Synthesis of revised structure of klaivanolide (acetylmelodorinol)

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Dedicated to Dr. Jhillu Singh Yadav on the occasion of his 65th Birthday

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Abstract
Klaivanolide (acetylmelodorinol) is an anti-leishmanial/anti-trypanosomal agent isolated from *Uvaria klaineana* and the structure was originally assigned as a 7-membered lactone with extended conjugation and *S*-configuration at the lactone junction. Very recently, the structure of klaivanolide was revised as previously known compound acetylmelodorinol. Now, we have synthesized the revised structure in racemic form using a short route.

Keywords: Klaivanolide; acetylmelodorinol; natural product; leishmaniasis

Introduction

Leishmaniasis and trypanosomiasis are the cause of suffering for millions of people in both tropical and subtropical zones of the world for last several years.[1-7] The available treatment for most parasitic diseases with the existing drugs suffer from several limitations such as toxicity, parenteral administration, emergence and spread of drug resistance. There is a need for the discovery of new drugs which address some of these issues. Along these lines, klaivanolide (**1**), a natural product isolated from the *Uvaria klaineana* by Lauren's group in 2002,[8] showed potent anti-leishmanial activity. Compound **1** showed an IC_{50} value of 1.75 μM against the sensitive strain and an IC_{50} value of 3.12 μM against the amphotericin B-resistant strain of *L. donovani*, which is three fold better than the marketed drug pentamidine (IC_{50} = 8.52 μM). The structure of **1** was elucidated by spectroscopic methods and the absolute configuration was assigned using the VCD spectroscopy by Figadère's group in 2009.[9] Very recently, structural revision of natural product klaivanolide was published by same group.[10] According to this report, the structure of klaivanolide was assigned to a previously known compound acetylmelodorinol (**2**)[11-13] (Figure 1). This natural product attracted our attention because of its potent biological activity and

unique structure. As a part of our research group activity towards finding novel chemotypes against different diseases,[14-16] we have initiated a medicinal chemistry programme to develop a lead compound against leishmaniasis based on klaivanolide (acetylmelodorinol). While we were struggling to synthesize the target compound **1** with original structure, structural revision of natural product klaivanolide was published. Accordingly, we have stopped all our efforts to synthesize the previously assigned structure and directed our efforts to the revised structure of klaivanolide. Our efforts on this project are described here.

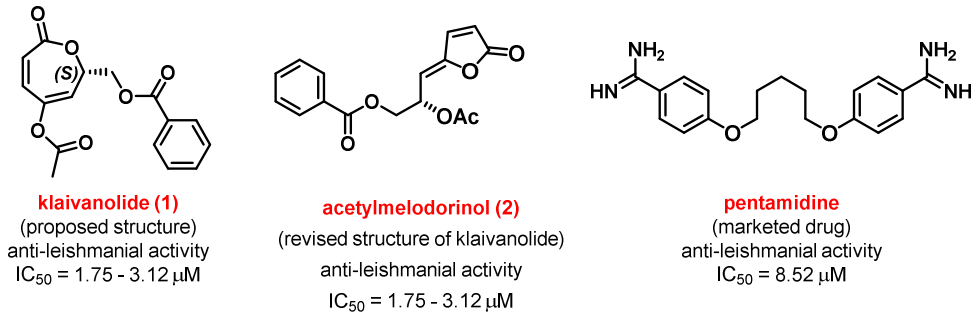
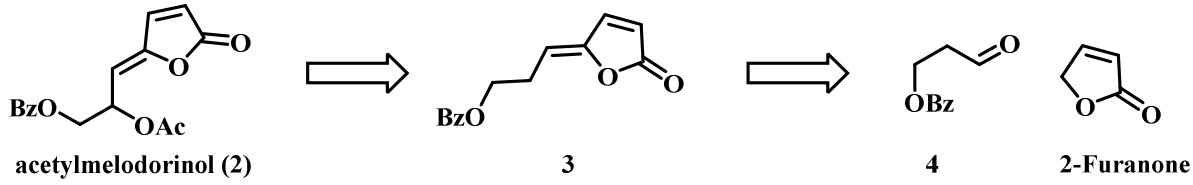


Figure 1. Structures of klaivanolide, acetylmelodorinol and pentamidine.

