H NMR ($CDCl_3$) δ 6.43 and 7.73 (d, 1 H, J = 16 Hz, and d, 1 H, J = 16 Hz, CH=CH), 7.50 (m, 4 H, Ar protons), 8.80 (s, 1 H, COOH).

4-Deuteriohydrocinnamic Acids. 4-Deuteriocinnamic acid (40.0 g, 0.27 mmol) was hydrogenated in 350 mL of acetic anhydride at 10 bar, with 0.5 g of PtO_2 Adams catalyst (Roth). The solvent was removed by distillation and the residue purified by fractionated distillation in vacuo: bp 112 °C (0.1 mm); yield, 38.2 g (94%); mp 47 °C; ^{1}H NMR ($CDCl_3$) δ 2.35–3.1 (m, 4 H, CH_2CH_2), 7.10 (s, 4 H, Ar protons), 10.80 (s, 1 H, COOH).

4-Deuteriohydrocinnamic acid chloride was obtained from the above acid and $SOCl_2$: yield, 92%; bp 96 °C (12 mm); ^{1}H NMR ($CDCl_3$) δ 2.87–3.27 (m, 4 H, CH_2CH_2), 7.20 (s, 4 H, Ar protons).

6-Deuterioindan-1-one was prepared by intramolecular Friedel–Crafts reaction. To a solution of 25.5 g (0.15 mol) of 4-deuteriohydrocinnamic acid chloride in 100 mL of hexane was added 24.1 g (0.18 mol) of anhydrous $AlCl_3$ with stirring. When the rigorous reaction and the generation of HCl gas had subsided, the reaction mixture was cooled with ice. To hydrolyze the remaining $AlCl_3$, ice–water was added dropwise to the mixture. The ketone was extracted with five portions of ether (each 50 mL). The combined ethereal layers were washed twice with saturated $NaHCO_3$ solution and with water and then dried over anhydrous $MgSO_4$. After evaporating the ether under reduced pressure, the ketone was purified by distillation: bp 62–65 °C (0.5 mm); yield, 14.3 g (72%); mp 41 °C; ^{1}H NMR ($CDCl_3$) δ 2.45–3.25 (m, 4 H, CH_2CH_2), 7.3–7.8 ("d", 3 H, Ar protons).

6-Deuterio-1-methyleneindan (3a) was prepared by Wittig reaction. Methyltriphenylphosphonium bromide (35.7 g, 0.1 mol) followed by 11.2 (0.1 mol) of potassium *tert*-butoxide was added to 12.0 g (0.09 mol) of 6-deuterioindan-1-one dissolved in 400 mL of anhydrous ether under nitrogen. The mixture was stirred for 20 h at 20 °C. The ether was removed by distillation, and the residue was extracted with five portions (each 50 mL) of dry pentane and filtered over a short (10 cm) silica gel column. After evaporation of the pentane the alkene was distilled in vacuo: yield, 8.25 g (70%); bp 81 °C (12 mm); ^{1}H NMR ($CDCl_3$) δ 2.60–3.00 (m, 4 H, CH_2CH_2), 5.00 and 5.43 ("s", 1 H, and "S", 1 H, $=CH_2$), 7.10–7.55 ("d", 3 H, Ar protons).

The compound rearranges easily in the presence of traces of acid to 3-methylindene. In the analogous reaction of indan-1-one-*2,-2-d*$_2$,[16] H/D exchange occurred; most of the deuterium was found in the 1-methylene group of the product **3**.

1-(Dideuteriomethylene)indan-*2,2-d*$_2$ (3b) was prepared by Wittig reaction of indan-1-one-*2,2-d*$_2$[16] with (methyl-*d*$_3$)triphenylphosphonium bromide[17] analogously to **3a**: yield, 70%; bp 81 °C (12 mm); ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 2 H, CH_2), 7.00–7.55 (m, 4 H, Ar protons).

General Procedure for the Ene Reactions of 1-Methyleneindan (3) with the Hetero Enophiles 2, 4b, 5, and 6. To a stirred solution of 2.0 g (15.4 mmol) of **3** in 5 mL of dry chloroform was added 13 mmol of the corresponding hetero enophile dissolved in 10 mL of chloroform (for **6**, in 30 mL of dry methylene chloride) under nitrogen at room temperature. The mixture was stirred for 2 h; usually the ene product precipitated during this time. To complete this precipitation, 30–50 mL of pentane was added. After filtration, the crude products **7a–d** (isolated in nearly quantitative yield in all cases) were purified by recrystallization. The characteristic data for these products are as follows:

N-[(3-1*H*-Indenylmethyl)sulfinyl]-*p*-toluenesulfonamide (**7a**): mp 145–148 °C dec (ethanol); IR (KBr) 3160–2820, 1330, 1165, 1060 cm^{-1}; ^{1}H NMR (Me_2SO-*d*$_6$ δ 2.32 (s, 3, CH_3Ar), 3.20 (s, 2, CH_2 ring), 4.30 (s, 2, CH_2SO), 6.35 (s, 1, CH=C), 7.0–7.6 (m, 9, Ar protons and NH); ^{13}C NMR (Me_2SO-*d*$_6$) δ 20.91, 37.74, 54.08, 119.23, 123.59, 124.79, 125.78, 129.33, 132.72, 135.89, 137.81, 143.06, 143.20, 143.44. Anal. Calcd for $C_{17}H_{17}NO_3S_2$: C, 58.77; H, 4.93; N, 4.03. Found C, 58.62; H, 4.88; N 4.05.

