Synthesis of Unnatural Diethyl 2-Hydroxysuccinate From 2,3-Dihydroxysuccinic Acid As a Starting Material for Annonine Building Blocks

Jewad K. Shneine
Ministry of Higher Education and Scientific Research
Department of Missions and Cultural Relations Cultural Attaché Berlin
Corresponding author: jkshneine@gmail.com

Abstract

Since Annonin I is considered as a biological active natural product, this work concerns on the synthesis of the side chain of this biologically important molecule as a part of total synthesis of the whole molecule. As a result of our retrosynthetic analytical method, the commercial available 2,3-Dihydroxysuccinic acid A and pentyl halide B represent generally the main building blocks for the synthesis. The synthesis begins with Fischer esterification of the dicarboxylic acid 1 and then conversion into Diethyl 3-bromo-2-hydroxysuccinate 3 which was the key compound to obtain the acetal (2-phenyl-1,3-dioxan-4-yl) methanol 6. In this respect, two different synthetic routs were evaluated to transform compound 3 into 6. Furthermore, the removal of bromide step (reduction of 3) was also studied using different reducing agents. [DOI: 10.22401/ANJS.21.4.05]

Keywords: Annonin, Natural products, Retro synthesis, Tartaric acid.

Introduction

Natural product chemistry has recently gained interest as many natural products are used in medicine, agriculture, and food chemistry. Recent research has provided us with interesting natural products, such as the taxol obtained from egg-needles of Taxon brevifolia and the acetogenins obtained from plants of the genus Annonacae [1]. These two compounds have proved to be cytotoxic in cancer cells in laboratory tests [2]. The Acetogenins also have an insecticidal effect on a large number of plant pests [3].

Cinnamon or cinnamon apple, which obtained from the seeds of the fruits of the cinnamon or raspberry, has proved to be particularly effective [4]. For this reason, the synthesis of the annonine I Fig.(1) is of great interest. The synthesis is very complicated, but justified, as it is later established, since the total synthesis can make the effectiveness of the individual building blocks verifiable beyond the synthesis of the molecule and give indications as to which partial structure of the molecule is responsible for the effect. The stereochemistry of the molecule, for example, usually plays a decisive role in its effect [4]. Annonin I has the following structure:

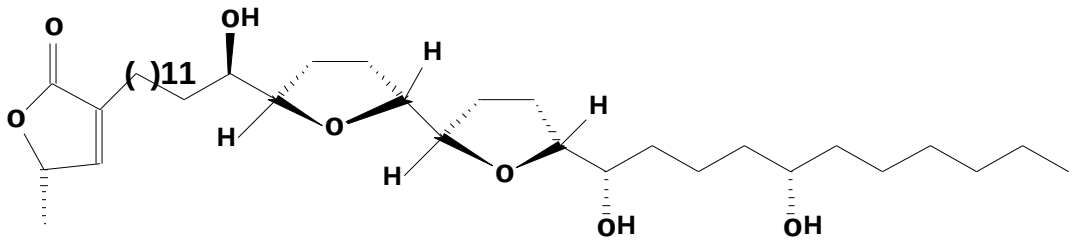
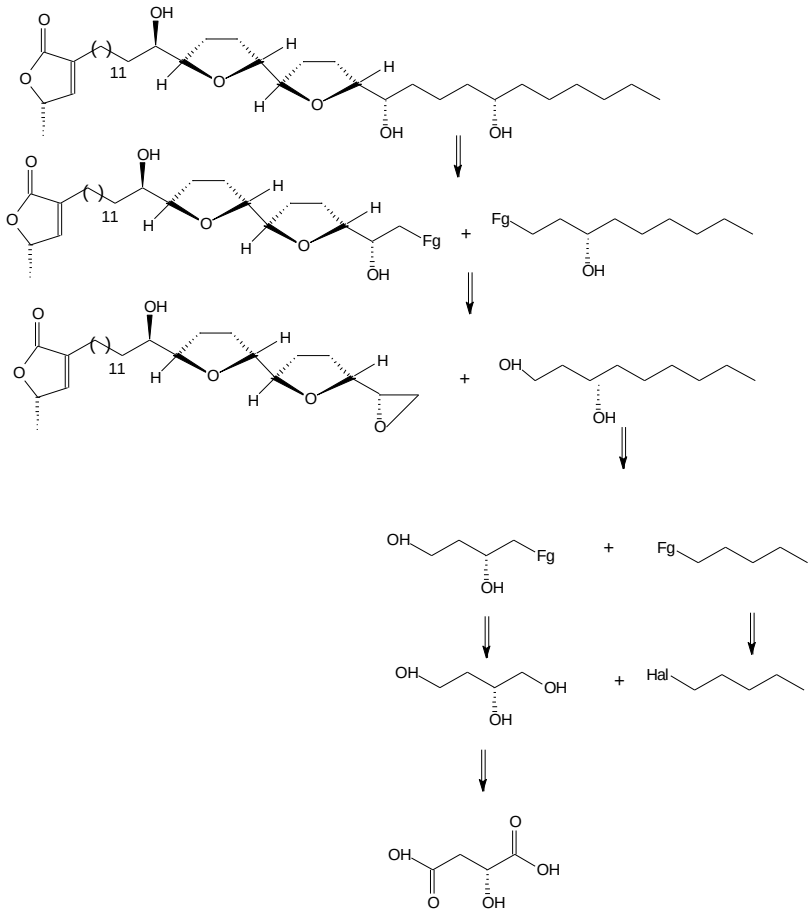


