112. Rhodium-Catalyzed Deuterioformylation of 3-Methyl-1-pentene

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Summary

3-Methyl-1-pentene was deuterioformylated in the presence of rhodium-catalyst. The extent of attack on each face of the olefin was evaluated from the diastereomeric composition of both positional isomers obtained as the products. An overall preferred attack on the *si-si* face of the (*S*)-enantiomer, and on the *re-re* face of the (*R*)-enantiomer was found.

In connection with our studies on the stereochemical aspects of the 'oxo' reaction, we carried out the deuterioformylation of 3-methyl-1-pentene intending to determine the extent of attack on each face of the olefin. The cobalt-catalyzed hydroformylation of (+)-(*S*)-3-methyl-1-pentene [1] afforded *threo*-2,3-dimethylpentanal (from the attack on the *re-re* face[1])) in substantial prevalence (2:1) over the *erythro* isomer (from the attack on the *si-si* face). However, the diastereoisomeric pair accounted for only a small percentage of the products (3%) and its composition might not reflect the measure of overall attack at the two faces of the olefin. If hydrogen is replaced by deuterium, the C(2) of the substrate during the reaction becomes asymmetric in one isomer by addition of a formyl group, and in the other by addition of a deuterium atom. In the last case, two epimers of 1,3-$[^2H]_2$-4-methylhexanal will result. The desired information about the asymmetric induction of the chiral carbon atom of the substrate on the stereochemical course of the reaction can thus be obtained from the epimeric composition of the main reaction product.

Racemic 3-methyl-1-pentene was reacted with deuterium and carbon monoxide at moderate pressure and temperature, in the presence of rhodium oxide as catalyst precursor, under conditions known to promote a smooth hydroformylation without isomerization [3]. 1,3-$[^2H]_2$-4-Methylhexanal and 1,2[1]-$[^2H]_2$-2,3-dimethylpentanal were the sole reaction products. The isomeric composition of the products and the epimeric composition of 2,3-dimethylpentanal were determined by well established procedures [1] [4] and are reported in *Scheme 1*, where, for simplicity, the sequence is represented for one enantiomer only. The correlation between the

[1]) See [2] for the nomenclature.

