

## On the Methylation and Demethylation of Optically Active Aliphatic Hydroxy Compounds

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A convenient reaction sequence involving methylation and demethylation in high yields of an optically active aliphatic hydroxy ester with retention of optical activity is described. The mass spectra of (-)-methyl 3D-hydroxynonanoate ( $[\alpha]_D^{25} - 20.0^\circ$ ) and (-)-methyl 3D-methoxynonanoate ( $[\alpha]_D^{25} - 2.8^\circ$ ) are discussed.

From a gas chromatographic and mass spectrometric point of view the methyl ether constitutes an ideal derivative of an aliphatic hydroxy compound due to the low molecular weight and stability of the protective group. However, difficulties encountered in the removal of the protective group have seriously restricted the use of methyl ether derivatives. A great number of methods for the methylation of hydroxyl groups are available, *cf.*, *e.g.* Ref. 1, but demethylation has proved more difficult.

Methods for the cleavage of methyl ethers under mild conditions have, however, appeared in the literature. For example, Foster *et al.*<sup>2</sup> working in the carbohydrate field, successfully used boron trichloride at  $-70^\circ$  to remove an *O*-methyl ether grouping of L-threitol. Youssefyeh and Mazur<sup>3</sup> reported in 1962 that aliphatic ethers can be cleaved by reaction with lithium bromide and boron trifluoride in acetic anhydride at room temperature. However, Narayanan<sup>4</sup> reported later that the presence of lithium halide is not essential.

Another interesting method for low temperature cleavage of ethers has been devised by Freeguard and Long.<sup>5-7</sup> In the presence of boranes or metal borohydrides and iodine one of the oxygen-carbon links of the ether is ruptured, the oxygen attaching itself to boron while the carbon links up with halogen.

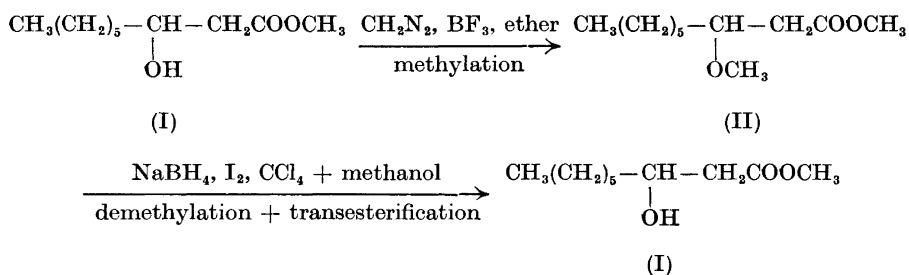
Very recently, Juenge and Beal<sup>8</sup> reported a method by which aliphatic ethers can be oxidatively transformed to carboxylic acid esters. The latter may of course be cleaved by hydrolysis. Trichloroisocyanuric acid in the presence of an excess of water served as oxidizing agent. Methyl ethers may also be oxidized to the corresponding formates in moderate yield with a suspension of chromium trioxide in a mixture consisting of acetic acid and dichloromethane.<sup>9</sup>

With the exception of the work by Foster *et al.* mentioned, very few investigations deal with the cleavage of methyl ethers containing additional functional groups. Work on the synthesis of optically active polyhydroxy-substituted aliphatic molecules is being undertaken in this laboratory, and it was thought of interest to investigate the possible transformation of optically active methoxy-substituted carboxylic esters to the corresponding hydroxy-substituted compounds.

The method devised by Freeguard and Long appeared, apart from being convenient, suitable with respect to retention of optical activity. In particular, ether linkages between primary and secondary carbon atoms rupture in such a manner that the halogen attaches itself to the primary carbon atom while the oxygen at the secondary carbon atom links up with boron, a borate ester being produced. It is furthermore known that borate esters normally hydrolyse by cleavage at the boron-oxygen bond.<sup>10</sup> It appeared thus possible that the bond between the secondary carbon atom and the oxygen might pass the series of chemical transformations without cleavage, *i.e.* conditions for retained optical activity would be fulfilled.

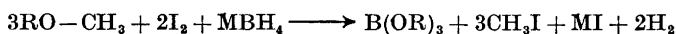
It is known that 3-hydroxy-substituted carboxylic esters are sensitive in respect of their ready elimination of water, a corresponding  $\alpha,\beta$ -unsaturated ester being formed. The methoxy derivative of an optically active such positional isomer was therefore considered particularly interesting in the attempted demethylation step.

3D-Hydroxynonanoic acid, available by oxidative cleavage of ricinoleic acid, was used in the experiment. It was esterified to methyl 3D-hydroxynonanoate(I) of  $[\alpha]_D^{25} -20.0^\circ$ .



The methyl ether of(I) was prepared according to the method of Müller *et al.*<sup>11</sup> involving diazomethane in ether as methylating agent in the presence of boron trifluoride etherate. After purification by chromatography methyl 3D-methoxynonanoate (II) of  $[\alpha]_D^{23} -2.8^\circ$  was obtained in 80 % yield.

