ORIGINAL RESEARCH ARTICLES

A GREENER APPROACH TO SYNTHESIS OF DIACEREIN

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ABSTRACT

Diacerein, also known as diacetylrhein (1,8-diacetoxy-3-carboxyanthraquinone), is a slow-acting active pharmaceutical ingredient of the anthraquinone class used to treat joint diseases such as osteoarthritis (swelling and pain in the joints). It works by inhibiting interleukin-1 beta and demonstrates anti-arthritic activity without inhibiting prostaglandin synthesis. Diacerein-containing medications are registered in some European Union and Asian countries and are included as a treatment option on several international therapeutic guidelines. Different approaches have been reported for the synthesis of this compound. Many approaches have been reported for preparation of diacerein specially employing reagents like hexavalent chromium compounds which are toxic and effluent-unfriendly. We report herein synthesis of diacerein, a potent antiarthritic ingredient, by employing a greener chemical method and also synthesis of acetyl vanillic acid by employing similar scheme having same functional groups.

Keywords: Aloe-Emodin, Rhein, Diacerein, Anti-artheritic drugs.

INTRODUCTION

Diacerein, known as diacetylrhein, is 4, 5-diacetyloxy-9, 10-dioxoanthracene-2-carboxylic acid. It is the parent member of the anthraquinone class of antiarthritic drugs. It has distinct advantages. It is one of the superior pain relieving agents and hence is used in the osteoarthritis condition of the joints as well as in chronic inflammation[1,2]. Due to its mode of action, it differentiates from the NSAIDs and other pain reliving classses of drugs[3]. Its current commercial synthesis initiates from intermediate 1,8-dihydroxy -3-hydroxymethyl- 9,10-anthracenedione commonly known as 'Aloe-emodin' (Fig.1). Aloe-emodin itself has cathartic and anticancer activity. Diacerein containing medications are registered in some European Union and Asian countries and is included as a treatment option in several international therapeutic guidelines.

In the known synthesis methods, aloin is used as the starting material, which is acetylated on the hydroxyl group and then oxidized with the help of chromic anhydride in acetic acid. The diacerein thus obtained requires many purification stages and encounters the difficulty of eliminating the chromium impurity, which is a very tedious process[4].

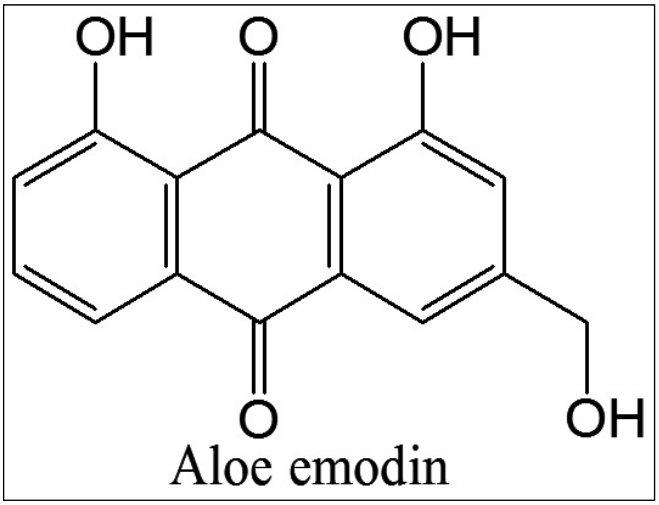

Fig.1: Aloe emodin Structure

MATERIALS AND METHODS

Melting points of all the compounds were recorded by Analab ThermoCal melting point apparatus in capillary tube and are uncorrected. IR spectra (KBr) were

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recorded on Perkin Elmer Fourier Transform infrared spectrophotometer. All the ^{1}H NMR spectra were recorded on MR400 Agilent Technology NMR spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as the solvent. Mass spectra were recorded on a direct insertion probe on Agilent Technologies 5975 series. GC-MS Spectra analyses were recorded on Shimadzu GC-MS QP2010 Ultra model. Chemicals and solvents used were of GR/ LR grade and purchased from SD Fine Chemicals. They were used without further purification. The reaction monitoring was accomplished by thin-layer chromatography (TLC) on Merck silica gel G F_{254} plates. All the compounds were characterized by IR, ^{1}H NMR and Mass Spectroscopy for structural elucidation.