Fig.(1): Structure of the natural product annonine I.

Retrosynthetic analysis is a commonly method to find synthetic building blocks for natural products synthesis in laboratory [5]. After reterosynthetic analysis, annonin I molecule can be theoretically cleaved into fractions which must be commercially viable and presents a reasonable reaction steps in a later synthesis [6] (scheme. 1). Consequently, malic acid and pentyl halide form the main building blocks of the side chain of Annonin I. Therefore, this work deals with the optimization of the synthesis of the side chain.



Scheme (1): Retrosynthetic analysis of annonin I.

Materials and methods

1 Chemicals

Commercially available chemicals from Bayer, Jansen, Merck, Riedel de Haen and Aldrich were used. The chemicals were not subjected to any further purification prior to use. Solvents used were purified by the ordinary methods, and were dehydrated and stored.

2 Instruments

The following instruments were used in this work:

1-NMR spectra were recorded on the following instruments: (in $CDCl_3$, internal standard: TMS)

^{1}H-NMR: Varian VXR 300 (300 MHz)

^{13}C-NMR: Varian VXR300 (75 MHz)

2-Thin layer chromatography (TLC): Aluminium sheets, Kieselgel 60F254 from Merck; Carrying agent: cyclohexane/ ethyl acetate 3: 1; Detection: EtOH / H_2SO_4 / P-anisaldehyde 36: 2: 2; Development temperature: 120-150 °C.

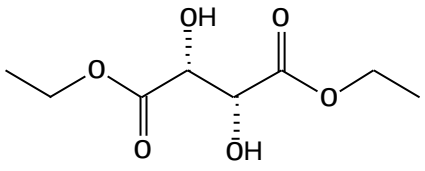
3-Column chromatography: Kieselgel 60 (0.1-0.2 nm) from Macherey & Nagel

3 Synthetic procedures

3.1 diethyl 2,3-dihydroxysuccinate 2 [7]

534 g (3.558 mol) of 2,3-dihydroxysuccinic acid 1 were dissolved in 653 ml (7.116 mol) of ethanol and 801 ml of chloroform and 2 g of p-toluenesulfonic acid were added. The mixture was then refluxed for 36 hours until no more water separates. After removal of the volatile constituents in the rotary evaporator, the ester was obtained by vacuum distillation.

b.p = 90 °C (0.01 Torr), Yield: 600 g (81.7 %); Lit.: 162 °C / 19 mm (311.0°C / 760 mm Hg) [8].



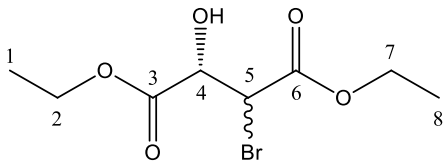
2

3.2 diethyl 2-bromo-3-hydroxysuccinate 3 [9]

309 g (1.5 mol) of diethyl 2,3-dihydroxysuccinate 2 were introduced into a 1 L three-necked flask. 125 ml (2 mol) of thionyl chloride (1.6 g/ ml) were added dropwise at 30° C with stirring, followed by 10 drops of abs. DMF. The mixture is then stirred at 50°C overnight under reflux. The remaining HCl was carefully removed in a vacuum. The reaction mixture is then cooled and diluted with acetone. 260 g (2 mol) of lithium bromide were added in portions with stirring and the mixture was stirred at 50° C for 24 hours. After cooling, so much water was added that the solid completely dissolves. After acetone evaporation, the mixture was extracted three times with methylene chloride, dried over $MgSO_4$, and the solvent was distilled off. The product is then purified by distillation. b.p: 81°C (0,01 Torr); Yield: 288 g (72%).