The cleavage of methoxyl groups in the presence of metal borohydrides and iodine proceeds according to the equation:



It was found that the reagents cleaved the ether bond of the 3-methoxy ester and that the desired hydroxy ester was formed, as proved by its refractive index, gas chromatographic retention time and mass spectrum.

As metal borohydride in the reaction the lithium and sodium compounds were tested. The latter afforded the highest yield. Furthermore the presence of an excess of iodine and slightly elevated temperature (45°) increased the yield of the hydroxy ester produced. The original method by Freeguard *et al.* was also modified in the respect that a small amount of solvent, preferably carbon tetrachloride, was used.

As indicated by GLC, about 70 % of the methoxy ester (II) cleaved to the corresponding hydroxy compound (I) on a single treatment under the conditions mentioned (see experimental). The rest consisted essentially of unreacted material. After purification by liquid chromatography on silicic acid and after a second treatment of the unreacted methoxy ester a 77 % yield of (I) of  $[\alpha]_D^{25} -19.9^\circ$  was obtained. The optical rotation is in excellent agreement with that of the starting material (I) ( $[\alpha]_D^{25} -20.0^\circ$ ). It is evident, therefore, that the reaction sequence consisting of methylation and demethylation under the conditions described involves no racemization.

The possible route for the preparation of polyhydroxy-substituted aliphatic acids *via* the corresponding polymethoxy-substituted compounds suggested by these findings is being further explored.

#### MASS SPECTROMETRIC INVESTIGATIONS

The mass spectrum of methyl 3D-hydroxynonanoate (I) is reproduced in Fig. 1. It shows no peak at  $m/e=M$ , the only significant peaks of high

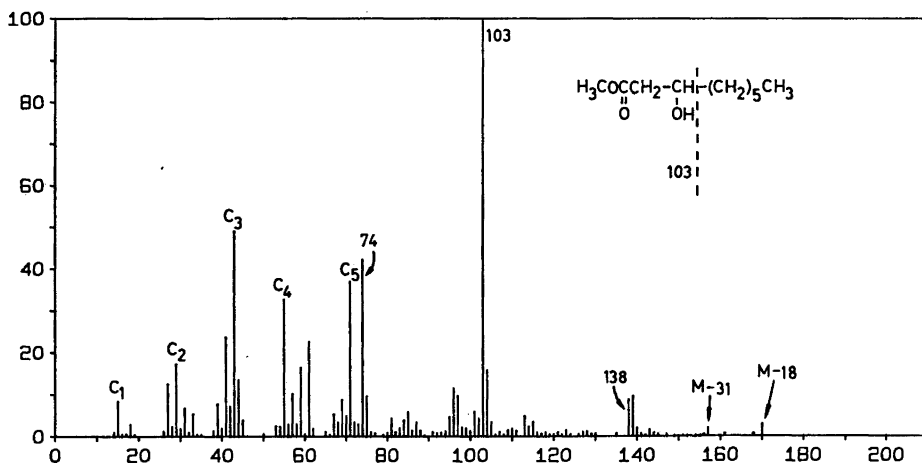


Fig. 1. Mass spectrum of methyl 3D-hydroxynonanoate.

$m/e$  being those at  $m/e$  170 ( $=M-18$ , loss of water),  $m/e$  157 ( $=M-31$ ) and 138 [ $=M-(18+32)$ , additional loss of methanol]. The base peak at  $m/e$  103 is formed through simple 3,4-cleavage. These characteristics agree excellently with those obtained for methyl 3DL-hydroxyoctadecanoate.<sup>12</sup>

Fig. 2 shows the spectrum of methyl 3D-methoxynonanoate (II). The peak of highest mass number is found at  $m/e$  187 ( $=M-15$ ). The general feature

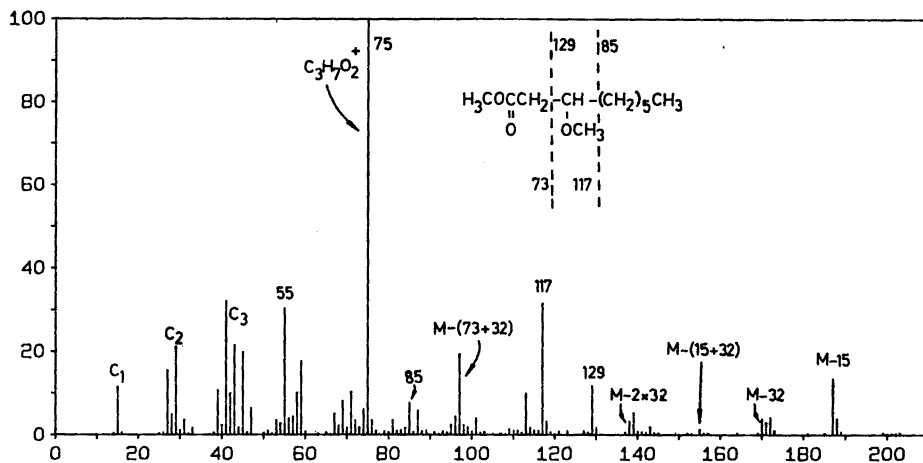


Fig. 2. Mass spectrum of methyl 3D-methoxynonanoate.