EXPERIMENTAL PROCEDURE:

Step 1: Synthesis of 9, 10-dihydro-4, 5-dihydroxy-9, 10-dioxoanthracene-2-carbaldehyde [II][10]

Aloe-emodin 2.70 g (10 mMol) was dissolved in 20 mL of N, N-dimethylformamide with the aid of magnetic stirring followed by addition of 10.25 gm barium manganate (40 mMol) to the resulting reaction mixture. The reaction mixture was stirred at room temperature for 6 h and was monitored by TLC. After completion of the reaction, the mixture was poured into 100 mL water and filtered to remove spent barium manganate. The resulting solution was extracted with (3 x 15 mL) ethyl acetate and evaporated to dryness and purified by column chromatography on silica gel by using petroleum ether/ ethyl acetate (60-80° C) (7:3V/V) as mobile phase. A yield of 1.80 g (66.91%) was obtained. The synthesized compound was characterized by FTIR, ^{1}H NMR and mass spectroscopy.

M.P. : 207-210°C (reported M.P.: 207-209°C)[14]

IR (KBr) ν_{max} cm^{-1}: 3236, 2922, 2852, 1702, 1637, 1616, 1453, 1373, 1267

^{1}H NMR (400 MHz, DMSod$_6$) δ 11.91 (s, 2H), 10.09 (s, 1H), 8.11 (s, 1H), 7.79 (t, *J* = 15.0 Hz, 3H), 7.40 (d, *J* = 8.0 Hz, 1H).

MS: ESI-MS m/z: 268.1 (M$^+$)

Step 2: Synthesis of Rhein [III][11,12,13]

To the solution of 1.34g, 9,10 dihydro-4,5-dihydroxy-9,10-dioxoanthracene- 2- carbaldehyde [II] (5mMol) in 10 mL N,N-Dimethylformamide with aid of magnetic stirring, catalytic amount of *p*-TSA was added and then 30% H_2O_2 (5mL) was added drop wise over a period of 2 h. The reaction mixture was stirred at room temperature for 3 h and progress was monitored by TLC. After completion of reaction, 50 mL water was added. The resulting solution was extracted with (3 x 15 mL) ethyl acetate and evaporated to dryness. It was purified by column chromatography on silica gel by using Petroleum ether/ethyl acetate (7:3 V/V) as the mobile phase - yield of 1.06 g (79%) of rhein was obtained. The synthesized compound was characterized by FTIR, ^{1}H NMR and Mass spectroscopy.

M.P.: 321-323°C (reported M.P.: 320-322°C)[12]

IR (KBr) ν_{max} cm^{-1} : 3405, 1692, 6132, 1571,1452,1268,1189

^{1}H NMR (400 MHz, DMSOd$_6$) δ 11.85 (s, 2H), 8.07 (d, *J* = 1.5 Hz, 1H), 7.79 (t, *J* = 7.9 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 1H).

MS: ESI-MS m/z: 284.3 (M$^+$)

Step 3: Synthesis of diacerein [IV]:

***In situ* preparation of acetic anhydride**: 0.6 g of acetic acid and 1.9 g of oxalyl chloride was refluxed for 0.5 h and allowed to cool. The resulting solution containing acetic anhydride *in situ* was, prepared, used as such for acetylation of rhein.

Acetylation of Rhein: To the *in situ* prepared acetic anhydride was added sequentially one drop of conc. sulphuric acid and 0.95 g of Rhein (25 mMol) were added. The resulting reaction mass was stirred at 0°C for 4 h. After completion of the reaction, water was added and the solid yellow colored product was filtered, dried and confirmed by comparing with standard diacerein by TLC. The compound, *viz.* diacerein, requires no additional purification by column chromatography. The synthesized compound was characterized by FTIR, ^{1}H NMR and mass spectroscopy.

M.P.:216-218°C (Reported M.P.:217-219°C)[4]

IR(KBr) ν_{max} cm^{-1} :3461,3069,1768,1693,1679,1668, 1450,1368,1291,1213

^{1}H NMR (400 MHz, DMSOd$_6$) δ 8.52 (d, *J* = 1.5 Hz, 1H), 8.11 (d, *J* = 6.7 Hz, 1H), 8.00 (d, *J* = 1.5 Hz, 1H), 7.92 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.0 Hz, 1H), 2.36 (d, *J* = 2.2 Hz, 6H).