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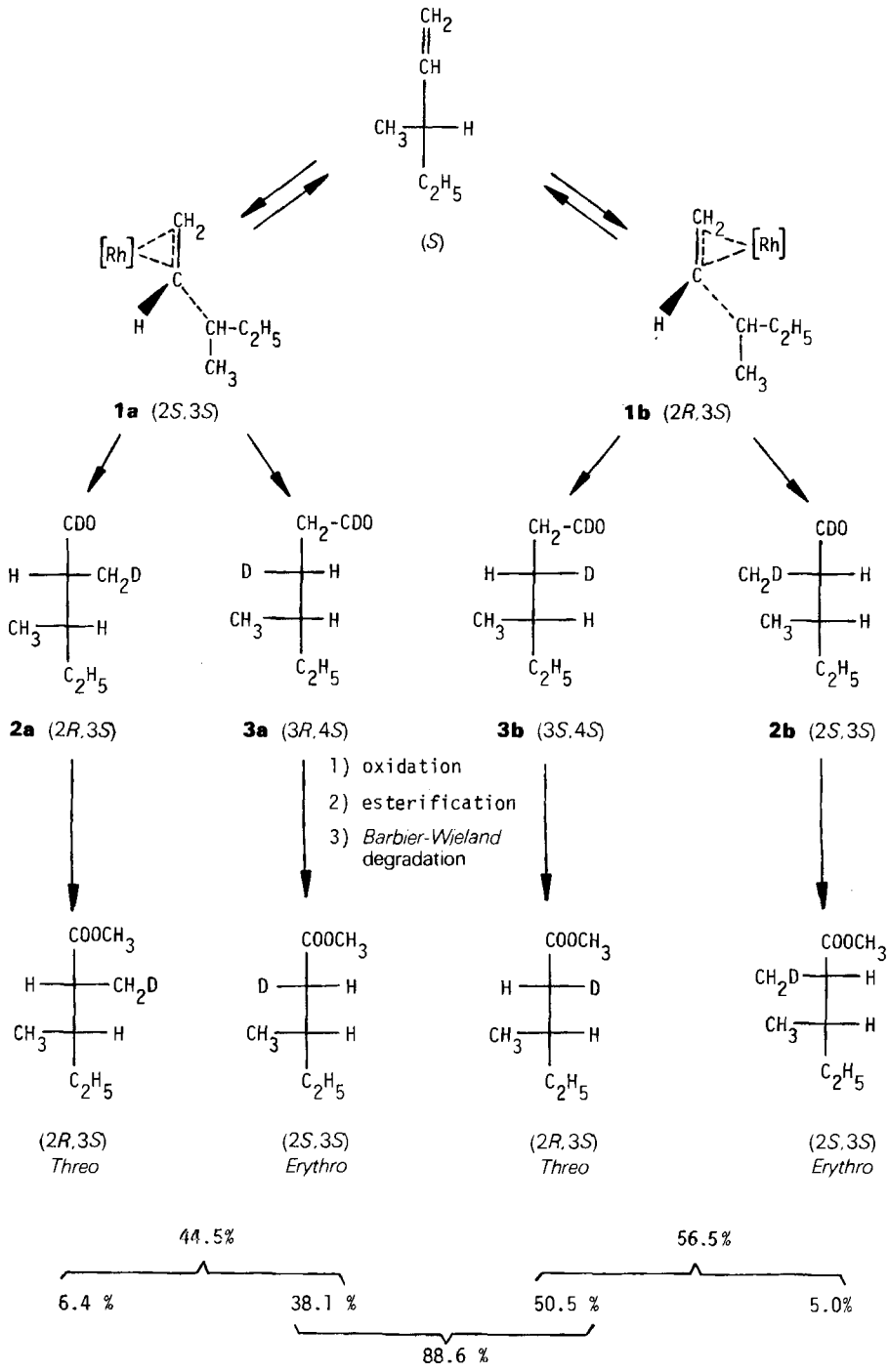
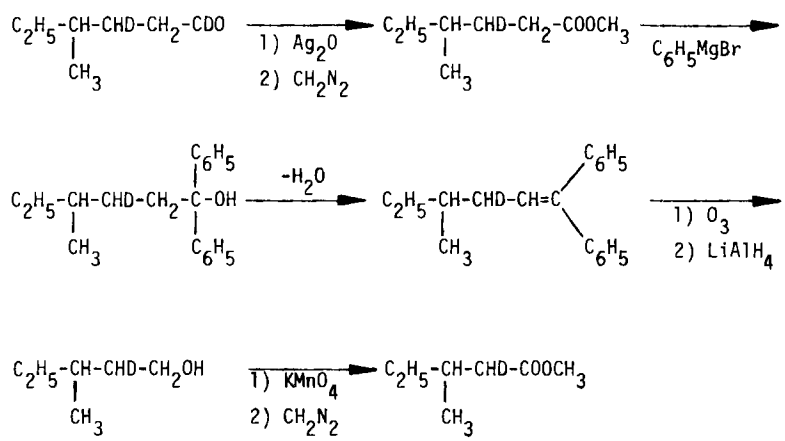
Scheme 1


(S)
1a (2S,3S)
1b (2R,3S)
2a (2R,3S)
3a (3R,4S)
3b (3S,4S)
2b (2S,3S)
1) oxidation
2) esterification
3) Barbier-Wieland degradation
(2R,3S) Threo
(2S,3S) Erythro
(2R,3S) Threo
(2S,3S) Erythro
44.5%
56.5%
6.4 %
38.1 %
50.5 %
5.0%
88.6 %

configuration of the products and that of their precursors, **1a** and **1b**, is based on the evidence that the addition of deuterium and formyl group to the double bond occurs with *cis*-configuration on the face interacting with the catalyst [4] [5]. As in the case of cobalt-catalyzed hydroformylation [1], *threo*-2,3-dimethylpentanal is prevailing over the *erythro*-isomer, although the prevalence is, in this case, less pronounced (1.3:1).

