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ASYMMETRIC SYNTHESIS OF (S)-METHYL-3-HYDROXYALKANOATES FROM KETENE AND 2,2-DICHLOROALDEHYDES VIA 4-(1,1-DICHLOROALKYL)-2-OXETANONES

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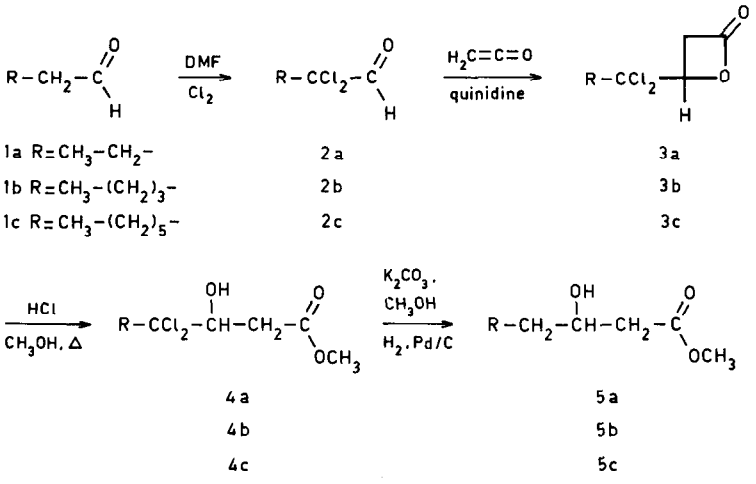
Abstract: Using the quinidine catalyzed cycloaddition reaction of ketene and 2,2-dichloroaldehydes, the preparation of several optically pure (S)-methyl-3-hydroxyalkanoates is reported.

Recently we reported a reasonably efficient enzymic synthesis of 1-octanol and optically active 1,2-epoxyoctane (70% e.e.) from n-octane and 1-octene by Pseudomonas oleovorans.[1,2,3]

We had reasons to believe that the intracellular inclusions[4] formed during this oxidation contained poly-3-hydroxyoctanoate.[5] The absolute configuration of the chiral centers of poly-3-hydroxybutanoate, also a well known constituent of intracellular inclusions[6] can be correlated to methyl-3-hydroxybutanoate by methanolysis of the polymer and was shown to be R.[7] In the same way the R-configuration was assigned to the chiral centers in poly-3-hydroxypentanoate.[8] In order to be able to confirm the structure of the monomer and to assign the absolute configuration of the chiral centers in poly-3-hydroxyoctanoate, we developed an independent synthesis of optically pure methyl-3-hydroxyalkanoates. Encouraged by the success of our synthesis of (S)-methyl-3-hydroxybutanoate from (R)-4-(trichloromethyl)-2-oxetanone,[10,11] obtained from the quinidine catalyzed cycloaddition of chloral and ketene, we decided to develop a synthesis of (S)-methyl-3-hydroxyalkanoates, using (R)-4-(1,1-dichloroalkyl)-2-oxetanones (3a,b,c) as chiral educt. The sequence of reactions leading to the desired products is depicted in Scheme I.

A typical procedure for the synthesis of these optically pure methyl-3-hydroxyalkanoates follows: 2,2-Dichloroaldehydes (2a,b,c) were prepared by direct chlorination according to the method described by de Buyck.[9] The crucial step in the reaction sequence is the asymmetric synthesis of (R)-4-(1,1-dichloroalkyl)-2-oxetanones (3a,b,c).[15] The formation of the chiral center was achieved by the reaction of the 2,2-dichloroaldehydes (2a,b,c) with ketene

Scheme 1



1a R=CH_3-CH_2- 2a 3a

1b R=$CH_3-(CH_2)_3-$ 2b 3b

1c R=$CH_3-(CH_2)_5-$ 2c 3c

4a 5a

4b 5b

4c 5c

in the presence of quinidine as a chiral catalyst.[10,11] The 2-oxetanones (3a,b,c) were formed in nearly quantitative yields (90-95%, 0.2 mole scale) and virtually optically pure (92% enantiomeric excess).

Both 3b and 3c are crystalline compounds and they can be obtained enantiomerically pure by one crystallization from methylcyclohexane. By the indirect DSC-method, described by Jacques, Collet and Wilen[12] compounds 3b and 3c were shown to have an e.e. $\geq$ 98% (3a, $[\alpha]_{578}^{20}$ 18.9, c 1, cyclohexane, 92% e.e.; 3b, $[\alpha]_{578}^{20}$ 7.9, c 1, cyclohexane, m.p. 36-37°C, > 98% e.e.; 3c, $[\alpha]_{578}^{20}$ 3.4, c 1, cyclohexane, m.p. 31-32°C, > 98% e.e.). The 2-oxetanones produced in other quinidine catalyzed ketene reactions, were shown to be of R-configuration by comparison of their CD-spectra with CD-spectra of 4-(trichloromethyl)-2-oxetanone of known absolute configuration.[10,11,13] In the CD-spectra of 2-oxetanones the n-π^* transition of the C=O chromophore at 200-220 nm is observed. All 4-(1,1-dichloroalkyl)-2-oxetanones obtained from the quinidine catalyzed reaction, show a positive Cotton-effect in this region and are of R-configuration.[8,10]