MASS: ESI-MS m/z: 368 (M$^+$)

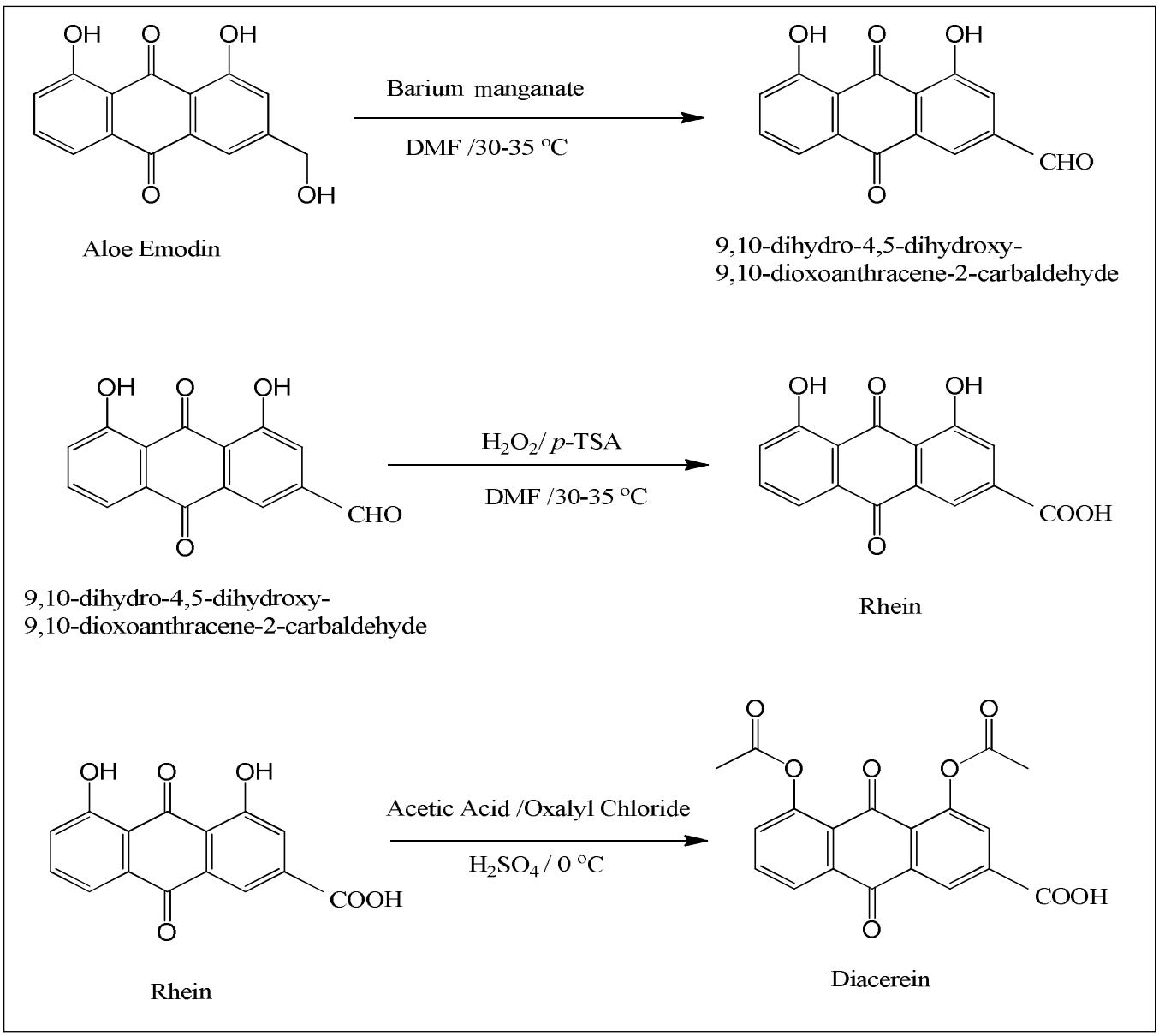

Fig. 2: Reaction Scheme for Diacerein

EXPERIMENTAL PROCEDURE FOR ACETYL VANILLIC ACID

Step 1: Synthesis of vanillin

Vanillyl alcohol 1.54 g (10 mMol) was dissolved in 10 mL of *N, N*-dimethylformamide with the aid of magnetic stirring, followed by addition of barium manganate 5.12 g (40 mmole) to the resulting reaction mixture. The reaction mixture was stirred at room temperature for 6 h and was monitored by TLC. After completion of the reaction, the mixture was poured in 100 mL water and filtered to remove spent barium manganate. The resulting solution was extracted with (3 x 15 mL) ethyl acetate and evaporated to dryness and purified by column chromatography on silica gel by using petroleum ether/ethyl acetate (7:3 V/V) as mobile phase. A yield of 0.912 g (60%) was obtained. The synthesized compound was characterized by FTIR, ^{1}H NMR and GC-MS spectroscopy.

M.P. : 82-84°C (Reported M.P.:81-83 °C)

IR (KBr) ν_{max} cm^{-1}: 3150, 1663.2, 1587, 1509, 1428.6, 1454.2, 1263.5, 1152, 1122.6

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.40 (s, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.27 (s, 1H), 3.94 (s, 3H).

MS: GC-MS m/z: 152 (M^+)