^{1}H-NMR: ($CDCl_3$, 300 MHz) δ (ppm) = 1,32 (t,t; 6H, J = 7,08 u.7,09 Hz CH3: 1 and 8), δ = 4,285 (d,d; 4H, J = 7,08 u. 7,09 Hz CH2: 2 and 7), δ = 4,718 (m; 1H, J = 4,72 Hz CH: 5) = 4,81 (m; 1H, J = 4,39 Hz CH: 4).

^{13}C-NMR: ($CDCl_3$; 75MHz) δ (ppm) = 13.95-13.99, C8; δ = 14.07- 14.13 C1; δ = 47.60- 47.59, C4; δ = 62.38, 62.753, C2/C7; δ = 71.34-72.169, C5; δ = 166.60- 166.73, C6; δ = 170.32-170.37, C3.



3

3.3 Procedures to synthesis of diethyl 2-hydroxysuccinate 4a

3.3.1 Reduction with Raney nickel [9]

0.367 ml of a 1N NaOH solution (14.7 g of NaOH in 135.5 ml of water and 230 g of ice) are placed in a 2 L three-necked flask and cooled to 0°C. To this 26.7 g (0.1 mol) of diethyl 2-bromo-3-hydroxysuccinate 3 was added under stirring. 16.55 g of Raney nickel were added with stirring in such a way that the reaction temperature is maintained between 5 and 10°C. The mixture is then stirred at this temperature range for 4 hours. Under ice-cooling and stirring, 130 ml of conc. HCl was added and the mixture is stirred for further 15 min. product was extracted with diethyl ether, washed with saturated saline solution and dried over $MgSO_4$. After removal of the ether, only crystals of the saponification product (carboxylic acid) could be isolated. TLC control showed no conversion to the desired product. R_F = 0,12.

^{1}H-NMR: ($CDCl_3$,300 MHz) δ (ppm) = 1,29-1,33 (t,t 6H, J = 8,08 and 8,09 Hz, CH3:1and 8), δ = 2,79 (d,d 2H, J = 7.0 Hz, CH2:5), δ = 2.80 for OH, δ = 4,13-4,22 (q,q 4H, J = 8,09 and 8,08 Hz, CH2:2 and 7), δ = 4,65 (m 1H, CH:4).

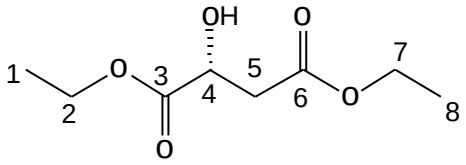
^{13}C-NMR: ($CDCl_3$, 75 MHz) δ (ppm) = 14.15, 14.16, C1/C8; δ = 38.4, C5; δ = 61.2, 61.5, C2/C7; δ = 67.6, C4; δ = 173.8, C6; δ = 174.8, C3.

3.3.2 Reduction method with C/Pd/H_2/MgO [9]:

26.7 g (0.1 mol) of diethyl 2-bromo-3-hydroxysuccinate 3, 8.0 g (2 mol) of MgO and 300 ml of solvent (150 ml of water and 150 ml of acetone) were added to a stirred flask, and 5 g of 10% Pd / C was added. The mixture is hydrogenated for 48 hours at room temperature and under 1 bar H_2 pressure. The catalyst is then filtered off, acidified with dilute HCl (pH = 6) and freed from the acetone to a large extent. It is extracted with ethyl acetate, washed with saturated NaCl solution and dried over $MgSO_4$. R_F = 0,16.

^{1}H-NMR: ($CDCl_3$,300 MHz) δ (ppm) = 1,23-1,32 (t,t 6H, J = 7,08 and 7,09 Hz, CH3:1and 8) δ = 2,835 (d,d 2H, J = 6,41 and 5,06 Hz, CH2:5) δ = 4,13-4,32 (q,q 4H, J = 7,09 and 7,08 Hz, CH2:2 and 7) δ = 4,55 (m 1H, CH:4)

^{13}C-NMR: ($CDCl_3$, 75 MHz) δ (ppm) = 14.09, 14.15, C1/C8; δ = 38.45-38.82, C5;δ = 61.19- 61.90, C2/C7; δ = 67.31- 67.44, C4; δ = 170.89, C6; δ = 173.86-173.36, C3.



