

Communication

A Three Step Synthesis of 11-Cycloheptylundecanoic Acid, a Component of the Thermoacidophile *Alicyclobacillus cycloheptanicus*

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Abstract: A simple synthesis of the methyl ester of 11-cycloheptylundecanoic acid (**1**), isolated from the lipid fraction of the thermoacidophile, *Alicyclobacillus cycloheptanicus* has been developed. This involved regioselective Grignard coupling between cycloheptylmagnesium bromide and methyl 11-bromoundecanoate (**2**), prepared from 10- undecanoic acid.

Keywords: *Alicyclobacillus cycloheptanicus*, Grignard coupling, regioselective reaction

Introduction

Recently, a fatty acid mixture was isolated from the lipids of the thermoacidophile *Alicyclobacillus cycloheptanicus* [1-3]. Subsequently, it was identified as a mixture of ϵ -cycloheptyl fatty acids which are unique in this organism [4]. It has been suggested that these acids enable the organism to grow in acidic, hot media by providing a more dense cell membrane. This has led to the important understanding of their biosynthetic relations. However, owing to their very low natural abundance, it is

necessary to synthesise these fatty acids in order to obtain them in sufficient amount both for their structural establishment and investigation of the involved biosynthetic pathway. One such compound of this class is 11-cycloheptylundecanoic acid (**1**).

Results and Discussion

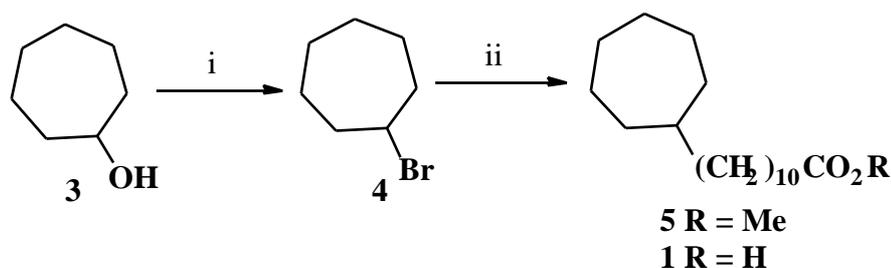
Our current endeavour in synthesis of bioactive compounds prompted us to develop a short and simple approach to the synthesis of the title compound which is shown in Scheme 1. To our knowledge, this is the first

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report of the synthesis of the title compound. The salient feature of our scheme is the Grignard coupling of the bromoester (**2**), that had been prepared by us [5], starting from the easily accessible undecanoic acid during our synthetic study of insect pheromones.

Commercially available cycloheptanol (**3**) was brominated using $\text{Ph}_3\text{P}/\text{Br}_2$ [6] to afford the bromide (**4**) in good yield. The Grignard reagent obtained from **4** was

coupled with **2** in the presence of Li_2CuCl_4 at $-70\text{ }^\circ\text{C}$ directly to give the ester (**5**). Here, the ester functionality of **2** remained unaffected by the Grignard during the coupling reaction condition. The structure of **5** has been confirmed from its spectral data which were found to be identical with those reported in the literature [4]. The formal synthesis of **1** can be achieved by saponification of **5**.



i) $\text{Ph}_3\text{P}.\text{Br}_2/\text{pyridine}/\text{CH}_2\text{Cl}_2$, ii) $\text{Mg}/\text{THF}/\text{Li}_2\text{CuCl}_4/\text{Br}(\text{CH}_2)_{10}\text{CO}_2\text{Me}$ (**2**)

Scheme 1.

Experimental

General

The bp's and mp's are uncorrected. The IR spectra were recorded on a Perkin-Elmer Spectrophotometer model 783 as a thin film and only the pertinent bands are reported. The $^1\text{H-NMR}$ spectra were obtained on a Varian EM 360 instrument (60 MHz) in CDCl_3 . The mass spectra were recorded on Shimadzu QP-1000A GC-MS. All solvents were dried and distilled prior to use, unless otherwise noted. Organic extracts were dried over anhydrous Na_2SO_4 .

Cycloheptyl bromide (**4**)

To a cooled (0°C) and stirred solution of triphenylphosphine (7.86 g, 0.03 mol) in CH_2Cl_2 (50 mL) was added Br_2 (1.6 mL) in CH_2Cl_2 (50 mL) dropwise over a period of 30 min. To the resulting white suspension was added a solution of cycloheptanol (**3**) (3.42 g, 0.03 mol) in pyridine (2.6 mL) over a period of 1 h while cooling was maintained externally. After stirring the mixture for 3 h, the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column, eluting with petroleum ether. The evaporation of the

solvent furnished **4** (3.7 g, 69.8%): b.p $82^\circ\text{C}/10\text{ mm}$; IR: 2928, 1458 cm^{-1} ; $^1\text{H-NMR}$: 1.5 (m, 12H, 6 x CH_2), 3.4 (m, 1H, CHBr).

Methyl 11-Cycloheptylundecanoate (**5**)

To a stirred suspension of Mg (1.44 g, 0.06 mol) in THF (15 mL) was added **4** (8.85 g 0.05 mol) in THF (50 mL) at room temperature over a period of 1 h. The mixture was cooled to -78°C , Li_2CuCl_4 (3.5 mL, 0.1 M, prepared by dissolving 85 mg of LiCl and 43 mg of CuCl_2 in 10 mL THF) added and the mixture stirred over a period of 30 min. A solution of **2** (12.6 g, 0.045 mol) in THF (50 mL) was then added dropwise over a period of 1 h. Stirring was continued overnight at room temperature. Saturated aqueous NH_4Cl solution was added to decompose the Grignard complex. The mixture was filtered and extracted with ether. The usual workup and removal of solvent, followed by column chromatography of the residue, furnished **5** (6.68 g, 50%): IR: 2942, 1745 cm^{-1} ; $^1\text{H-NMR}$:

1.3 (m, 18 H, 9 x CH_2), 1.4-1.7 (m, 13H, 6 x CH_2 and CH), 2.3 (t, $J = 6\text{ Hz}$, 2H), 3.7 (s, 3H, OCH_3). MS: 296 (19), 200 (M- C_7H_{12}) (23), 171 (2), 157 (9), 143 (22), 129 (8), 111 (12), 97 (C_7H_{13}) (68), 87 (90), 74 ($\text{C}_3\text{H}_6\text{O}_2$) (100).

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Sample Availability: Samples available from the authors.