For the determination of the stereochemical composition of 1,3-[^{2}H]$_2$-4-methylhexanal, the main product of the reaction (88.6%), the aldehyde was subjected to a series of transformations, without involving the asymmetric centers, and eventually converted to 2-[^{2}H]-2-methylpentanoic acid, methyl ester *(Scheme 2)*. The determination of the epimeric composition of the ester was possible by ^{1}H-NMR. analysis, as shown from preliminary measurements made on unlabelled and labelled standard samples. In fact, the 360-MHz spectrum of 3-methylpentanoic acid, methyl ester, shows separate signals for all the non-equivalent protons; in particular the α-protons give two quartets centred at $\delta_A = 2.31$ and $\delta_B = 2.11$ ppm ($J_{A,B} = 14.7$ Hz, $J_{A,M} = 6.1$ Hz, $J_{B,M} = 8.1$ Hz). The NMR. spectrum of a sample of α-monodeuterated ester prepared by boron deuteride addition to 3-methyl-1-pentene, followed by oxidation to acid and treatment with diazomethane, showed for the α-proton two unresolved multiplets well separated from each other. As expected, their chemical shifts were the same as those observed for the unlabelled ester and the sum of their integrals corresponded to one proton. The ratio between the two integrals was taken as a measure of the relative abundance of the two epimers in the sample. For the correct assignment of the two signals to the pair of diastereotopic α-protons, *erythro-* and *threo*-2,3-[^{2}H]$_2$-3-methylpentanoic acid, methyl esters, were separately prepared by *cis*-addition of deuterium to (*Z*)- and (*E*)-3-methyl-2-pentenoic acid, methyl ester, respectively, catalyzed by tris(triphenylphosphine)chlororhodium [6]. The NMR. spectrum of the *erythro* showed for the α-proton only a broad signal at $\delta = 2.30$ ppm, and that of the *threo* showed only a broad signal at $\delta = 2.10$ ppm.

Scheme 2



The NMR. spectrum of the 2-[^{2}H]-3-methylpentanoic acid, methyl ester, from the deuterioformylation reaction, was practically identical to that of the methyl ester prepared through the boron deuteride addition, the relative abundance of the two diastereomers being practically the same and the *threo*-configuration prevailing in both samples.

The following remarks can be made concerning *Scheme 1*: a) In the deuterioformylation of 3-methyl-1-pentene, the sum of the products that originate from the attack on the *si-si* face in the antipode (*S*), and on the *re-re* face in the antipode (*R*), prevail; b) The epimeric composition of the two products indicate that in the deuterioformylation the regioselectivity on the two diastereofaces of the substrate is different. As a consequence the relative abundances of *threo*- and *erythro*-2,3-dimethylpentanal do not reflect, even qualitatively, the extent of the overall attack on the corresponding diastereofaces of the olefin; c) The olefin face predominantly attacked in the deuterioformylation is also preferred in the boron deuteride addition. Incidentally, the same face is the one preferentially complexed to the metal in *cis*- and *trans*-dichloro(benzylamine)platinum (II) complexes at the equilibrium [7]. Whether the preference of attack shown by the product composition actually reflects the existence and the position of the equilibrium between the two diastereomeric π-olefin complexes **1a** and **1b** *(Scheme 1)*, cannot be ascertained, because the relative values of the energy barriers in the single steps of the hydroformylation, successively leading to the pairs of diastereomeric products **2a**, **2b** and **3a**, **3b** respectively, are not known.

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Experimental Part

VPC. analyses were performed with a *Perkin-Elmer* 990 gas chromatograph; mass spectra were measured with a *Hitachi* RMU-6L spectrometer; NMR. spectra were measured with *Bruker* WH 90 and HXS 360 spectrometers. VPC. preparative separations were performed with a *Perkin-Elmer* F 21 fractometer, and the rectification was made with a *Perkin-Elmer* 251 spinning band column.

