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A convenient general method for the synthesis of hydroxy diacids

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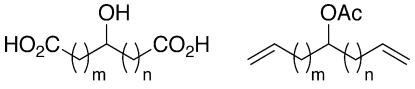
Abstract—Olefinic aldehydes and epoxides with terminal double bonds react with Grignard reagents, and the acetates made from the resulting alcohols undergo double bond cleavage on treatment with $RuCl_3{\cdot}xH_2O$ in the presence of $NaIO_4$ to give acetoxy diacids. Hydrolysis with LiOH then affords hydroxy diacids.

1. Introduction

During the course of a project aimed at providing a bank of samples of human metabolites that are present in body fluids at concentrations above 1 μM, we needed to synthesize a number of hydroxy diacids of general structure **1**, where $n = 0$–1, and $m = 1$–10. The purpose of obtaining these acids—and the other types of compounds we have prepared—is to make available samples for quantitation, so that levels and ratios of these metabolites can be determined as a diagnostic tool in medical practice.



1 **2**

We have developed a general method that allows complete control of the values of *m* and *n* in **1**, although in the present work we have examined only the range $m = 2$–10 and $n = 0$–1, as the corresponding hydroxy diacids appear to be the most important for our diagnostic studies of fatty acid metabolism. The approach is experimentally simple and is based on the fact that terminal double bonds are cleaved efficiently by catalytic amounts of $RuCl_3{\cdot}xH_2O$ in the presence of stoichiometric $NaIO_4$.[1] The cleavage proceeds smoothly at room temperature in a mixture of MeCN, EtOAc and water and gives good yields of the required acids, generally after a 2–12 h reaction period. The reagent combination is compatible with the presence of acetate groups and so we have used the corresponding bis olefinic acetates **2** as precursors of the diacids. These acetates, in turn, are made from the corresponding alcohols, which are themselves readily available by reaction of an appropriate olefinic Grignard reagent with an olefinic aldehyde or olefinic epoxide.

The acids we have made and the synthetic routes are shown in Table 1.

In the particular case of 2-hydroxyhexanedioic acid (**5**), cyclohexenyl acetate (**3**) was the substrate used for the ruthenium-mediated cleavage. In the other examples, except that of entry 7, bis-olefins were used, and they were made by direct Grignard addition to aldehydes or by copper-catalyzed addition to epoxides.

It is known that silicon protecting groups are removed by $NaIO_4$ solutions,[11] although this may not be due to the acidity of the solutions (pH 2.5[12]) because desilylation (at least of Et_3Si-groups) occurs even in a buffered neutral or slightly basic medium.[11] Nonetheless, we find that the $RuCl_3{\cdot}xH_2O$–$NaIO_4$ system removes *t*-$BuMe_2$-Si-groups from oxygen and oxidizes the resulting primary alcohol to a carboxylic acid; this very convenient feature was used in the synthesis of **35** for which the substrate for reaction with allylmagnesium bromide was ω-siloxy aldehyde **31**. In contrast to the present work, *tert*-butyldimethylsilyl ethers of secondary alcohols appear to be reasonably stable to $RuCl_3{\cdot}xH_2O$-$NaIO_4$.[13–15]

The present method is operationally simple and the precursors are available by standard methods. The reactions are clean, and it is convenient to use the

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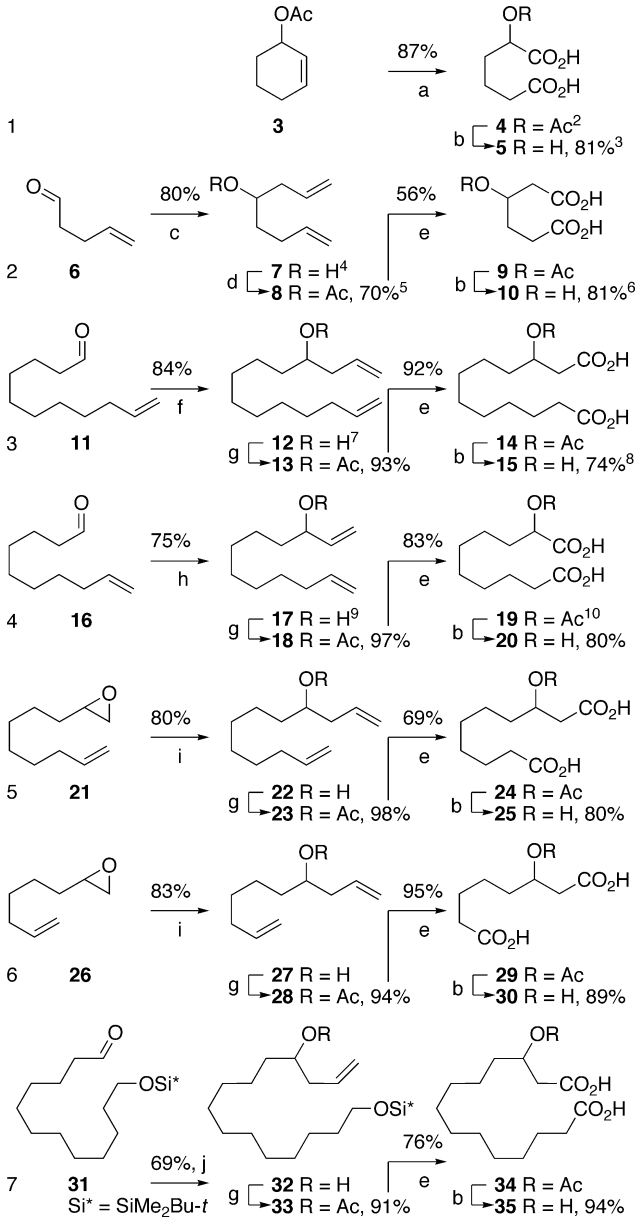
Table 1. Synthesis of hydroxy diacids