of the cleavage pattern is caused by cleavage at the branched point, eventually followed by further loss of a molecule of methanol as indicated by the large abundance of fragments at  $m/e$  85,  $m/e$  129,  $m/e$  97 ( $=129-32$ ), and  $m/e$  117. The base peak at  $m/e$  75 deserves particular mentioning. It is also base peak in the spectrum of methyl 3DL-methoxyoctadecanoate<sup>12</sup> and appears characteristic for 3-methoxy-substituted methyl esters. Its mass number corresponds to the formula  $\text{C}_3\text{H}_7\text{O}_2^+$  but its mode of formation is as yet not completely understood. However, in the spectrum of trideuteromethyl 3D-methoxynonanoate the mass number of the base peak shifted to 78. This suggests that the fragments are formed through 2,3-cleavage with rearrangement of two hydrogen atoms.

#### EXPERIMENTAL

*Methyl 3D-hydroxynonanoate (I).* 10.0 g (57.5 mmol) of 3D-hydroxynonanoic acid was refluxed overnight in a mixture of 5 % sulphuric acid in methanol (150 ml). 75 ml of methanol was removed at reduced pressure and the residue distributed among ether and water. The organic phase was washed successively with 5 % sodium carbonate in water and water, dried ( $\text{MgSO}_4$ ), and finally filtered through a small column with deactivated  $\text{Al}_2\text{O}_3$ . After evaporation of the solvent 9.0 g (83 %) of (I),  $n_D^{20}$  1.4370, was obtained. The purity was better than 99 % as indicated by GLC.

*Methyl 3D-methoxynonanoate (II).* 7.5 g (39.9 mmol) of (I) was dissolved in 75 ml of dry ether containing 1 % by weight of boron trifluoride etherate. To this stirred and cooled solution ( $+4^\circ$ ) was dropwise added a solution of diazomethane in ether (prepared from *N*-nitrosomethylurea<sup>13</sup>) until the diazomethane colour persisted. The reaction mixture was then washed with water, dried ( $\text{MgSO}_4$ ), and examined by GLC. It contained about 50 % of unreacted material. The methylation process was therefore repeated, after which the yield of (II) increased to 80 %. (II) was purified by chromatography

on silicic acid (50 g) with a mixture of ether-light petroleum (b. p. 40–60°) (1/1: v/v) as eluent. A colourless liquid, 5.6 g, (70 %) of pure (II) was obtained.

*Methyl 3D-hydroxynonanoate (I) [by demethylation of (II)]*. 2.9 g. (14.4 mmol) of (II) was dissolved in 10 ml of carbon tetrachloride in a large test tube. 16.5 g of iodine (64.3 mmol) was added and the tube partly immersed in a water bath at 45°C. The reaction mixture was continuously stirred by allowing nitrogen to bubble through the slurry. 1.02 g (36.7 mmol) of sodium borohydride was subsequently added in small portions over a period of 15 min and the reaction completed by heating at 45° for a further hour. The reaction mixture containing the borate ester formed was added 50 ml of methanol and refluxed for 2 h. The desired hydroxy ester was thereby set free through transesterification. About 30 ml of the solvents were removed at reduced pressure and the residue distributed among ether and water. The ether layer was washed with a solution of sodium thiosulphate in water to destroy the excess of iodine, then with water and finally dried (MgSO<sub>4</sub>). GLC indicated that about 70 % of (II) had been converted into (I). The remainder consisted essentially of unreacted (II). (I) was purified by chromatography on silicic acid as described for (II). 1.69 g, (63 %) of (I) of  $[\alpha]_D^{25} = -19.9^\circ$ ,  $n_D^{26} = 1.4368$  with a purity better than 99 % was obtained. A second treatment of the unreacted methoxy ester afforded another 400 mg of (I) showing identical physical data. The total yield of (I) after two treatments amounted to 77 %.

### Optical rotations

(–)-Methyl 3D-hydroxynonanoate (I).  $\alpha_D^{25} = -1.00^\circ$  (chloroform; *l*, 1; *c*, 4.97).  $[\alpha]_D^{25} = -20.0 \pm 0.3$  degr. cm<sup>3</sup> dm<sup>-1</sup> g<sup>-1</sup>.  $[M]_D^{25} = -37.6 \pm 0.4$ .

(–)-Methyl 3D-methoxynonanoate (II).  $\alpha_D^{23} = -0.07^\circ$  (chloroform; *l*, 0.5; *c*, 5.00).  $[\alpha]_D^{23} = -2.8 \pm 0.4$  degr. cm<sup>3</sup> dm<sup>-1</sup> g<sup>-1</sup>.  $[M]_D^{23} = -5.6 \pm 0.8$ .

(–)-Methyl 3D-hydroxynonanoate (I) (prepared from (II)).  $\alpha_D^{25} = -0.99^\circ$  (chloroform; *l*, 1; *c*, 4.97).  $[\alpha]_D^{25} = -19.9 \pm 0.3$  degr. cm<sup>3</sup> dm<sup>-1</sup> g<sup>-1</sup>.  $[M]_D^{25} = -37.4 \pm 0.4$ .

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