

Synthesis of the 9-oxo-diene derivative of methyl dimorphecolate by an efficient Oppenauer oxidation procedure

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Abstract

Oxidation of methyl dimorphecolate (**1**) to methyl 9-oxo-10,12-E,E-octadecadienoate (**2**) has been studied, using Oppenauer conditions. Acetone and cyclohexanone have been used as oxidizing ketones. Combination of cyclohexanone with inert solvents has been performed to minimize the side reactions: degradation of the aluminum alkoxide catalyst and transesterification of the desired product (**2**). The optimal procedure is reported on 25 g scale using cyclohexanone (1.5 eq) and aluminum *t*-butoxide (0.2 eq) in hexane at 50°C (30 min).

Keywords: Methyl 9-oxo-10,12-E,E-octadecadienoate; Cyclohexyl 9-oxo-10,12-E,E-octadecadienoate; Catalysis

1. Introduction

Dimorphecolic acid, *S*(+)-9-hydroxy-10,12-E,E-octadecadienoic acid, is a highly functionalized fatty acid that can be isolated from the seed oil of *Dimorphotheca pluvialis* [1–4]. The hydroxy diene system of this compound or its methyl ester (**1**) is an interesting building block for organic synthesis. Mild reaction conditions are preferable, because of the lability of the hydroxy group [1–4]. Conversion of the hydroxy group to a keto function will result in the more stable methyl 9-oxo-10,12-E,E-octadecadienoate (**2**), which enlarges the possibilities for organic conversions based on this natural source [4–9].

Up to now only an oxidation method was reported with chromic anhydride in pyridine [1,5]. This reaction is rather cumbersome for development of the keto derivative **2** as starting material, while an Oppenauer oxidation [10,11] as a mild and clean method should provide the same product [4]. We investigated the reaction conditions of this catalytic reaction in order to establish a method that could be useful in fatty acid chemistry.

2. Experimental procedures

Dimorphotheca pluvialis seeds were milled and extracted with petroleum ether (b.p. 40–60°C), and the oil was transesterified as previously described [4].

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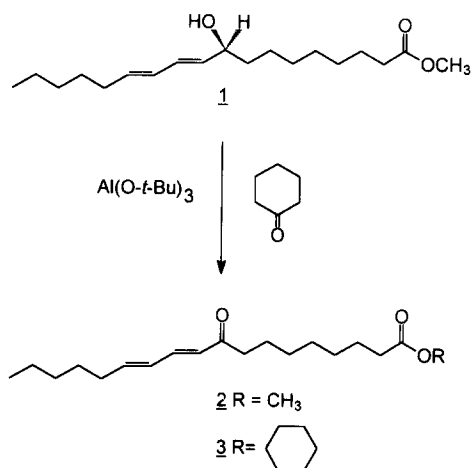


Fig. 1. Oppenauer oxidation of methyl dimorphecolate (1) to methyl 9-oxo-10,12-*E,E*-octadecadienoate (2) and cyclohexyl 9-oxo-10,12-*E,E*-octadecadienoate (3) as a by-product.

GC analysis was carried out with a Varian model 3600 instrument equipped with a split/splitless capillary injector model 1077. The compounds were separated on an analytical fused silica column coated with DB-5 chemically bonded phase (30 m × 0.25 mm i.d., 0.25 μm d_f) (J&W Scientific). Helium was used as a carrier gas (linear velocity = 29 cm/s, split ratio 1:100). The injector and detector temperatures were 270°C. The oven temperature was 210°C for 3 min, raised by 4°C/min to 250°C and held for 17 min.

GC/MS was performed as previously described [4].

2.1. Identification of cyclohexyl 9-oxo-10,12-*E,E*-octadecadienoate (3)

m/e (%): 376 (4, M⁺); 305 (19, M-C₅H₁₁); 294 (12, M-82 (cyclohexene)); 171 (43); 166 (44, McLafferty rearrangement at C9-carbonyl); 151 (55, α-cleavage between C8 and C9); 95 (100); 83 (42); 81 (86); 67 (45); 55 (77).

The progress of the Oppenauer oxidation of 1 was followed by GC. Samples were vigorously shaken with water, filtered, extracted with hexane, washed again with water, dried (sodium sulphate) and concentrated under reduced pressure. Samples (20 mg) were silylated with 450 μl of BSTFA (*N,O*-bis(trimethylsilyl)trifluoroacetamide) and 50 μl of

TMCS (trimethylchlorosilane) for 20 min at 70°C. After evaporation of the solvents under nitrogen 1 ml of hexane was added for GC analysis.

2.2. Oppenauer oxidation of methyl dimorphecolate (1)

To a solution of 25 g of 1 (94% purity) in 125 ml of hexane (conc. 1 0.32 mol/l) was added 11.75 ml of cyclohexanone (1.5 mol/mol 1) and 3.74 g of aluminum *t*-butoxide (0.2 mol/mol 1). The mixture, protected with a calcium chloride drying tube, was stirred for 30 min at a bath temperature of 50°C. After being cooled to room temperature, the reaction mixture was washed with 455 ml 0.1 N hydrochloric acid, twice with 140 ml of 0.05 N hydrochloric acid, 125 ml of 1% aqueous sodium bicarbonate and 125 ml of water, dried (magnesium sulphate) and evaporated (12 mmHg, 50°C). The residue contained 91% of methyl 9-oxo-*E,E*-10,12-octadecadienoate (2) (24 g evaporated in high vacuo at 50°C).