Methyl-4,4-dichloro-3-hydroxyalkanoates (4a,b,c) were prepared by the reaction of (R)-2-oxetanones in CH_3OH-HCl at reflux temperature (0.2 mole scale). Evaporation of the solvent and purification by bulb to bulb distillation (110°C, 0.05 mmHg) yielded 4a, b, and c (c.y. 75-80%, R-configuration; 4a, $[\alpha]_{578}^{20}$ 8.2, c 1, cyclohexane, e.e. 92%; 4b, $[\alpha]_{578}^{20}$ 12.4, c 1, cyclohexane, e.e. $\geq$ 98%; 4c, $[\alpha]_{578}^{20}$ 10.2, c 1, cyclohexane, e.e. $\geq$ 98%). The final reaction step, the hydrogenolysis of (R)-methyl-4,4-dichloro-3-hydroxyalkanoates (4a,b,c) to obtain (S)-methyl-3-hydroxyalkanoates (5a,b,c) was performed in a Parr-apparatus on a 0.05 mole

scale, using Pd/C (10%) as a catalyst under a hydrogen atmosphere (3 atm. H_2-pressure) in dry methanol as a solvent. It was necessary to add base (K_2CO_3, slight excess) to neutralize HCl formed during the reaction. Addition of a drying agent ($MgSO_4$) proved to be advantageous. Probably the water liberated upon neutralization of HCl tends to hydrolyse the esters, thus decreasing yields. Flash chromatography (SiO_2, pentane-ether, 1:3) and bulb to bulb distillation (60°C, 0.05 mmHg), yielded the esters,[16] (S)-methyl-3-hydroxyhexanoate (5a), c.y. 85%, $[\alpha]_{578}^{20}$ 18.9, c 1, cyclohexane; (S)-methyl-3-hydroxy octanoate (5b), c.y. 87%, $[\alpha]_{578}^{20}$ 23.6, c1, cyclohexane; (S)-methyl-3-hydroxy decanoate (5c), cy 83%, $[\alpha]_{578}^{20}$ 25.8, c 1, cyclohexane.

No inversion takes place during hydrogenolysis, but change in R/S nomenclature is caused by change in substituents. Using the method by Feringa, Smaardijk and Wynberg,[14] the esters 5b and 5c were shown to have enantiomeric purities of $\geq$98%. Compound 5a is only 92% enantiomerically pure.

In this paper only the synthesis of (S)-methyl-3-hydroxyalkanoates is described . However, using optically pure (S)-2-oxetanones as chiral starting materials, allows the preparation of the (R)-enantiomers of the methyl-3-hydroxyalkanoates. The (S)-4-(1,1-dichloroalkyl)-2-oxetanones can be prepared using quinine or benzoylquinine as a catalyst in the cycloaddition reaction of ketene and the dichloroaldehydes.

Physical, analytical and spectroscopic data of compounds 5a,b,c are as follows:

5a. Methyl-3-hydroxy hexanoate: $C_7H_{14}O_3$ (MW = 146); b.p. 55-58°C, 0.05 mmHg. Anal. calcd.: C, 57.51; H, 9.65; O, 32.84. Found: C, 58.10; H, 9.85; O, 32.55. MS: M^+ at m/e = 145; IR: 1110, 1160, 1400, 1430, 1440, 1720, 2865, 2930, 2975, 3480 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ 0.94 ppm (m, 3H), 1.46 (m, 4H), 2.45 (d, 2H), 3.36 (s, 1H), 3.72 (s, 3H), 3.99 (t, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 13.7 (q), 18.4 (t), 38.5 (t), 41.0 (t), 51.4 (q), 67.5 (d), 173.1 (s).

5b. Methyl-3-hydroxyoctanoate: $C_9H_{18}O_3$ (MW = 174); b.p. 63-65°C, 0.05 mmHg. Anal. calcd.: C, 62.04; H, 10.41; O, 27.55; found: C, 61.11, H, 10.37; O, 28.22. MS: M^+ at m/e = 173; IR: 1120, 1160, 1410, 1440, 1450, 1730, 2860, 2925, 2970, 3520; ^1H NMR ($CDCl_3$, 60 MHz): δ 0.89 (m, 5H), 1.40 (m, 6H), 2.43 (d, 2H), 3.37 (s, 1H), 3.68 (s, 3H), 3.98 (t, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 13.8 (q), 22.4 (t), 25.0 (t), 31.5 (t), 36.4 (t), 41.1 (t), 51.5 (q), 62.9 (d), 173.2 (s).

5c. Methyl-3-hydroxydecanoate: $C_{11}H_{22}O_3$ (MW = 202); b.p. 74-76°C, 0.05 mmHg. Anal. calcd.: C, 65.35; H, 10.96; O, 23.64; found: C, 64.95; H, 10.64; O, 24.14. MS: M^+ at m/e = 201; IR: 1125, 1170, 1410, 1440, 1460, 1730, 2850, 2920, 2970, 3470; ^1H NMR ($CDCl_3$, 60 MHz): δ 0.88 (m, 6H), 1.39 (m, 9H), 2.45 (d, 2H), 3.35 (s, 1H), 3.70 (s, 3H), 3.95 (t, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 13.9 (q), 22.5 (t), 25.3 (t), 29.0 (t), 29.3 (t), 31.6 (t), 36.3 (t), 41.0 (t), 51.5 (q), 67.8 (d), 173.3 (s).

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