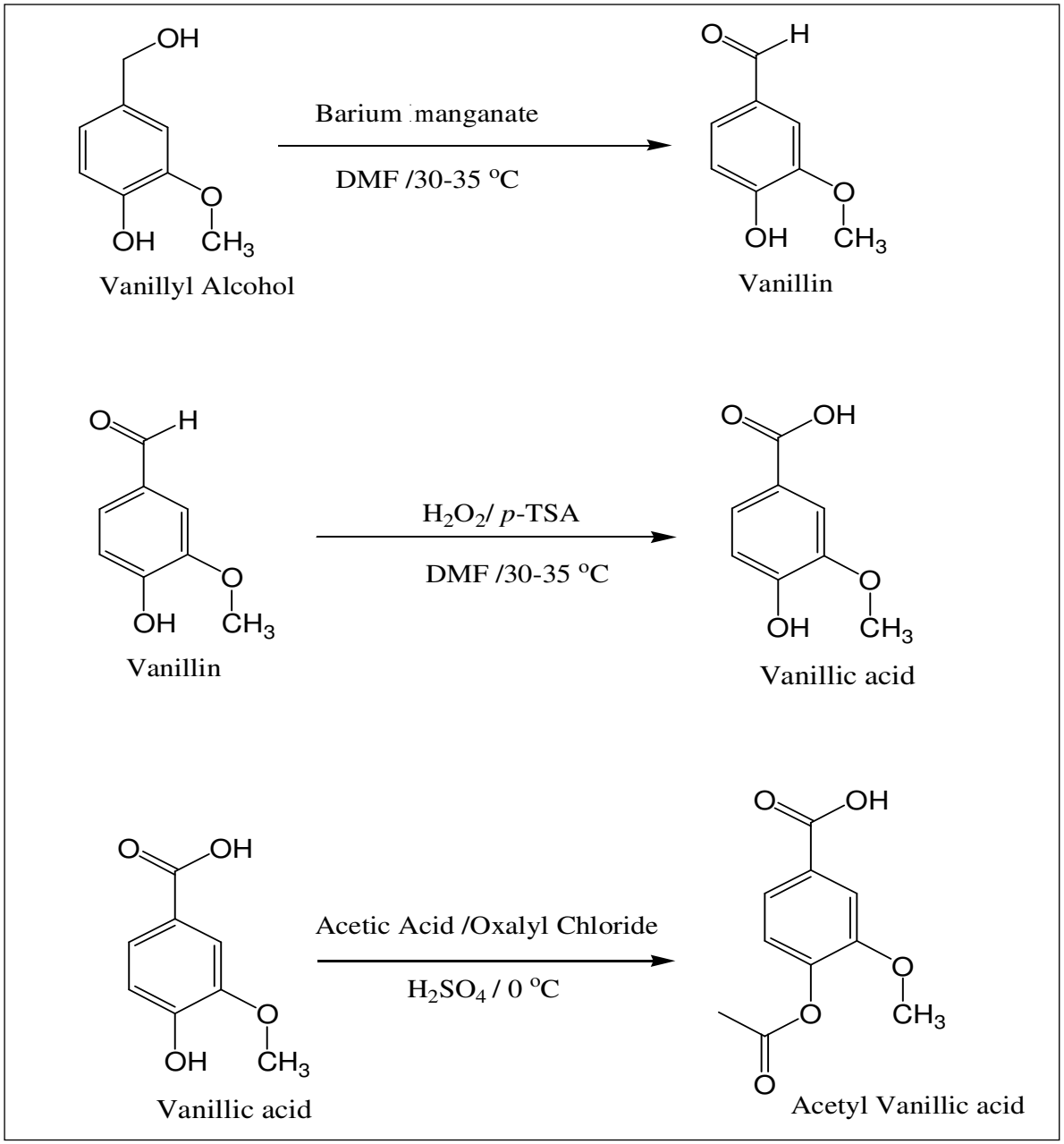

Fig.3: Reaction Scheme for Acetyl Vanillic acid

Step 2: Synthesis of vanillic acid

To the solution of vanillin 0.76 g (5mMol) in 10 mL N,N-Dimethylformamide with aid of magnetic stirring, catalytic amount of *p* -TSA was added and then 30% H_2O_2 (3 mL) was added drop wise over the period of 2 h. The reaction mixture was stirred at room temperature for 3 h and was monitored by TLC. After completion of reaction, 50 mL water was added. The resulting solution was extracted with (3 x 15 mL) ethyl acetate and evaporated to dryness and purified by column chromatography on silica gel by using Petroleum ether/ ethyl acetate (7:3 V/V)as mobile phase. A yield of 0.675g (75%) vanillic acid was obtained. The synthesized compound was characterized by FTIR, ^{1}H NMR and GC-Mass spectroscopy.

M.P.: 209-212°C (Reported M.P.:210-213 °C)

IR (KBr) ν_{max} cm^{-1} : 3482.5,1673,1596,1521.6,1433.5,1280,1203,1110,1027,756.6

^{1}H NMR (400 MHz, $DMSOd_6$) δ 7.40 (d, J = 6.5 Hz, 2H), 6.80 (d, J = 8.3 Hz, 1H), 3.77 (s, 3H).

Step 3: Synthesis of acetyl vanillic acid:

