

Synthesis of Belallosides of *Belamcanda Chinesis* and its Analogs

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ABSTRACT

Two compounds namely Belallosides A and B (6-O-benzoyl esters of 2-methoxy-4-acetyl-O-phenyl- β -glucopyranosides) isolated from Thai medicinal plant *Belamcanda chinesis* were synthesized by using simple approach. Further, three new analogs (1c-1e) of the belallosides (1a and 1b) were also synthesized by using the approach. The yields of the compounds were also good.

INTRODUCTION

In the present investigation an attempt was made to synthesize naturally isolated compounds (Belallosides) from the Thai medicinal plant *Belamcanda chinesis* [1]. This plant is commonly known as Blackberry lily, is a perennial herbaceous plant having fan shaped leaves that reach 2 to 3 feet in length on branching stems. The dried rhizomes are used in Chinese traditional medicine for treatment of inflammation and asthma as well as throat disorders [2]. Moreover, in Thai folk medicine, the rhizomes used for the regulation of menstrual disorders [3].

Generally, the synthesis of naturally isolated compounds from medicinal plants has much importance and leads to the development of highly potent molecules, like 6-O-Caffeoyl arbutin, 6-O-Tiglyl Arbutin, Lomaiviticin B, Olivomycin A, Durhamycin, etc. The synthesis of arbutin was taken as a model approach [4,5] in order to emphasize the method of O-glycosylation, followed for the synthesis of present compounds. In this report we synthesized Belallosides A and B i.e., 6-O-benzoyl esters of 2-methoxy-4-acetyl O-phenyl glucopyranosides (1a and 1b) isolated from *Belamcanda chinesis* [1] along with three other new analogs shown in **Figure 1**.

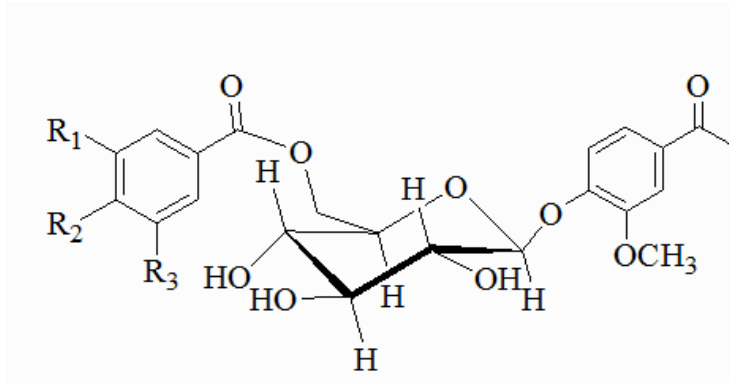
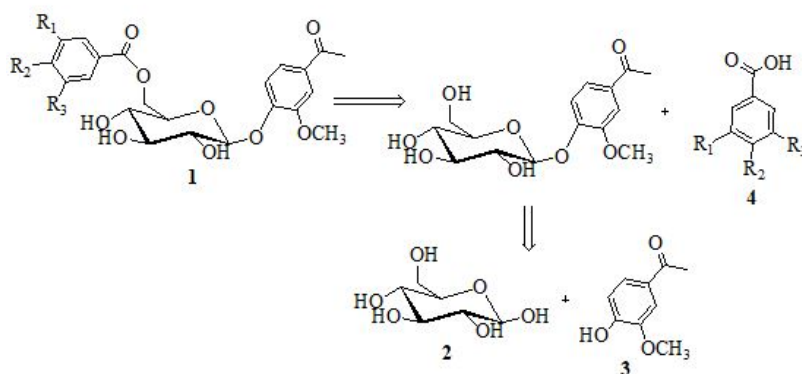


Figure 1. Belallosides (1a-e) where 1a: R1=OMe, R2=OH, R3=H; 1b: R1=R3=H, R2=OH; 1c: R1=R2=R3=OMe; 1d: R1=R3=OMe, R2=H; 1e: R1=R2=OMe, R3=H.