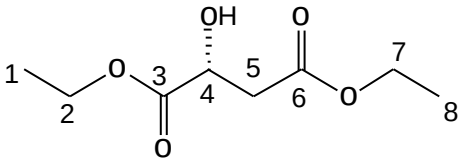
4a

3.3.3 Reduction with Zn/H_2O [9]:

First, 110 g (2.5 mol) of zinc powder are washed with 10% HCl solution, twice with acetone and finally with ether. 133.5 g (0.5 mol) of diethyl 2-bromo-3-hydroxysuccinate 3, the water-free and washed zinc and 600 ml of acetone were placed in a 2 l three-necked flask. 600 ml of water were gently dripped with stirring. After the dropwise addition is complete, the mixture was heated at 55°C. with stirring overnight. After cooling, the mixture of zinc residues and zinc salts is purified by filtration. The acetone is stripped off on a rotary evaporator. The solution is acidified with dilute HCl and extracted three times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and dried over $MgSO_4$. After removal of the solvent, the crude product was purified by distillation. b.p: 60°C (0,008 Torr); Yield: 45,36 g (48,5%).

^{1}H-NMR: ($CDCl_3$,300MHz) δ (ppm) = 1,23-1,33 (t,t 6H, J = 7,08 and 7,09 Hz CH3: C1 and C8) δ = 2,97-2,84 (d,d 2H, J = 4,73 and 6,08 CH2: 5) δ = 3,4(s. 1H, OH) δ = 4,13-4,31 (q,q 4H, J = 7,08 and 7,09 Hz CH2: 2 and 7) δ = 4,47-4,52 (m. 2H,J=5,4 and 4,06 Hz CH2:4).

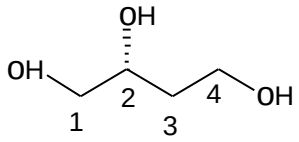
^{13}C-NMR: ($CDCl_3$, 75 MHz) δ (ppm) = 14.138, C1/C8; δ = 38.810, C5; δ = 160.96, C7; δ = 61.973, C2; δ = 67.36, C4; δ = 170.52, C6;δ = 173.39, C3.



4a

3.4 butane-1,2,4-triol 5 [10]

250 ml of ethanol were placed in a 250 ml three-necked flask and cooled to 0°C. 16 g (1.7 mol) of sodium borohydride were added all at once. To this suspension, a solution of 45.36 g (0.243 mol) of diethyl 2-hydroxysuccinate 4a in 100 ml of ethanol was carefully added under ice cooling in such a way that the reaction temperature remains within the range of 20°C. The ice cooling was then removed, the mixture heated up and the temperature rose up to 50°C. As soon as the reaction temperature begins to fall, the mixture is refluxed for 2 h. The mixture was then cooled to 5°C., 50 ml of acetone were added (to destroy residual boranals) and the mixture was acidified with conc. HCl (pH: 3, for which 50 ml are consumed). The salts precipitated during the hydrolysis were filtered off and the readily volatile constituents were removed. The crude product was then mixed three times with 250 ml of methanol each time, and the mixture is concentrated by evaporation. Finally, it was distilled in high vacuum. Light yellowish, viscous oil is obtained. b.p: 107°C (0,025 Torr); Yield: 14,5 g (57%).



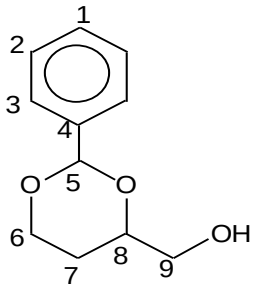
5a

3.5 (2-phenyl-1,3-dioxan-4-yl)methanol 6 [10]:

14.46 g (13.64 mmol) of butane-1,2,4-triol 5 in 70 ml of abs. DMF, and 21.15 g (15 mmol) of benzaldehyde dimethyl acetal were added. The mixture was then mixed with excess of strongly acidic ion exchanger (Lewatit S 100), the resulting methanol is continuously withdrawn at 30°C. The bath temperature was then increased slowly to 70°C and a part of DMF is thus removed. To complete the reaction, stirring is continued at 60°C for 24 hours. The remaining DMF is removed as above. Finally, the crude product is liberated from the strongly adherent benzaldehyde and benzaldehyde dimethyl acetal within 4 hours at 80°C. The resulting clear oil is used in the next step. Yield: 16,05 g (60,54%).

^{1}H-NMR: ($CDCl_3$, 300MHz) δ (ppm) = 1,86-2,0 (m, 2H, J =11,48 u. 11,167 Hz CH2: 7) δ = 3,64-3,69 (m, 2H, J = 6,41 and 6,75 Hz CH2:9) δ = 3,95-4,05 (m, 1H, CH: 8) δ = 5,55 (s. 1H, CH2: 5) δ = 7,34-7,39 (m, 3H, CH-arom.) δ = 7,47-7,51(m, 2H, CH- arom.).