Deuterioformylation. 3.35 g (0.04 mol) 3-methyl-1-pentene, 76 mg rhodium oxide, and 0.79 g triphenylphosphine in 120 ml benzene, were treated in a stainless steel autoclave with deuterium and carbon monoxide (70 atm, measured at room temperature, in equimolar mixture) at 100° for 20 h. The VPC. analysis of the crude reaction mixture indicated the complete conversion of the olefin, and the presence of 2,3-dimethylpentanal (11.4%) and 4-methylhexanal (88.6%) as the only products. The aldehydes were oxidized with silver oxide according to [1], and the crude mixture of acids obtained was treated in ether solution with diazomethane in excess. The VPC. analysis of the crude product [8] indicated the presence of *erythro*- and *threo*-2,3-dimethylpentanoic acid, methyl esters, in the ratio of 44:56. The mixture of methyl esters was added to an ether solution of phenylmagnesium bromide (0.12 mol), and a product was obtained, after working up the reaction mixture, which consisted mostly of (2-[^{2}H]-3-methylpentyl)diphenylmethanol. The alcohol was dehydrated by refluxing in toluene (30 ml) in the presence of a catalytic amount of iodine to afford 6.5 g of a mixture of 3-[^{2}H]-1,1-diphenyl-4-methyl-1-hexene and 2^1-[^{2}H]-1,1-diphenyl-2,3-dimethyl-1-pentene, b.p. 120–140°/0.1 Torr. A stream of ozone was passed through a solution of the product thus obtained in pentane (50 ml) at $-70°$ for 6 h; the mixture was then added to a suspension of lithium aluminium hydride (3 g) in ether, and after working up and removal of the solvents, 1.5 g of product was collected in a cooled trap by heating the residue on a steam bath under high vacuum. This product, consisting mostly of 2-[^{2}H]-3-methyl-1-pentanol, was oxidized with potassium permanganate according to [9] and the 2-[^{2}H]-3-methylpentanoic

acid obtained was finally converted to the methyl ester by treatment with diazomethane in ether. A pure sample of the ester was obtained by preparative VPC. The isotopic purity was over 95% according to mass spectrometric determination. The NMR. spectrum ($CDCl_3$, 360 MHz) showed for the α-protons two completely separated multiplet centred at $\delta = 2.09$ and 2.29 ppm, the integrals of which were in the ratio of 43:57.

2-[^2H]-3-methylpentanoic acid, methyl ester. 3 g (0.02 mol) boron trifluoride etherate was added under nitrogen to a suspension of 0.63 g (0.015 mol) lithium aluminium deuteride in tetrahydrofurane (20 ml) containing 5 g (0.06 mol) 3-methyl-1-pentene, while cooling the vessel at 0°. The mixture was stirred overnight at room temperature, filtered and the filtrate directly oxidized with hydrogen peroxide according to a general procedure [10]. The crude alcohol obtained was converted to 2-[^{2}H]-3-methylpentanoic acid, methyl ester, b.p. 138–140°, as described above. The overall yield was 35%. Mass spectrometric measurement indicated over 98% isotopic purity, and the NMR. spectrum ($CDCl_3$, 360 MHz) showed the signals at $\delta = 2.09$ and 2.29 ppm (see above) in the ratio of 44:56.

Erythro- *and* threo-*2,3-[^2H]$_2$-3-methylpentanoic acid, methyl esters.* A mixture of (*E*)- and (*Z*)-3-methyl-2-pentenoic acid, prepared according to [11], was treated in ether solution with diazomethane in excess. (*Z*)-3-Methyl-2-pentenoic acid, methyl ester, b.p. 148°, and (*E*)-3-Methyl-2-pentenoic acid, methyl ester, b.p. 153°, were then separated by rectification through a spinning band column. 2 g (0.015 mol) of each ester was separately reacted with deuterium at room temperature and atmospheric pressure, in the presence of tris(triphenylphosphine)chlororhodium [6] (50 mg) in benzene (20 ml). Several days were needed to afford good conversions, as indicated by periodic VPC. controls. Both esters were eventually obtained as pure samples by preparative VPC. The isotopic purities, determined by mass spectrometry, were over 90%. The NMR. spectrum ($CDCl_3$, 90 MHz) showed for the α-proton of *erythro*-2,3-[^{2}H]$_2$-3-methylpentanoic acid, methyl ester (from the (*Z*)-unsaturated ester) one broad signal at $\delta = 2.30$ ppm, and for that of the *threo*-isomer (from the (*E*)-unsaturated ester) one broad signal at $\delta = 2.10$ ppm.

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