RESULTS AND DISCUSSION

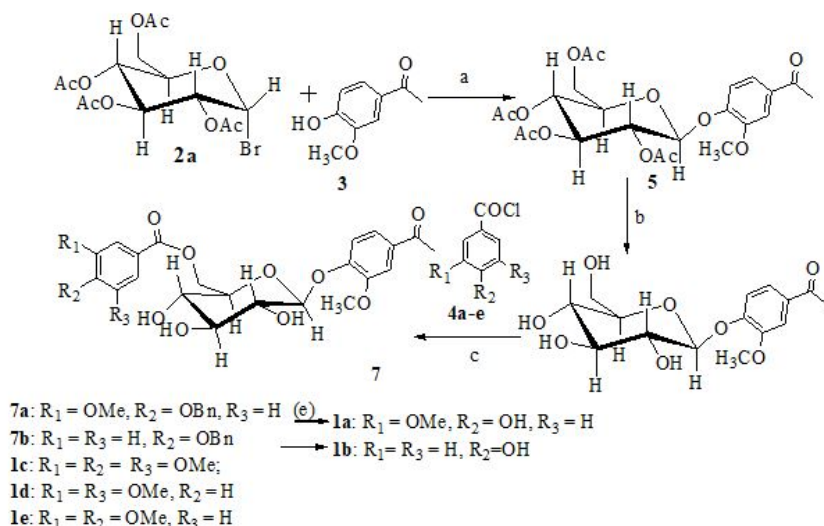
Umehara, et al. [1] isolated three new compounds from rhizomes of *Belamcanda chinensis* and were named as belalloside A (M.F. $C_{23}H_{26}O_{11}$; **Figure 1**), belalloside B (M.F. $C_{22}H_{24}O_{10}$; **Figure 1**) and belamphenone (M.F. $C_{14}H_{12}O_4$). In the present investigation, a simple method was developed for the synthesis of belalloside A (1a; 6-O-4-hydroxy-3-methoxybenzoic acid ester of 2-methoxy-4-acetylphenyl β -glucopyranoside) and belalloside B (1b; 6-O-4-hydroxybenzoic acid ester of 2-methoxy-4-acetylphenyl- β -glucopyranoside) by using the following retrosynthetic (**Scheme 1**).



Scheme 1. Retrosynthetic scheme for belallosides.

The disconnection approach of the structure of Belalloside A (1a) as in **Scheme 1** manifests that the gross structure identifies, D-Glucose (2), substituted acetophenone (3) and substituted benzoic acid chlorides (4), are the precursors. Basing on this disconnection approach the possible scheme (**Scheme 2**) for the synthesis of the above said compounds was given below.

In the first stage the tetra acetyl- α -D-glucosylbromide (2a) obtained initially from β -D-glucose4 was treated with substituted acetophenone (3) using sodium methoxide to get 4 2-methoxy-4-acetylphenyl- β -D-glucopyranoside (6). As we know that 1,2-trans Glycosidic linkage can be obtained stereo selectively by the use of anchimeric assistance of a neighboring participating group, generally an acyl moiety⁶⁻⁸ such as O-acetyl, O-benzoyl, 2-phthalimido, etc. However, in the present investigation minor amounts of α -isomer is also obtained and was separated by column chromatography by eluting the mixture with 5% methanol in chloroform.



Scheme 2. 6-O-benzoyl esters of 2-methoxy-4-acetyl O-phenyl- β -glucopyranosides.

Reagents and conditions: a) 1,4-Dioxane, NaOMe, rt, 48h; b) MeOH, NaOMe, H_2O , Δ ; c) Acid chloride, pyridine, 0-5°C, 36 h; e) Pd/C, H_2 , 4 h.

The glucopyranoside 6 obtained above is treated with substituted benzoyl chlorides 4a-e to get the compounds 7a, 7b and 1c-e. After that the benzyl groups in compounds 7a and 7b are de-protected using catalytic amount of Pd/C in ethyl acetate followed by introduction of hydrogen gas for 4 hours in to the reaction mixture to get the titled belallosides 1a and 1b (**Scheme 2**). The compounds 1a and 1b (Belallosides A and B) were confirmed by comparing their spectral data and physical constants. The overall yields and M.P.'s of all the synthesized compounds were given in **Table 1**.

Table 1. The yields and melting points of the synthesized glucopyranosides.

Compound	Yield (%)	MP(°C)
1a	55.4	196-202
1b	45.2	170-178
1c	61.3	164-168
1d	63.0	196-200
1e	52.8	190-194

The compound with m-di-methoxy substitutions (1d) has given highest yield (63%) and the compound 1c with m- and p-trimethoxy substitution has also given good yield (61%). The compound with m- and p-di-methoxy substitutions (1e) has given lowest yield. The belalloside 1a with additional m- methoxy substitution was obtained in high amount compared to 1b. The chemical shift of anomeric proton was obtained in the range 4.93 to 5.14 as doublets with coupling constants 6.8 and 7.2 Hz for compounds 1a-e. Similarly, the carbon NMR chemical shifts are obtained in the range of 99.1 to 101.7.

MATERIALS AND METHODS

All the chemicals were obtained from Merck Specialties Private Limited, Mumbai, India. Reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent and the solvent systems are indicated at appropriate places. Silica gel (100-200 mesh, Merck grade) has been used for column chromatography.

The ^1H NMR spectra of the compounds were recorded on Bruker AMX 400 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm. The ^{13}C NMR spectra of the compounds were recorded on Bruker AMX 100 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm. The Mass spectra of the compounds were recorded on API-ES Mass Spectrometer using positive/negative mode ionization method.