^{13}C-NMR: ($CDCl_3$, 75 MHz) δ (ppm) = 26.81, C7; δ = 65.64, C6; δ = 66.62, C9; δ = 77.60, C8; δ = 101.31, C5; δ = 126.15, 128.30, 129.03, C3/C2/C1; δ = 138.32, C4.



6

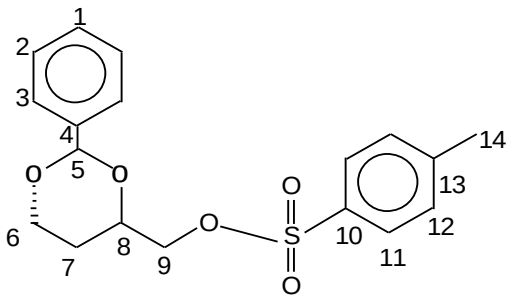
3.6 (2-phenyl-1,3-dioxan-4-yl)methyl 4-methylbenzenesulfonate 7 [10]:

In a 250 ml three-necked flask, 15.74 g (82.50 mmol) of tosyl chloride were dissolved in 9.79 g (123.9 mmol) pyridine. A solution of 16.02 g (82.50 mmol) of (2-phenyl-1,3-dioxan-4-yl)methanol 6 in 30 ml of methylene chloride was added dropwise, with stirring and ice-cooling, and the mixture is stirred for 24 hours at RT. The contents were then added to a solution of 6.07 g (41.25 mmol) of conc. sulfuric acid in 60 ml of ice water. Product was then extracted with methylene chloride and dried over $MgSO_4$. After removing the solvent, the crude product was filtered through a 10 cm column of silica gel. The product was washed out with 1: 1 ether / pentane. After drawing off the solvents, a colorless thick liquid is obtained.

R_F = 0,21, Yield: 14,14 g (51%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) = 1,11-1,28 (m, 2H, CH2: 7) δ = 2,47 (m, 3H, CH3: 14) δ = 3,95-4,22 (m, 4H, CH: 6, CH2: 9) δ = 4,22-4,38 (m, 1H, CH: 8), δ = 5,27 (s. 1H, CH: 5) δ = 7,30-7,37 (m. 7H, CH-arom.), δ = 7,74-7,84 (m. 2H, CH-arom.).

^{13}C-NMR: ($CDCl_3$, 75 MHz) δ (ppm) = 21.61, C14; δ = 27.12, C7; δ = 66.28, C6; δ = 71.55, C9; δ = 74.09, C8; δ = 100.97, C5; δ = 127.94, C2; δ = 128.10, C3; δ = 128.85, C12; δ = 129.79, C11; δ = 132.66, C13; δ = 137.935, C4; δ = 144.86, C10.

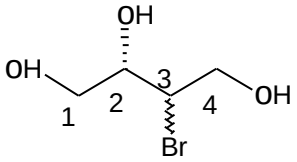


7

3.4b Synthesis of 2-bromo-3-hydroxysuccinic acid 4b from diethyl 2-bromo-3-hydroxysuccinate 3:

The procedure corresponds to the one described in point 3.4.

(R_F = 0,22), Yield: 10,7 g (15,7%).



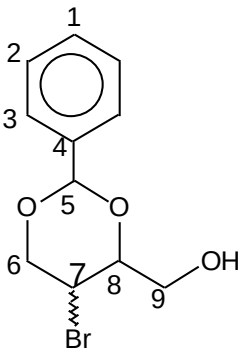
4b

3.5b Synthesis of (5-bromo-2-phenyl-1,3-dioxan-4-yl)methanol 5b from 2-bromo-3-hydroxysuccinic acid 4b:

The procedure corresponds to the acetalization procedure described in 3.5. Yield: 15,52 g (100 %).

^{1}H-NMR: (CDCl3, 300 MHz) δ (ppm) = 1,18-1,25 (m. 1H, CH: 7), δ = 3,60-3,94 (m. 5H, CH_2: 9/ CH: 8), δ = 5,58 (s. 1H, CH: 5) δ = 7,34-7,40 (m. 5H, CH arom).

^{13}C-NMR: ($CDCl_3$, 75 MHz) δ (ppm) = 31.47, C7; δ = 65.93, 66.72, C6/C9; δ = 77.71, C8; δ = 102.00, C5; δ = 126.40, 126.74, 128.69, 128.99, C3/C2/C1; δ = 134.46, C4.