Results and Discussion

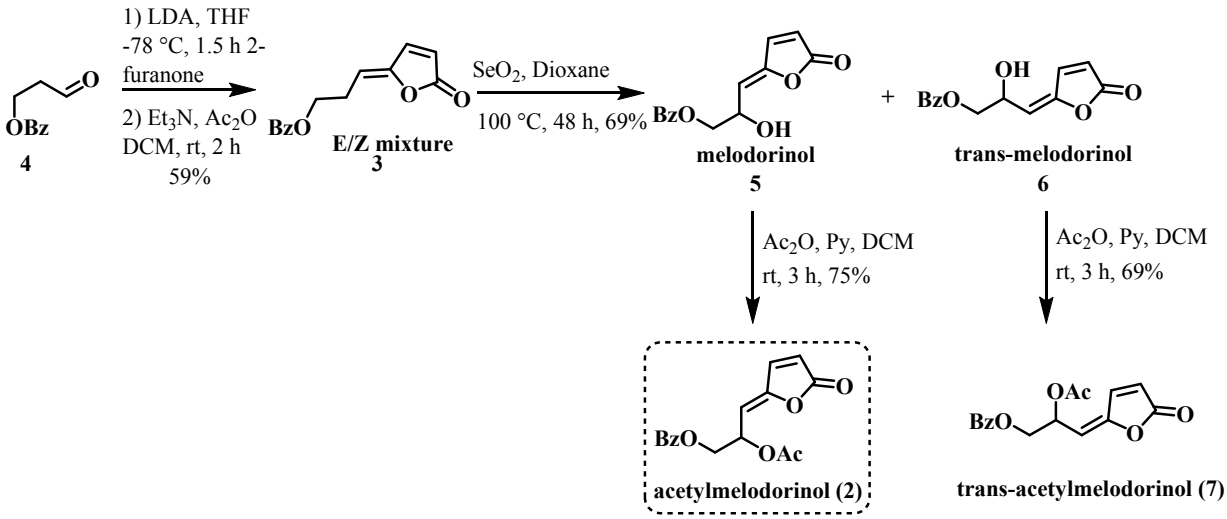
Retrosynthetic analysis of the target molecule is shown in scheme 1. The natural product **2** can be visualized from the exocyclic olefin **3** via allylic oxidation with selenium dioxide. The olefin **3** could be synthesised by aldol reaction between the known aldehyde (**4**) and 2-furanone.



Scheme 1. Retrosynthetic analysis of acetylmelodorinol (revised structure of klaivanolide).

Although synthesis of acetylmelodorinol was known in the literature by four different routes,[17-21] we wanted to synthesize the same target using a short sequence which is amenable to analogues synthesis. Our planned synthesis began with a known aldehyde **4** prepared from corresponding olefin through ozonolysis,[22-23] which was subjected to aldol condensation with 2-furanone[24] followed by exposure to triethylamine/acetic anhydride produced a mixture of E/Z-isomers of **3** (~1:3 ratio).[25] Allylic oxidation of exocyclic olefin present in **3** using selenium dioxide in 1,4-dioxane furnished two alcohols **5** and **6** in 69% yield. Both the compounds were

cleanly separated on silica gel column. Compound **5** with *cis* double bond happened to be a known compound in the literature as melodorinol (natural product).[11-13, 17-21] All the spectral data was compared with published data and found to be identical.[11-13, 17-21] The compounds *cis*-melodorinol (**5**) and *trans*-melodorinol (**6**) were subjected to acetylation to give corresponding acetylmelodorinol **2** and its *trans*-isomer **7**, respectively. All the spectral data of the synthetic racemic acetylmelodorinol **2** is in complete agreement with the literature reports.[8, 11-13]



Scheme 2. Synthesis of acetylmelodorinol and related compounds.

Conclusions

In summary, we have accomplished the total synthesis of acetylmelodorinol (revised structure of klaivanolide) and its related compounds in racemic form using a short sequence. The present route is useful for the generation of variety of analogues which ultimately can be useful for the identification of anti-leishmanial agents with novel chemotypes.

Experimental Section

General. All reactions were carried out in oven-dried glassware under argon or nitrogen unless otherwise specified, with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25

mm precoated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, iodine vapours, or by immersion in ethanolic solutions of phosphomolybdic acid, *para*-anisaldehyde, or $KMnO_4$ followed by heating with a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). High resolution mass spectra (HRMS, ESI) were recorded with an ORBITRAP mass analyser (Q Exactive). Mass spectra were measured with electro spray ionization with an MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded on an FT-IR spectrometer as thin films. Optical rotations were recorded on a P-2000 polarimeter at 589 nm. Chemical nomenclature was generated using Chem Bio Draw Ultra 13.0.