Preparation of acid chlorides (4a-e) and 4-hydroxy, 3-methoxy acetophenone (3)

The required aromatic acid chlorides (4a-e) were prepared from their corresponding benzoic acids with thionyl chloride at 80°C for 30-40 min by following regular approach and 4-hydroxy-3-methoxy acetophenone (3) was obtained from 1,2-di-methoxybenzene by using known methods (9-11).

Preparation of 2-Methoxy,4-acetyl phenyl-β-D-glucopyranoside (6): A mixture of tetraacetyl-α-D-glucosyl bromide (2a) (23 g, 0.051 mol) thus obtained from penta acetyl β-D-glucose_{1,2,4,6}, 1,4-dioxane (9 mL), 4-hydroxy-3-methoxy acetophenone (12.69 g, 0.0765 mol), sodium methoxide (11 g, 0.205 mol) was stirred at room temperature for 48 hours. Then the reaction mixture was concentrated under vacuum, a tetra acetyl compound 5 was formed; to it added methanol (100 mL), sodium methoxide (16.5 g, 0.307 mol), water (10 mL) and refluxed for 2 hours and concentrated to obtain the tetra hydroxyl compound 6. The crude was subjected to column chromatography, CHCl₃/MeOH mixtures as eluents. Pure compound eluted in 15% MeOH/CHCl₃ and concentrated to get off-white solid (8.7 g, 51.7%). The compound was melted at 192-196°C.

General procedure for 6-O-substituted benzoic acid esters of 2-methoxy, 4-acetylphenyl-β-D-glucopyranoside (7a, 7b, 1c-1e)

A mixture of 2-methoxy, 4-acetylphenyl-β-D-glucopyranoside (0.001 mol) and pyridine (5 mL) was cooled at 0-5°C and added substituted benzoyl chloride (0.002 mol). After completion of addition stir the reaction mixture for 36 hours. Then the reaction mixture was adsorbed on silica gel and subjected to column chromatography using chloroform-methanol mixtures as eluents. Pure compound was eluted in 4-6% methanol in chloroform. For the benzoyl chlorides 4a and 4b the respective products 7a and 7b were obtained unlike for products 1c-1e obtained directly.

Preparation of 1a and 1b by deprotection of compounds 7a and 7b

To a mixture of compound (7a or 7b) and ethyl acetate, catalytic amount of Pd/C was added then hydrogen gas was introduced with a balloon on top of the RB flask. Stir the reaction for 4 hours and filtered the reaction mixture on super cell and washed with ethyl acetate. After concentration the reaction mixture was passed on a silica column using chloroform-methanol mixtures as eluents. Pure compound (1a,1b) was eluted in 15-20% methanol in chloroform.

Spectral data of (6-O-4-hydroxy-3-methoxybenzoyl 2-methoxy-4-acetyl-O-phenyl-β-D-glucopyranoside) (1a)

M.P. 196-202°C; Yield=55.4 g. ¹H NMR (d₄-MeOH; 400 MHz): δ 7.48 (¹H, dd, J=2.0, 8.4 Hz), 7.41 (²H, d, J=1.6 Hz), 7.05 (¹H, dd, J=1.6, 8.8Hz), 6.92 (¹H, d, J=8.4 Hz), 6.77 (¹H, d, J=8.0 Hz), 4.93 (¹H, d, J=7.2 Hz), 4.55 (¹H, dd, J=1.6, 11.6 Hz), 4.33 (¹H, m), 3.77 (³H, s), 3.72 (³H, s), 3.45 (²H, m), 3.33 (¹H, t, J=9.2 Hz), 2.36 (³H, s). ¹³C NMR (d₄-MeOH; 100 MHz): δ 199.2, 167.7, 153.0, 152.1, 150.7, 148.8, 132.9, 126.2, 125.3, 124.2, 122.6, 116.3, 116.0, 114.0, 112.4, 101.7, 77.9, 75.7, 74.4, 72.1, 64.9, 56.7, 56.6, 26.2. LC-MS: 501 (M+Na)⁺ positive ion mode.