5b

3.6b Preparation of (2-phenyl-1,3-dioxan-4-yl)methanol 6 from (5-bromo-2-phenyl-1,3-dioxan-4-yl)methanol 5b by reduction with $LiAlH_4$ [10,11]:

A suspension of 1.2 g (17.84 mmol) of lithium aluminum hydride was first prepared in 150 ml of diethyl ether, to which a solution of 15.52 g (59.46 mmol) of alcohol 5b in 30 ml of diethyl ether was added such that no Violent reaction. After the dropwise addition was complete, the mixture was heated under reflux and stirring for 1 h. After the reaction

was complete, a solution of 1.2 g of potassium hydroxide in 30 ml of water was heated for 1 h. The resulting phases were separated off and the aqueous phase was extracted with ether. The combined phases were washed with water and with saturated saline solution, dried over $MgSO_4$ and the solvent was distilled off in a rotary evaporator. A light yellowish viscous oil was obtained, and the mixture was then placed in the next step. Yield: 8,07 g (74,6 %).

^{1}H-NMR ($CDCl_3$, 300 MHz)

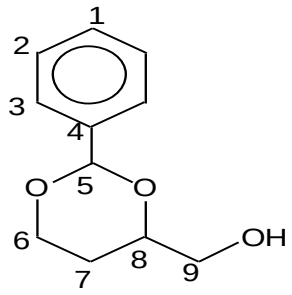
^{13}C-NMR ($CDCl_3$, 75 MHz)

See the evaluation of the spectra under point 4.2.5.

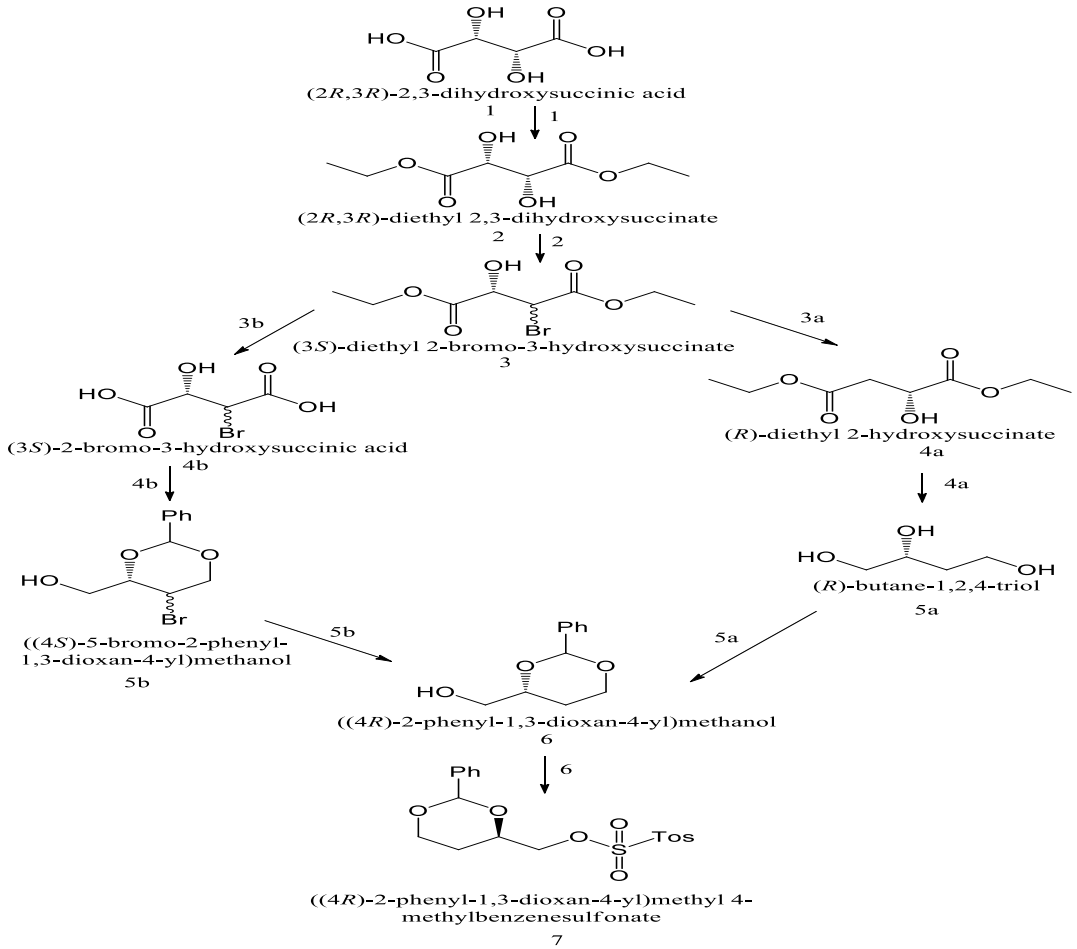
Results and Discussion

1 Background

Scheme (2) includes the synthetic routs to the aimed product. The first step of this work includes Fischer transformation of the readily available 2,3-dihydroxysuccinic acid 1. Then the formed symmetrical diester 2 will be transformed via a two-step reaction into diethyl 2-bromo-3-hydroxysuccinate 3, which is considered as the bromine derivative of the malic acid ester and represents the key compound for this study.