Superscript numbers 2–9 refer to references. (a) $RuCl_3{\cdot}xH_2O$, $NaIO_4$, 2:2:3 MeCN–EtOAc–water, 2 h; (b) LiOH, 1:10 water–THF, 12 h; (c) allylmagnesium bromide, THF, −78 °C, 2 h; (d) AcCl, pyridine, CH_2Cl_2, 3 h; (e) $RuCl_3{\cdot}xH_2O$, $NaIO_4$, 2:2:3 MeCN–EtOAc–water, 12 h; (f) allylmagnesium bromide, Et_2O, −78 °C, 2 h; (g) Ac_2O, Et_3N, CH_2Cl_2, 3 h; (h) vinylmagnesium bromide, THF, −78 °C, 2 h; (i) vinylmagnesium bromide, CuI, THF, −78 °C, 1.5 h; (j) allylmagnesium bromide, Et_2O, −78 °C, 5 h.

crude acetates directly for hydrolysis, to liberate the desired hydroxy acids. Representative procedures are as follows.

2. (±)-2-Acetoxydecanedioic acid (19)[10]

$RuCl_3{\cdot}3H_2O$ (50 mg, 0.24 mmol) and $NaIO_4$ (9.69 g, 45.34 mmol) were added to a stirred mixture of acetic acid 1-vinyldec-9-enyl ester (1.24 g, 5.53 mmol) and 3:2:2 water–MeCN–EtOAc (35 mL), and stirring was continued for 12 h. The mixture was then diluted with EtOAc (50 mL) and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give (±)-2-acetoxydecanedioic acid (1.20 g, 83%) as an oil which was used directly in the next step.

3. (±)-2-Hydroxydecanedioic acid (20)

LiOH (332 mg, 13.84 mmol) was added to a stirred solution of (±)-2-acetoxydecanedioic acid (1.20 g, 4.61 mmol) in 10:1 THF–water (15 mL) and stirring was continued overnight. Most of the organic solvent was evaporated and the aqueous phase was acidified with 1 N hydrochloric acid and extracted with EtOAc (5×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give 2-hydroxydecanedioic

acid (800 mg, 80%) as a solid: mp 118–121 °C (from EtOAc); FTIR (DMSO cast) 3510 (sharp), 3400–2000 (br), 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ plus DMSO-d_6) δ 1.15–1.39 (m, 8H), 1.40–1.60 (m, 3H), 1.60–1.71 (m, 1H), 2.13 (t, $J = 7.7$ Hz, 2H), 3.99 (dd, $J = 7.2$, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.4 (t), 24.6 (t), 28.4 (t), 28.6 (t), 33.6 (t), 33.9 (t), 69.5 (d), 174.4 (s), 175.9 (s); exact mass m/z calcd for $C_{10}H_{17}O_5$ (M−H) 217.10705. Found: 217.10655.

4. (±)-3-Acetoxytetradecanedioic acid (34)

$RuCl_3 \cdot 3H_2O$ (27.6 mg, 0.133 mmol) and $NaIO_4$ (2.33 g, 10.91 mmol) were added to a stirred mixture of 1-[(11-(*t*-butyldimethylsilyl)oxy]undecyl]but-3-enyl ester (530 mg, 1.33 mmol) in 3:2:2 H_2O–MeCN–EtOAc (14 mL), and stirring was continued for 12 h. The mixture was then extracted with EtOAc (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. The resulting residue was neutralized with saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (2×20 mL). The aqueous phase was acidified with 20% hydrochloric acid and extracted with EtOAc (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give (±)-3-acetoxytetradecanedioic acid (320 mg, 76%) as a white solid, which was used directly for the next step.

5. (±)-3-Hydroxytetradecanedioic acid (35)

LiOH (95 mg, 3.98 mmol) was added to a stirred solution of (±)-3-acetoxytetradecanedioic acid (315 mg, 0.99 mmol) in 1:1 THF–water (5 mL) and stirring was continued overnight. Most of the organic solvent was evaporated and the aqueous phase was acidified with 1 N hydrochloric acid and extracted with EtOAc (5×10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give (±)-3-hydroxytetradecanedioic acid (260 mg, 95.2%) as a white solid: mp 113–116 °C; FTIR (DMSO cast) 3565 (sharp), 3400–2000 (br), 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ plus DMSO-d_6) δ 1.15–1.59 (m, 18H), 2.19 (t, $J = 7.2$ Hz, 2H), 2.29 (dd, $J_{AB} = 16.3$, $J_{BX} = 8.8$ Hz, 1H), 2.41 (dd, $J_{AB} = 16.3$, $J_{AX} = 3.4$ Hz, 1H), 3.84–3.95 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.5 (t), 25.0 (t), 28.5 (t), 28.7 (t), 28.9 (t), 28.9 (t), 29.0 (t), 33.6 (t), 36.9 (t), 42.7 (t), 67.0 (d), 173.0 (s), 174.4 (s); exact mass m/z calcd for $C_{14}H_{25}O_5$ (M−H) 273.16965. Found: 273.17045.

Acknowledgements

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