N-[1,1,1-Trichloro-3-(3-1*H*-indenyl)propan-2-yl]-*p*-toluenesulfonamide (**7b**): mp 156 °C ($CHCl_3$); IR (KBr) 3260, 1350, 1160 cm^{-1}; 1H NMR ($CDCl_3$) δ 2.30 (s, 3, CH_3Ar), 2.82 and 3.06 (AB system, 2, J = 23 Hz, CH_2 ring), ca. 2.85 (dd, partially covered, 1) and 3.45 ("d", 1, J = 14 Hz, CH_2), 4.62 (m, 1, CH cCl_3), 5.62 (d, 1, NH, J = 9.5 Hz), 6.19 (s, 1, CH=C, 6.9–7.4 (m, 8, Ar protons); ^{13}C NMR (Me_2SO-*d*$_6$) δ 21.43, 31.23, 37.85, 68.05, 102.72, 118.69, 123.69, 124.86, 126.16, 126.36, 128.95, 132.98, 137.85, 138.17, 142.72, 144.02, 144.21. Anal. Calcd for $C_{19}H_{18}Cl_3NO_2S$: C, 52.98; H, 4.21; N, 3.25. Found: C, 52.55; H, 4.24; N, 3.27.

1-(3-1*H*-Indenylmethyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**7d**): mp 183–187 °C dec (hexane/benzene); IR (KBr) 3160–3000, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 2, CH_2 ring), 4.73 (s, 2, CH_2N), 6.52 (s, 1, C=CH), 7.2–7.7 (m, 10, NH and Ar protons); ^{13}C NMR (Me_2SO-*d*$_6$) δ 38.06, 44.15, 119.31, 123.57, 125.43, 126.45, 128.18, 129.03, 134.45, 137.03, 142.56, 144.14, 152.49, 153.39. Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 69.85; H, 4.90; N, 13.47.

N-(3-1*H*-Indenylmethyl)(pentafluorophenyl)hydroxylamine (**7c**): mp 133 °C dec; ($CHCl_3$) IR (KBr) 3600–3100 cm^{-1}; ^{1}H NMR (Me_2SO-*d*$_6$) δ 3.30 (s, 2, CH_2 ring), 4.30 (s, 2, CH_2N), 6.47 (s, 1, CH=C), 6.95–7.75 (m, 4, Ar protons), 9.10 (s, 1, OH); ^{13}C NMR (Me_2SO-*d*$_6$) δ 37.53, 56.49, 119.66, 123.43, 124.41, 127.77, 133.11, 139.27, 143.02, 143.95 [CF signals in the noise]; ^{19}F ^{19}F NMR (Me_2SO) δ 68.10 (d, 2), 81.13 ("t", 1), 85.92 ("t", 2). Anal. Calcd for $C_{16}H_{10}F_5NO$: C, 58.72; H, 3.08; N, 4.28. Found C, 58.34; H, 3.08; N 4.09.

The ene adducts of allylbenzene (**1**) with **2**[18] and **4a**[5] have been described previously.

Determination of the Kinetic Isotope Effects. (i) The 1-Methyleneindan System. Solutions of the mono- (**3a**) and the tetradeuterated (**3b**) 1-methyleneindan (each 5 mmol in 5 mL of dry chloroform) were mixed. To this mixture thermostated at 20 °C was added 2.5 mmol of the hetero enophile dissolved in 5 mL of chloroform in such a manner that the temperature remained constant regardless of the exothermic reaction. After the mixture was stirred for 2 h at 20 °C, 50 mL of pentane was added to precipitatae the ene product completely. The crystals were filtered off under nitrogen, washed five times with 10-mL portions of pentane, and dried in vacuo. The organic layers were collected, and the pentane was distilled off. By treatment with H_2O, the ND and the OD deuterium of the ene product was exchanged. ^{2}H NMR spectra were taken of the solid material, taken up in DMF, as well as of the residue of the pentane solutions (the starting alkenes).

(ii) The Allylbenzene (1) System. The procedure for measuring the intramolecular KIE was described earlier[3] for TosNSO as the enophile. For the imine, a 1:1 mixture of the educts **1c** + **4a** (5 mmol) dissolved in 5 mL of $CHCl_3$ each, was kept at 20 °C for 30 h. The procedure for determining the isotopic composition was analogous to that described above. Care should be taken to achieve complete exchange of the ND deuterium.

