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BIOMIMETIC SYNTHESIS OF CHROBISIAMONE A FROM *CASSIA SIAMEA*

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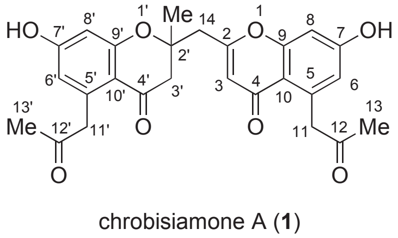
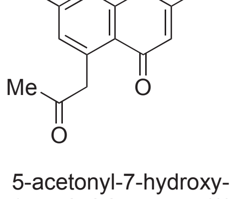
Abstract – Chrobisiamone A (**1**), an unique chromone dimer from leaves of *Cassia siamea* Lam. (Leguminosae), was synthesized from 5-acetonyl-7-hydroxy-2-methylchromone (**2**) in 4 steps through biomimetic Michael addition.

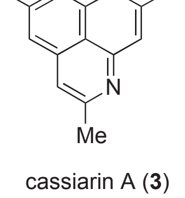
Chromones with a fused [6+6] system are a group of naturally occurring compounds widely distributed in nature. These structures represent molecules capable of binding to multiple receptors with high affinity and have a wide range of biological activities viz., tyrosine and protein kinase C inhibitors, anticancer, antifungal, antiviral, antitubulin, and antihypertensive agents.[1] A khellin-based 7,7’-glycerol-bridged bischromone exhibits more effective anaphylactic activity than cromoglycate.[2] Nebivolol, a 2,2’-bischroman tethered by 3-aza-1,5-pentanediol moiety, is an antihypertensive drug.[3] In the investigation of the bioactive chromone-based compounds from tropical plants, we have isolated cassiarins A (**3**) and B with an unprecedented tricyclic skeleton from the leaves of *C. siamea*[4], which showed a potent antiplasmodial activity. Cassiarin A (**3**) colud be derived from 5-acetonyl-7-hydroxy-2-methylchromone (**2**)[5] based on a plausible biogenetic path.[6]



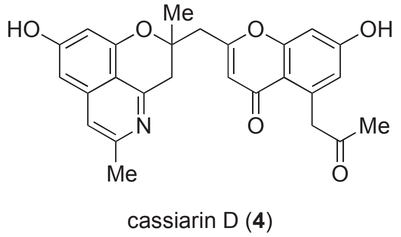
chrobisiamone A (**1**)



5-acetonyl-7-hydroxy-2-methylchromone (**2**)



cassiarin A (**3**)



cassiarin D (**4**)

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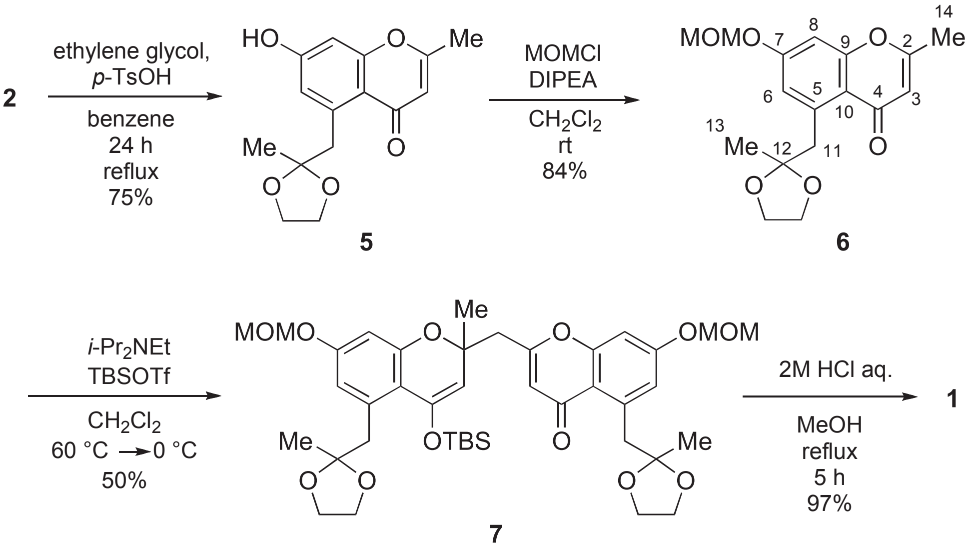
†Dedicated to Professor Ei-ichi Negishi, Purdue University, on the occasion of his 77th birthday.