***In situ* preparation of acetic anhydride**: 0.3 g of acetic acid and 0.95 g of oxalyl chloride was refluxed for 0.5 h and allowed to cool. The resulting solution containing acetic anhydride *in situ* was, prepared, used as such for acetylation of vanillic acid.

Acetylation of vanillic acid: To the *in situ* prepared acetic anhydride was added sequentially one drop of conc. sulphuric acid and 0.84 g of vanillic acid (12.5 mMol) was added. The resulting reaction mass was stirred at 0°C for 4 h. After completion of the reaction, water was added and the solid product obtained was filtered, dried and confirmed by TLC. The synthesized compound was characterized by FTIR, ^{1}H NMR and GC-Mass spectroscopy.

M.P.: 215-218°C

IR (KBr) ν_{max} cm^{-1} : 3483.4,1672,1596,1522,1433.6, 1276.3,1199,1165.7,1026.8,755.7

^{1}H NMR (400 MHz, DMSOd$_6$) δ 13.03 (s, 1H), 7.60 – 7.49 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 2.25 (s, 3H).

RESULT AND DISCUSSION

The ongoing interest in isolation of phytochemicals in these laboratories have resulted in the development of a commercial process for preparation of aloe-emodin from aloe sap containing 20% of barbaloin and many other phytoconstituents of medicinal value[12].