For the intermolecular KIE measurements, equimolar mixtures of mono- (**1b**) and dideuterated (**1a**) allylbenzene (20 mmol each in 5 mL of $CCCl_3$) and 10 mmol of **2** or 5 mmol of each **1a** and **1b** and 2.5 mol of **4a** were used, respectively (reaction time, 30 h). The determination of the isotopic composition was done by 2H NMR spectra measurements. In the case of **4a**, the procedure was analogous to that described above. In the reactions of **2**, the ene products were converted back to the starting alkene by the following method (cf. ref 3): The adduct was dissolved in a mixture

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(18) Kresze, G.; Bussas, R. *Liebigs Ann. Chem.* **1980**, 843.

of 10 mL of water and 50 mL of 1,2-dimethoxyethan and refluxed for 12 h. After cooling, this solution was poured into a two-phase mixture of pentane (100 mL) and water (50 mL) to precipitate the toluenesulfonamide. This was filtered off and washed with pentane. The pentane layers were dried, the solvent was distilled off, and the allyl benzene (**1a** + the $C_6H_5CHDCH{=}CH_2$ derivative) was isolated by distillation in vacuo.

To gain a better precision in the determination of the isotopic composition by ^2H NMR experiments, we used the 4-deuteriophenyl derivatives **1b** and **3a** and measured the relative signal intensities of the D atom resonances **1a**/**1b** or **3a**/**3b**, respectively.

Acknowledgment. This work has been stimulated by discussions with the late Harold Kwart. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support and grants.

Registry No. 1, 300-57-2; **1b**, 99532-28-2; **1c**, 99532-29-3; **2**, 4104-47-6; **3**, 1194-56-5; **3a**, 99532-33-9; **3b**, 99532-34-0; **4a**, 99532-23-7; **4b**, 13707-44-3; **5**, 1423-13-8; **6**, 4233-33-4; **7a**, 99532-24-8; **7b**, 99532-25-9; **7c**, 99532-27-1; **7d**, 99532-26-0; D_2, 7782-39-0; allyl bromide, 106-95-6; 1-bromo-4-deuteriobenzene, 13122-33-3; malonic acid, 141-82-2; methyltriphenylphosphonium bromide, 1779-49-3; 1-indanone-2,2-d_2, 10036-02-9; methyl-d_3-triphenylphosphonium bromide, 1787-44-6; 4-deuteriobenzaldehyde, 33836-85-0; 4-deuteriocinnamic acid, 99532-30-6; 4-deuteriohydrocinnamic acid, 99532-31-7; 4-deuteriohydrocinnamic acid chloride, 61233-31-6; 6-deuterioindan-1-one, 99532-32-8.

A Short, Efficient, Highly Selective Synthesis of (1*R*,3*S*)-*cis*-Chrysanthemic Acid through the Microbiological Reduction of 2,2,5,5-Tetramethyl-1,4-cyclohexanedione

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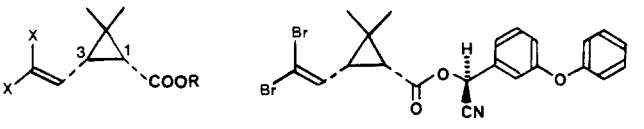
A highly selective synthesis of (1*R*,3*S*)-*cis*-chrysanthemic acid (**1a**), a key intermediate in the industrial preparation of major unnatural pyrethrinoid-type insecticides [deltamethrin (**2**) given as example] is reported. 2,2,5,5-Tetramethyl-1,4-cyclohexanedione (**3**), a key compound in that synthesis, was obtained either by direct tetramethylation of 1,4-cyclohexanedione (**4**) or, in a more efficient manner, by dimethylation of 2,5-dimethyl-1,4-cyclohexanedione (**5**). Microbiological reduction, using various mold strains of dione **3**, afforded enantiomerically pure (*S*)-ketol **11** in 85% yield. This ketol was then transformed into mesylate **12** which was oxidized by means of *m*-chloroperbenzoic acid into the seven-membered ring lactone **16**. Sodium *tert*-amylate promoted transannular cyclization of this lactone was highly selective and gave enantiomerically pure (+)-dihydrochrysanthemolactone **17** (in 70% overall yield, calculated from dione **3**), a direct precursor of acid **1a**.

Chrysanthemic acids, which are cyclopropane ring-containing components of the widely used insecticide pyrethrins, have received much attention in the chemical literature.[1]

It was reported in 1974 by a British group led by M. Elliott that certain unnatural *cis*-chrysanthemic esters **1** (especially their dihalogeno derivatives **1b**) show greater activity and greater photostability than the corresponding trans derivatives[2] (Scheme I). Remarkably, the physiological activity of these pyrethrinoids is closely associated with the 1*R* configuration of the chrysanthemic acid component, the 1*S* enantiomers being many times less effective. For this reason, suitable routes to optically active

Scheme I

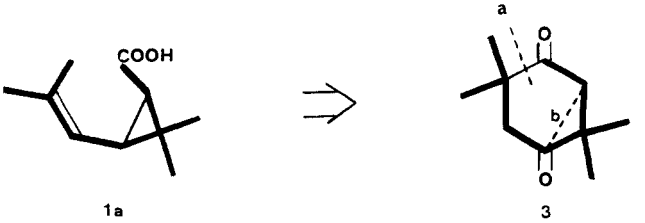


1 2

1a: X = Me, R = H

1b: X = Br or Cl

Scheme II



1a 3

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