3-Butenyl benzoate. To a solution of but-3-en-1-ol (1 g, 13.9 mmol) in dry DCM was added pyridine (2.24 mL, 27.8 mmol) and benzoyl chloride (2 mL, 20.8 mmol) at 0 ºC. Reaction mixture was warmed slowly to room temperature, quenched with water and washed well with 1N HCl, saturated solution of $NaHCO_3$, water, dried over Na_2SO_4 and purified by flash column chromatography eluting with 5% ethyl acetate: pet ether gave 3-butenyl benzoate (2.24 g, 91%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04 (m, 2 H), 7.55 (m, 1 H), 7.44 (t, *J* 7.7 Hz, 2 H), 5.91 - 5.84 (m, 1 H), 5.20 - 5.10 (m, 2 H), 4.38 (t, *J* 6.7 Hz, 2 H), 2.54 (q, *J* 6.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 134.0, 132.9, 130.3, 129.5, 128.3, 117.3, 64.0, 33.2. HRMS calculated for $C_{11}H_{13}O_2$ $[M + H]^+$ 177.0910, found 177.0906.

3-Oxopropyl benzoate (4). A solution of 3-butenyl benzoate (2.2 g, 12.5 mmol) in dry DCM (20 mL) was cooled to -78 ºC and stream of O_3 passed through it till reaction mixture becomes blue and excess of ozone was removed by passing a stream of oxygen for 3 minutes. Dimethyl sulfide (1.37 mL, 18.75 mmol) was added and reaction mixture was warmed slowly over the period of 3 h to room temperature and stirred for another 3 h. Solvent was removed under reduced pressure and crude aldehyde **4** (2.11 g, 95%) which was used as such without further purification for next step.

3-(5-Oxofuran-2(5*H*)-ylidene)propyl benzoate (3). To a solution of diisopropylamine (2.5 ml, 17.8 mmol) in dry THF (20 mL) was added *n*-BuLi (1.5 M in hexane, 11.9 mL, 17.8 mmol) at -78 ºC dropwise and reaction mixture stirred for 45 minutes. The solution of 2-furanone (1 g, 11.9 mmol) in dry THF (10 mL) was added dropwise and stirring continued for another 30 minutes before addition of aldehyde **4** (2.11 g, 11.9 mmol) in 10 mL of dry THF. The reaction mixture stirred for 1.5 h at -78 ºC and quenched with 5 ml of saturated solution of NH_4Cl and slowly warmed to room temperature, diluted with ether and washed with saturated solution of NH_4Cl (10 mL). Solvent was removed under reduced pressure and crude product was dissolved in dry DCM, treated with triethylamine (1.5 mL), acetic anhydride (1.0 mL) and DMAP (catalytic) at room temperature for 2 h. diluted with water and washed with 1N HCl, saturated solution of $NaHCO_3$, brine and dried over Na_2SO_4 and purified by column chromatography gave **3** (1.7 g, 59% over two steps) as colorless oil. IR υ_{max} ($CHCl_3$ film cm^{-1}): 3020, 1773, 1718, 1214, 1068 cm^{-1}. Spectral data given only for *cis*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (dd, *J* 8.1, 1.0 Hz, 2 H), 7.57 (m, 1 H), 7.44 (m, 2 H), 7.35 (d, *J* 5.6 Hz, 1 H), 6.19 (d, *J* 5.6 Hz, 1 H),

5.38 (t, *J* 7.7 Hz, 1 H), 4.45 (t, *J* 6.4 Hz, 2 H), 2.89 (q, *J* 6.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.6, 166.4, 151.0, 143.4, 133.1, 129.9, 129.6, 128.4, 119.9, 111.8, 63.1, 26.2. HRMS calculated for $C_{14}H_{12}O_4Na$ $[M + Na]^+$ 267.0628, found 267.0619.