6



Scheme (2): synthetic routs A and B, reaction conditions: 1= EtOH/$CHCl_3$/H^+, 2= 1-$SOCl_2$/DMF/2-LiBr/Acetone, 3a= reduction (debromination), 4a, 3b= $NaBH_4$/EtOH, 4b, 5a = Benzaldehyde, DMF/H^+, 5b= $LiAlH_4$/EtOH, 6= Tosylchloride/pyridine/H^+.

In scheme 2, two different routes have been studied. In the first route A, compound 3 would be converted into diethyl 2-hydroxysuccinate 4a by a debromination step. In the synthetic route A, obtained compound 4a which can be reduced into butane-1,2,4-triol 5a, selectively protected in the 1,3-positions as (5-bromo-2-phenyl-1,3-dioxan-4-yl)methanol 6, and then tosylated as (2-phenyl-1,3-dioxan-4-yl)methyl 4-methylbenzenesulfonate 7. The compound 7 can then be converted into the side chain, a chiral secondary alcohol, over further three steps.

On the other hand, the following reducing agents were studied to achieve the debromination reaction in the route A:

1. Zn/H_2O
2. $Pd/C/H_2/MgO$
3. Raney-Nickel

The synthesis up to the preparation of the bromide derivative 3, which could be detected cleanly by means of the ^{1}H-NMR spectrum, proceeds without problems. The yield was very good. It should be mentioned here that the preparation of 3 was carried out via the cyclic sulfite without isolating it Fig. (2):

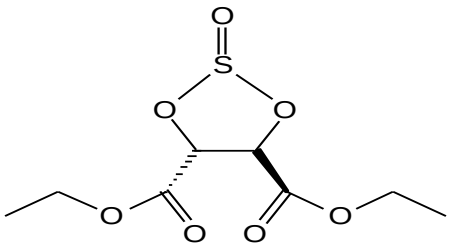


Fig. (2): 2-Thio-2-Oxo-4,5-Cis(ethoxycarbonyl)-[1,3]-dioxolan.

Synthesis pathway A

1-Removal of bromide

1-1 Reduction with Raney-Nickel

The reduction was carried out in a 1 N NaOH solution at 5 °C in a manner similar to the reduction of the dibromo rolinic acid methyl ester into methyl sulfonic acid methyl ester. After extraction with ether, a solid could be isolated which, however, corresponds to the corresponding carboxylic acid. The strongly basic solution probably activated the saponification reaction. Thus, the Raney nickel reduction appears to be less suitable in this case because it will involve a great deal of effort to prevent the saponification reaction.

1-2 Reduction with $C/Pd/H_2/MgO$:

The reaction was too slow in view of the amount of H_2 consumed, so MgO and catalyst were added to allow the reaction to proceed more rapidly. However, a serious change could not be noticed. Nevertheless, the reaction mixture was worked up. A small amount of the desired product, such as the ^{1}H NMR spectrum and DC control, could be isolated. It is likely that there are still sulfur compounds from the precursors in the product, which immediately poison the catalyst. If the yield could be increased, the reduction would be optimal since working with this reducing agent is clean and easy.

1.3 Reduction with Zn/H_2O:

As the ^{1}H NMR spectrum and TLC control showed, the reduction product was consistently formed with high purity. So a possible saponification reaction was prevented and the yield was large. The disadvantage of this reduction is only the zinc waste, which is considered as a problem for the environment. Therefore, this problem must be eliminated either by examining an alternative reducing agent or by recovering the zinc.

Subsequently, compound 4a was used for total reduction with sodium borohydride. As the TLC control shows, the reaction proceeds to the desired 1,2,4-triol 5a smooth and uniform.

Before the tosylation of the triol 5, it was necessary to provide the two 1,3-hydroxy groups with a protective group. The product, as the ^{1}H NMR spectrum shows, was impregnated with benzaldehyde, the starting compound acetal and the by-product five-membered acetal, which could not be completely removed despite purification in the HV Fig.(3). Since these impurities are not a problem for the next stage and the tosylate 6 can be isolated cleanly, no further cleaning was dispensed with.

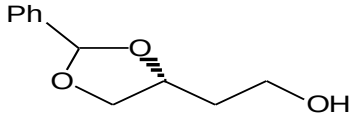


Fig.(3)

Synthetic pathway B

The synthetic route B initially involves the reduction of 3 into butane-1,2,4-triol 4b, which

is also selectively protected in the 1,3-position and finally dehalogenated. In scheme 2 the important conversion step of 3 into 4a have been investigated. To realize these topic two different routes were applied.