Diacerein (4, 5-diacetyloxy-9, 10-dioxoanthracene-2-carboxylic acid), a molecule with antiarthritic activity, has been used in therapy for a very long time. Many syntheses of diacerein are known, the majority of which use 'Aloin' as the starting product, which, after acetylation of the hydroxy groups, is oxidized with chromic anhydride in acetic acid. The diacerein thus obtained from glycoside requires many purification stages in order to eliminate the residues of hexavalent chromium and the reaction by-products (e.g. EP 636602, WO 98/56750, WO 01/96276, US 2006/0135797, US 2007/0037992, 1997/US 5,670,69545, 2006/EP 1666446A1). Repeated purifications are labor-intensive on an industrial scale and are not sufficient to eliminate the residue of hexavalent chromium and the by-products. In particular, aloe-emodin and its acetyl derivatives are found as impurities in the end product. WO 2006/051400 describes a process for the preparation of diacerein which uses sodium nitrite in sulphuric acid instead of the chromic anhydride/acetic acid oxidizing system. The said process is extremely exothermic and hence cannot be controlled during the large-scale production; furthermore, the volumes of solvent necessary for the reactions are excessive and the yields reported are very low. This reported process is thus not suitable for industrial production.

The goal of the present study was to provide a process for the preparation of diacerein which overcomes the drawbacks of the prior art and allows the production of diacerein with a high level of purity and high yields, *via* safe and industrially feasible synthesis[4,5].

Aloe-Emodin is thus a natural choice as a key starting material for diacerein by oxidation and acetylation.[6,7,8] The conventional reported synthesis makes use of oxidation via. chromium trioxide to yield 1, 8-dihydroxy-3-anthraquinone carboxylic acid (Rhein), leading to generation of huge amount of effluent with hazardous hexavalent chromium and is thus is an industrially unattractive process. Rhein obtained is then acetylated using acetic anhydride (a controlled substance) and sodium acetate to yield diacerein[9].

The present study undertaken at our end was to eliminate both the problems viz. (i) eliminate use of chromium trioxide by a safe greener reagent and (ii) carry out acetylation without the direct use of acetic anhydride. The careful study undertaken has addressed both the problems.

The synthesis of diacerein was initiated from commercially available 'aloe-emodin'. Oxidation of Aloe-emodin (I) with mild oxidizing agent barium manganate at 30-35^{0}C in *N, N*-dimethyl formamide(DMF) as solvent, gave aldehyde derivative (II).The reaction was monitored by TLC and after 6 h, complete conversion to aldehyde derivative was observed.This was confirmed by 2,4-DNP test followed by recording the ^{1}H NMR of isolated pure product. In the ^{1}H NMR spectra of (II) the characteristic signal due to aldehyde proton was located at 10.09 ppm, Compound (II) was next subjected to further oxidation by employing hydrogen peroxide (30%) in catalytic *p*-TSA to yield Rhein (III). The product (III) showed a characteristic peak in its FTIR spectrum at 3405 cm^{-1} which was attributed to the carboxy group. ^{1}H NMR spectrum was in conformity with assigned spectra *viz.* rhein (III). The free hydroxyl group in rhein was next acetylated using oxalyl chloride/ acetic acid, producing acetic anhydride "On Demand" to yield diacerein.

Diacerein obtained was purified by crystallization and was fully characterized by recording its FTIR, proton NMR and MASS Spectrum. The reaction sequence is

scale-up friendly and the scale up on multigram scale is being currently pursued.

In order to validate the method developed at our end, we thought it worthwhile to extrapolate the same strategy to a known compound having the functional groups like Ar-OH and Ar-COOH. As anticipated, the acetylation occurred on phenolic hydroxy group of vanillic acid to yield acetyl vanillic acid. It is pertinent to mention that we synthesized acetyl vanillic acid from corresponding vanillyl alcohol employing similar strategy with full characterization in place.

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OBITUARY

Mr Kapil Bhargava

Mr Kapil Bhargava, Chairman, IDMA Quality Management & Technical Committee passed away on 19 March 2019 at Mumbai. He was 70 years old. Mr Bhargava was earlier the Deputy Drugs Controller (I) with an overall experience of more than 40 years in enforcement of Indian drug rules related to manufacturing and testing of pharmaceuticals and as an academician. An M. Pharm. in Pharmaceutical Chemistry, he was trained in USA/WHO in the fields of GMP & GLP. He was WHO advisor and WHO Expert for Quality of Vaccines. He was also advisor to many pharmaceutical companies and Public sector undertakings.

In his passing away, the Indian Pharmaceutical Industry has lost a friend, philosopher and guide. May God grant his departed Soul eternal peace and provide strength to his family to bear this irreparable loss.