2-Hydroxy-3-(5-oxofuran-2(5*H*)-ylidene)propyl benzoate (5) & (6). To a solution of compound **3** (0.1 g, 0.4 mmol) in dry 1,4-dioxane (5 mL) was added SeO_2 (0.068 g, 0.6 mmol) and reaction mixture was refluxed for 48 h. Cooled to room temperature, filtered through whatman paper and solvent was removed under reduced pressure, product was purified by silica gel column chromatography eluting with 30% ethyl acetate: pet ether to afford the melodorinol **5** (0.054 g, 52%) and **6** (0.017 g, 17%) as oil. *cis*-melodorinol (**5**): IR υ_{max} ($CHCl_3$ film cm^{-1}): 3664, 3413, 2857, 1878, 1719, 1271. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04 (m, 2 H), 7.58 (m, 1 H), 7.45 (m, 2 H), 7.39 (d, *J* 5.5 Hz, 1 H), 6.26 (d, *J* 5.2 Hz, 1 H), 5.40 (d, *J* 8.2 Hz, 1 H), 5.19 (ddd, *J* 7.9, 6.1, 4.3 Hz, 1 H), 4.47 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.8, 166.7, 150.1, 143.6, 133.4, 129.7, 128.6, 128.5, 121.1, 113.0, 67.5, 66.0. HRMS calculated for $C_{14}H_{12}O_5Na$ $[M + Na]^+$ 283.0577, found 283.0570. *trans*-melodorinol (**6**): IR υ_{max} ($CHCl_3$ film cm^{-1}): 3664, 3413, 2857, 1878, 1719, 1271. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04 (d, *J* 7.6 Hz, 2 H), 7.91 (d, *J* 5.5 Hz, 1 H), 7.60 (m, 1 H), 7.46 (t, *J* 7.6 Hz, 2 H), 6.28 (d, *J* 5.8 Hz, 1 H), 5.81 (m, 1 H), 4.94 (dt, *J* 7.1, 3.8 Hz, 1 H), 4.51 (dd, *J* 11.6, 3.7 Hz, 1 H), 4.39 (dd, *J* 11.6, 7.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.9, 166.7, 152.0, 140.9, 133.6, 129.7, 129.3, 128.6, 121.7, 111.9, 68.3, 67.2. HRMS calculated for $C_{14}H_{12}O_5Na$ $[M + Na]^+$ 283.0577, found 283.0570.

(*Z*)-2-Acetoxy-3-(5-oxofuran-2(5*H*)-ylidene)propyl benzoate [acetylmelodorinol] (2). A solution of compound **5** (0.05 g, 0.19 mmol) in dry DCM (3 mL) was added pyridine (31 μL, 0.38 mmol), and acetic anhydride (38 μL, 0.38 mmol). Reaction mixture was stirred at room temperature for 3 h and quenched with water, washed well with 1N HCl, saturated $NaHCO_3$, water, dried over Na_2SO_4 and purified by flash column chromatography with 20% ethyl acetate: pet ether gave acetylmelodorinol (**2**) (0.04 g, 75%) as colorless oil. IR υ_{max} ($CHCl_3$ film cm^{-1}): 3020, 1784, 1744, 1723, 1214. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (d, *J* 7.3 Hz, 2 H), 7.58 (t, *J* 7.3 Hz, 1 H), 7.45 (t, *J* 7.7 Hz, 2 H), 7.37 (d, *J* 5.5 Hz, 1 H), 6.28 (d, *J* 5.5 Hz, 1 H), 6.14 (ddd, *J* 7.9, 6.0, 4.4 Hz, 1 H), 5.32 (d, *J* 7.8 Hz, 1 H), 4.59 - 4.50 (m, 2 H), 2.10 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.8, 168.5, 166.0, 150.7, 143.3, 133.3, 129.7, 129.5, 128.5, 121.6, 108.9, 67.3, 64.6, 20.9. HRMS calculated for $C_{16}H_{14}O_6Na$ $[M + Na]^+$ 325.0683, found 325.0671 and $C_{16}H_{18}O_6N$ $[M + NH_4]^+$ 320.1129, found 320.1122.

(*E*)-2-Acetoxy-3-(5-oxofuran-2(5*H*)-ylidene)propyl benzoate (7). Compound **7** was synthesised from compound **6** following the same procedure as mentioned for compound **2**. IR υ_{max} ($CHCl_3$ film cm^{-1}): 3020, 1784, 1744, 1723, 1214. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (m, 2 H), 7.90 (d, *J* 5.6 Hz, 1 H), 7.58 (m, 1 H), 7.46 (t, *J* 7.7 Hz, 2 H), 6.34 (dd, *J* 5.6, 1.7 Hz, 1 H), 5.96 (ddd, *J* 10.2, 6.4, 4.4 Hz, 1 H), 5.72 (d, *J* 10.0 Hz, 1 H), 4.54 - 4.44 (m, 2 H), 2.09 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 170.0, 168.6, 166.0, 153.5, 140.2, 133.5, 129.7, 129.3, 128.5, 122.5, 107.5, 66.8, 65.0, 21.0. HRMS calculated for $C_{16}H_{14}O_6Na$ $[M + Na]^+$ 325.0683, found 325.0671 and $C_{16}H_{18}O_6N$ $[M + NH_4]^+$ 320.1129, found 320.1122.

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