Further investigation of new bioactive compounds led to the isolation of a new dimeric chromone, chrobisiamone A (**1**) from the leaves of *C. siamea*.[6] Chrobisiamone A (**1**) linked through their 2,2'-positions by methylene moiety. Few bischromone from natural resources has this type of ring system. Biogenetically, **1** might be derived from 5-acetonyl-7-hydroxy-2-methylchromone (**2**) by Michael addition of the chromone carbanion of C-2 methyl to C-2' of a second chromone. Thereafter, some new dimeric alkaloids such as cassiarins D (**4**) and E have been isolated, which may be biosynthesized from **1**.[7] In this paper, we would like to describe the biomimetic synthesis of chrobisiamone A (**1**) via the known chromone, 5-acetonyl-7-hydroxy-2-methylchromone (**2**).



Scheme 1

5-Acetonyl-7-hydroxy-2-methylchromone (**2**) was prepared by modified methods as described previously in 27% overall yield in 7 steps from 2,4,6-trihydroxylacetophenone.[8] Two reactive moieties were protected before carrying out Michael addition. Ketalization with ethylene glycol and MOM protection of the hydroxyl group by Hegedus' procedures gave a desired compound **6** (Scheme 1). One report about dimerization of chromone has published by Smith *et al.*[9] In their attempts to remove the methyne proton from position 3 in 2,6-dimethylchromone, they found the treatment of 2,6-dimethylchromone by lithium di-isopropylamide (LDA) forming the chromone-chromanone skeleton by Michael addition. We carried out the same reaction condition for compound **6**. Michael addition of compound **6** to the second molecule under LDA or LiHMDS failed to obtain a desired dimeric compound and only recovered starting material. In contrast to 2,6-dimethylchromone, a substituent at C-5 may have an influence on forming carbanion at C-14 by means of LDA. Ihara *et al* have succeeded to obtain a silyl enol ether of 3-methyl-2-cyclohexen-1-one by treatment of *i*-Pr_2NEt and TBSOTf.[10] In the same manner, compound **6** was treated with *i*-Pr_2NEt and TBSOTf to afford an enol ether. Surprisingly, this attempt led directly to the formation of chromone-chromanone skeleton and gave **7** in 50% yield along with recovered starting material in 50% yield. Compound **7** was comparatively stable and did not decompose or convert into compound **6** by retro-Michael addition. Treatment of compound **7** with 2M HCl aqueous solution in MeOH gave chrobisiamone A (**1**) in 97% yield.

In summary, biomimetic conversion of 5-acetonyl-7-hydroxy-2-methylchromone (**2**) to chrobisiamone A (**1**) (4 steps, 31% overall yield) by Michael addition have been achieved. This biomimetic transformation would support a biogenetic pathway proposed for chrobisiamone A (**1**).

EXPERIMENTAL

General Experimental Procedures. Commercial reagents were used without purification. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Highresolution ESIMS were obtained on a LTQ Orbitrap XL (Thermo Scientific). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400 spectrometers, and chemical shifts were referenced to the residual solvent peaks (δ_H 7.26 and δ_C 77.0 for chloroform-*d* and δ_H 3.31 and δ_C 49.0 for methanol-d_4).