The bromide derivative 3 was reacted with sodium borohydride, without cleaving the bromine atom, as in synthetic route A. The low yield of the desired product 4b represents the real problem of the synthetic route B. The reaction has most likely proceeded in the direction of undesired decomposition products, which could be interfered from the unexpected violent reaction and from the unusual colour.

The 2-bromo-1,2,4-butanetriol 4b was also selectively protected in the 2,4-position with benzaldehyde dimethyl acetal, as on route A, yielding a better result in terms of yield and a poor result with respect to the selectivity than in the A-path. Subsequently, the acetal 5b is dehalogenated via lithium aluminum hydride in ethanol. The protected alcohol 6 obtained from this step was clean and the yield was large. Finally, as on route A, 6 was transferred into compound 7, which could be obtained cleanly and in large yield. Thus, the reactions of route B, with the exception of the reduction step with $NaBH_4$, proceed without problems.

Conclusions

It can be concluded that the pathway A is clearly better in comparison with the pathway B. The main reason for this was the limited yield of compound 4b on Route B. The subsequent steps on route B, however, gave good results. If the step in the direction of 4b were improved and thus the yield was increased, pathway B would also be conceivably suitable for the synthesis of the side chain of Annonin I. Within route A, the reduction with Zn/H_2O was the most suitable despite the waste problem. An improvement in the reduction of 3 in the direction of the demanding expensive unnatural malic acid ethyl ester 4a could not be achieved.

Acknowledgment

Department of chemistry of the college of science of Al-Nahrain University is gratefully acknowledged for the support and providing all required materials and apparatus.

References

[1] Acetogenins from Annonaceae: recent progress in isolation, synthesis and mechanisms of action, Acetogenins from Annonaceae: recent progress in isolation, synthesis and mechanisms of action, Nat. Prod. Rep. 2005, 22, 269-303.

[2] M. C. Zafra-Polo, M. C. Gonz´alez, E. Estornell, S. Sahpaz and D. Cortes, Acetogenins from Annonaceae, Inhibitors of Mitochondrial Complex I, Phytochemistry, 1996, 42, 253–271.

[3] M. C. Zafra-Polo, B. Figad`ere, T. Gallardo, J. R. Tormo and D. Cortes, Natural Acetogenins from Annonaceae, synthesis and mechanisms of action, Phytochemistry, 1998, 48, 1087–1117.

[4] L. Zeng Q. Ye, N. H. Oberlies, G. Shi, Z.-M. Gu, K. He and J. L. McLaughlin, Recent Advances in Annonaceous Acetogenins, Nat. Prod. Rep., 1996, 13, 275–306.

[5] J. Le Ven, I. Schmitz-Afonso, D. Touboul, D. Buisson, B. Akagah, T. Cresteil, G. Lewin,; P. Champy, "Annonaceae fruits and parkinsonism risk: Metabolisation study of annonacin, a model neurotoxin; evaluation of human exposure". Toxicology Letters, 2011, 205, 50-63.

[6] S. Latypov, X. Franck, J. C. Jullian, R. Hocquemiller and B. Figad`ere, NMR determination of absolute configuration of butenolides of Annonaceous type, Chem. Eur. J., 2002, 8, 5662–5666.

[7] M. Mangal, M. I. Khan, S. M. Agarwal, "Acetogenins as Potential Anticancer Agents". Anti-cancer agents in medicinal chemistry, 2015, 16 (2): 138–59.

[8] W.M. Haynes, CRC Handbook of Chemistry and Physics (96th ed.). Boca Raton, FL: CRC Press, 2015.

[9] L. F. Potts, F. A. Luzzio, S. C. Smith, M. Hetman, P Champy, I. Litvan, "Annonacin in Asimina triloba fruit: Implication for neurotoxicity". Neurotoxicology. 2012, 33 (1): 53–8.

[10] R. A. Levine; K. M. Richards; K. Tran; R. Luo; A. L. Thomas & R. E. Smith. "Determination of Neurotoxic Acetogenins in Pawpaw (Asimina triloba) Fruit by LC-HRMS". J. Agric. Food Chem. 2015, 63 (4): 1053–1056.

[11] L. Chih-Chuang; L. Jing-Ru; W. Tung-Ying; C. Fang-Rong; W. Yang-Chang. "Acetogenins from Annonaceae". Progress in the Chemistry of Organic Natural Products. 2016, 101: 113-122.