2.3. Purification of methyl 9-oxo-*E,E*-10,12-octadecadienoate (2)

The crude material was dissolved in 106 ml of 91:9 petroleum ether (b.p. 40–60°C):ethyl acetate. The solution, kept overnight at 4°C, deposited a solid. The precipitate was filtered, washed twice with 60 ml petroleum ether (–20°C) and dried in high vacuo to afford 2 (10.3 g, purity 97.4%). The mother liquor was concentrated to a volume of 60 ml, and at 4°C a second crop was formed (6.1 g, purity 95.2%). The combined crops (16.4 g) were redissolved in 44 ml of 91:9 petroleum ether:ethyl acetate. Overnight (at 4°C) 6.24 g of white crystals was obtained (99.6% purity by GC). The yield (26.8%) of purified material can be increased by further processing of the mother liquors, but for practical applications such purification may be unnecessary.

The onset temperature of the melting peak of 2 (99.8% purity) was determined with a Perkin Elmer DSC-7. Samples (5.5 mg) were heated with a scan rate of 5°C/min in a hermetically sealed stainless steel cup. Onset temperature 33.1°C. Melting temperature lit. 33–34°C [5].

CAS registry numbers: 1: 6114-34-7; 2: 71201-23-5.

3. Results and discussion

Oxidation of methyl dimorphocolate (**1**) in acetone (0.08 mol/l) with aluminum *t*-butoxide (0.63 mol/mol **1**) as the catalyst gives the keto derivative (**2**) in poor yield (70% in 24 h). Aluminum alkoxide catalyzed selfcondensation of acetone degrades the catalyst by hydrolysis [10,11]. The addition of an extra amount of catalyst, up to 3 mol/mol **1**, enlarges the yield to more than 90%.

The addition of cyclohexanone to the acetone solution as a stronger oxidizing ketone results in a higher conversion degree up to 96%. Thus the ratio of the reaction rates of oxidation over hydrolysis of the catalyst becomes larger. Complete conversion can be reached by refluxing in cyclohexanone, which has to be separated from the reaction products by steam distillation [10].

It is of interest to study the conversion degree with low amounts of cyclohexanone in a solvent that does not degrade the catalyst. Compound **1** appears to be completely oxidized in refluxing toluene (0.16 mol/l) with cyclohexanone (3 mol/mol **1**) within 1 h. GC-MS analysis of the reaction mix-

ture showed cyclohexyl 9-oxo-10,12-E,E-octadecadienoate (**3**) as a major by-product from **4** to 27%. This product **3** has to be formed by an aluminum alkoxide catalyzed transesterification of **2** with cyclohexanol. The amount of **3** was decreased by lowering the reaction temperature. At 60°C **1** is almost completely converted into **2**, with minor formation of **3**, 92 and 4%, respectively.

Since a high temperature appears to be unnecessary, toluene can be replaced with hexane. In this system the influence of temperature and amount of catalyst is further investigated. The best result is obtained at 50°C with aluminum *t*-butoxide (0.2 mol/mol **1**) and cyclohexanone (1.5 mol/mol **1**) in hexane.

The procedure, applied on 25 g scale (conc. 1.032 mol/l) affords **2** within 30 min. High-purity material (99.6–99.8%, m.p. 33.1°C) is easily obtained by recrystallization (petroleum ether:ethyl acetate, 91:9).

4. Conclusions

Methyl dimorphocolate (**1**), despite the labile hydroxyl function, can be readily oxidized by an Oppenauer procedure. The side reactions, degradation of the aluminum alkoxide catalyst and transesterification of the desired product (**2**), can be minimized by applying the optimal reaction conditions.

The clean catalytic procedure described here may be a convenient method for the oxidation of hydroxy fatty acids in general.

References

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Table 1

Oppenauer oxidation of methyl dimorphocolate (**1**) in hexane

Exp.	Oxid. Cat.	<i>t</i> (h)	<i>T</i> (°C)	cv.	2	3	
1a	3	0.63	0.5	68	99	90	5
1b	3	0.63	1	68	99	84	10
2	3	0.32	0.5	68	99	92	5
3a	1.5	0.32	0.25	68	99	89	7
3b	1.5	0.32	0.5	68	99	87	11
3c	1.5	0.32	1	68	99	73	23
4	1.5	0.32	0.5	50	98	93	2
5a	1.5	0.32	0.25	40	66	62	—
5b	1.5	0.32	0.5	40	88	85	—
5c	1.5	0.32	1	40	98	93	1
6a	1.5	0.20	0.5	50	95	92	—
6b	1.5	0.20	1	50	99	94	3
7	1.5	0.10	2	50	79	74	0.1

0.16 mol/l of **1** in hexane. Oxid., mol cyclohexanone/mol **1**; Cat., mol Al(O-*t*-Bu)₃/mol **1**; cv., percentage conversion of **1**; **2**, area per cent methyl 9-oxo-10,12-E,E-octadecadienoate by GC; **3**, area per cent cyclohexyl 9-oxo-10,12-E,E-octadecadienoate.

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