Spectral data of (6-O-(4-hydroxybenzoyl 2-methoxy-4-acetyl-O-phenyl-β-D-glucopyranoside) (1b)

M.P.=170-178°C; Yield=45.2g. ¹H NMR(d₆-DMSO; 400 MHz): δ 10.29 (¹H, br s), 7.71 (1H, d, J=8.8 Hz), 7.65 (¹H, dd, J=2.0, 8.4 Hz), 7.61 (¹H, d, J=2.0 Hz), 7.08 (¹H, d, J=8.4 Hz), 6.76 (²H, d, J=8.8 Hz), 5.38 (¹H, d, J=4.4 Hz), 5.21 (¹H, m), 5.14 (¹H, d, J=7.2 Hz), 4.53 (¹H, d, J=12.0 Hz), 4.12 (¹H, dd, J=7.2, 11.6 Hz), 3.83 (³H, s), 3.33 (²H, m), 3.23 (¹H, m), 2.46 (³H, s). ¹³C NMR (d₆-DMSO, 100 MHz): δ 196.1, 165.2, 162.1, 150.3, 147.8, 131.2, 130.7, 121.9, 114.8, 114.2, 111.3, 99.3, 76.5, 73.8, 73.1, 70.1, 64.2, 55.8, 26.2. LC-MS: 471 (M+Na)⁺ positive ion mode.

Spectral data of 6-O-3,4,5-trimethoxybenzoyl 2-methoxy-4-acetyl-O-phenyl-β-D-glucopyranoside (1c)

¹H NMR (d₆-DMSO; 400 MHz): δ 7.43 (¹H, s), 7.22 (²H, s), 7.16 (¹H, d, J=8.0 Hz), 7.10 (¹H, d, J=8.4 Hz), 5.14 (¹H, d, J=6.8 Hz), 4.63 (¹H, J=11.2Hz), 4.27 (¹H, dd, J=8.0, 11.2Hz), 3.82 (¹H, s), 3.78 (³H, s), 3.76 (³H, s), 3.73 (³H, s), 3.36 (²H, m), 3.26 (¹H, m), 2.44 (³H, s). ¹³C NMR (d₆-DMSO, 100 MHz): δ 196.0, 166.85, 164.9, 150.3, 148.6, 124.7, 122.0, 99.1, 76.6, 73.9, 73.0, 70.2, 64.2, 56.0, 55.9, 55.6, 26.0. LC-MS: 545 (M+Na)⁺ +ve ion mode, 557(M+2H₂O-H)⁻ -ve ion mode.

Spectral data of 6-O-(3,5-di-methoxybenzoyl 2-methoxy-4-acetyl-O-phenyl-β-D-glucopyranoside (1d)

¹H NMR (d₆-DMSO; 400 MHz): δ 7.44 (¹H, s), 7.32 (¹H, d, J=8.0Hz), 7.16 (¹H, d, J=8.4Hz), 7.06 (²H, s), 6.82 (¹H, s), 5.24 (¹H, m), 5.13 (¹H, d, J= 6.8 Hz), 4.60 (¹H, d, J=11.2Hz), 4.42 (⁴H, m), 4.24 (¹H, dd, J=8.0Hz), 3.86 (²H, m), 3.81 (³H, s), 3.79 (⁶H, s), 3.35 (²H, brs), 3.26 (¹H, m), 2.47 (³H, s). ¹³C NMR (d₆-DMSO; 100 MHz): δ 196.0, 165.0, 160.5, 150.34, 148.6, 131.5, 130.9, 122.1, 114.1, 111.1, 107.01, 106.8, 99.2, 76.6, 73.8, 73.1, 70.1, 64.4, 55.5, 55.4, 26.0. LC-MS: 515 (M+Na)⁺, +ve ion mode; 1007 (2M+Na)⁺ +ve ion mode; 527 (M+2H₂O-H)⁻ -ve ion mode.

Spectral data of 6-O-(3,4-dl-methoxybenzoyl 2-methoxy-4-acetyl O-phenyl-β-D-glucopyranoside (1e)

¹H NMR (d6-DMSO, 400 MHz): δ 7.62 (2H, m), 7.43 (2H, d, J=6.4Hz), 7.24 (1H, d, J=8.4Hz), 7.16 (2H, m), 5.37 (2H, m), 5.23(1H, m), 5.14 (1H, d, J=7.2 Hz), 4.58 (1H, d, J=10.8 Hz), 4.22 (1H,m), 3.85 (3H, s), 3.83 (3H, s), 3.76 (3H, s), 3.36 (2H, m), 3.27 (1H, m) 2.45 (3H, s). ¹³C NMR (d6-DMSO, 100 MHz): δ 196.2, 165.1, 158.1; 150.2, 148.6, 148.4, 130.8, 123.3, 122.1, 121.8, 114.2, 112.0, 111.1, 111.0, 99.1, 76.6, 73.9, 73.0, 70.2, 63.9, 55.7, 55.6, 55.5, 26.0. LC-MS: 515 (M+Na)⁺ +ve ion mode; 1007 (2M+Na)⁺ +ve ion mode; 527(M+2H₂O-H)⁻ -ve ion mode.

CONCLUSION

A simple approach was developed for the synthesis of glycosides Belalloside A (1a) and Belalloside B (1b) of Thai medicinal plant *Belamcanda chinensis*. In addition three new analogs (1c-1e) of the above belallosides were also prepared using the approach with good yields.

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