7-Hydroxy-2-methyl-5-[(2-methyl-1,3-dioxolan-2-yl)methyl]chromone (5) A solution of 5-acetonyl-7-hydroxy-2-methylchromone (**2**) (100 mg), ethylene glycol (60 μL), and *p*-TsOH•H_2O (16 mg) in benzene (50 mL) was refluxed for 24 h in a Dean-Stark apparatus. The reaction mixture was cooled, poured into saturated aqueous $NaHCO_3$ solution, the aqueous layer extracted with $CHCl_3$, and washed with brine. The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel. Elution with hexane/EtOAc (1:1, v/v) gave ketal **3** (90 mg, 75%) as a colorless amorphous solid; IR (neat) 1560, 1616, 1647, 2883, 2932, 2980, 3101 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.25 (3H, s), 2.33 (3H, d, *J* = 0.6 Hz), 3.78 (2H, m), 3.80 (2H, s), 3.86 (2H, m), 6.00 (1H, d, *J* = 0.6 Hz), 6.70 (1H, d, *J* = 2.4 Hz), 6.80 (1H, d, *J* = 2.4 Hz); HRESIMS *m/z* 277.1074 [calcd. for $C_{15}H_{17}O_5$ $(M+H)^+$, 277.1071].

7-(Methoxymethoxy)-5-[(2-methyl-1,3-dioxolan-2-yl)methyl]chromone (6) To a solution of **5** (90 mg) in CH_2Cl_2 (5 mL) were added successively *i*-Pr_2NEt (68 μL) and MOMCl (37 μL) at 0 °C under Ar atmosphere. The resulting mixture was stirred at rt for 1.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution, the aqueous layer extracted with EtOAc, and washed with 1M HCl aqueous solution and brine. The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel. Elution with hexane/EtOAc (1:1, v/v) gave **6** (88 mg, 84%) as a colorless amorphous solid; IR (neat) 1610, 1657, 2885, 2931, 2959, 2982 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.25 (3H, s), 2.35 (3H, d, *J* = 0.6 Hz), 3.48 (3H, s), 3.75 (2H, m), 3.83 (2H, s), 3.85 (2H, m), 5.29 (2H, s), 6.06 (1H, d, $J = 0.6$ Hz), 6.97 (1H, d, $J = 2.5$ Hz), 7.03 (1H, d, $J = 2.5$ Hz); HRESIMS *m/z* 321.1331 [calcd. for $C_{17}H_{21}O_6$ $(M+H)^+$, 321.1333].

7,7'-Bis(methoxymethoxy)-12,12'-bis(1,3-dioxolan-2-yl)-4'-(*tert*-butyldimethylsilyloxy)-chrobisiamone A (7) To a solution of **6** (5 mg) in CH_2Cl_2 (2 mL) was added *i*-Pr_2NEt (20 μL) and stirred for 30 min at 60 °C. After cooling to 0 °C TBSOTf (4 μL) was added dropwise and stirred for 30 min at the same temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution, the aqueous layer extracted with $CHCl_3$, and washed with brine. The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel. Elution with hexane/EtOAc (2:1, v/v) gave **7** (2.9 mg, 50%) as a colorless amorphous solid; IR (neat) 1608, 1653, 2859, 2887, 2932, 2954 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.15 (3H, s), 0.16 (3H s), 0.92 (9H, s), 1.22 (3H, s), 1.25 (3H, s), 2.95 (2H, s), 3.23 (1H, d, $J = 13.3$ Hz), 3.47 (3H, s), 3.48 (3H, s), 3.63 (1H, d, $J = 13.3$ Hz)3.77 (4H, m), 3.85 (4H, m), 4.94 (1H, s), 5.12 (2H, s), 5.30 (2H, s), 6.11 (1H,s), 6.51 (1H, d, $J = 2.6$ Hz), 6.55 (1H, d, $J = 2.6$ Hz), 6.99 (1H, d, $J = 2.5$ Hz), 7.02 (1H, d, $J = 2.5$ Hz); HRESIMS *m/z* 755.3465 [calcd. for $C_{40}H_{55}O_{12}Si$ $(M+H)^+$, 755.3457]

Chrobisiamone A (1) A mixture of **7** (3 mg) and 2M HCl aqueous solution (10 drops) in MeOH (2 mL) was refluxed for 5 h. MeOH was removed and water was added. The mixture was extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel. Elution with hexane/EtOAc (1:3, v/v) gave **1** (1.8 mg, 97%) as a colorless amorphous solid; Spectroscopic data were corresponding to those of the article.[6]

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