Synthesis of Benzyl-Protected Robtein (2′,3,4,4′,5-Pentahydroxychalcone) as an Intermediate to (–)-Robidanol

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Abstract

(–)-Robidanol 1 is a tetrahydroxyflavan-3-ol that has been isolated from Indonesian merbau *hardwood (*Intsia palembanica*). Several bioactivities have been reported as a skin-whitening, anti-acne, and antioxidant agent. However, to isolate this compound from natural sources with reasonable yield requires a tedious work. This study aims to synthesize(–)-robidanol 1 through three major steps: (1) synthesis of benzyl-protected 2′,3,4,4′,5-pentahydroxychalcone robtein 2; (2) reductive cyclization of protected robtein 2 into the corresponding flav-3-ene3 followed by functional group modifications into (+)-epirobidanol4; and (3) epimerization of 4 into (–)-robidanol1. Herein, we report the synthesis of compound 2. Resacetophenone 5 and methyl gallate6were used as the starting materials. Benzyl protection gave monobenzyl resacetophenone 7 and methyl tribenzylgallate 8 in 85% and 98% yield respectively.*

*The reduction of the latter with lithium aluminum hydride gave tribenzylgallyl alcohol 9 in 98% yield which was oxidized with pyridinium chlorochromate to give tribenzylgallaldehyde 10 in 93% yield. Sodium hydride-catalyzed condensation betweenacetophenone 7 and aldehyde 10 in dimethylformamide produced a protected robtein 2 in 61% yield. The total yield of compound 2 is 54% over four steps from the methyl gallate 6 starting material. The acid-deprotection of the benzyl groups is in progress in order to determine anticancer activity of the robtein. Polyhydroxychalcones with similar structures have been reported to show this activity. Several attempts have also been carried out to cyclize the protected robtein 2 into flav-3-ene 3. However, the high instability of flav-3-ene**3** hampered further synthesis.*

Keywords: Anticancer, chalcone, condensation, *merbau*, skin whitening agent.

Introduction

(–)-Robidanol 1 is the common name of (2*S*,3*S*)-3,3′,4′,5′,7-pentahydroxyflavene, a flavonoid that structurally belongs to the flavan-3-ol class[1]. It was first isolated from the bark of *Acacia mearnsii*[2]. Batubara et al[3] reported flavan-3-ol 1 as anactive component in *merbau* hardwood (*Intsia palembanica*) collected from Samarinda, East Kalimantan, Indonesia. The 3*R* epimer, (+)-robinetinidol or (+)-epirobidanol and its chalcone, robtein (2′,3,4,4′,5-pentahydroxychalcone), are more common in nature, and have been isolated from other plants such as *Robinia pseudoacacia*[4], *Euphorbia palustris*[5], and *Erythrophleum fordii*[6].The unstable 2,3-*cis* geometry is the primary reason for the scarcity of (–)-robidanol 1 in nature.

(–)-Robidanol 1 is a potent skin whitening agent. The 50% inhibition concentrations (IC_{50}) against mono- and diphenolase are 8.7 and 26.6 μM respectively. It also inhibits 46% of melanin synthesis in B-16 cells at 100 μM concentration, comparable with 44% inhibition by 12 μM of kojic acid as a positive control[3]. A modest inhibition activity (IC_{50} 100 μM) against lipase isolated from *Propionibacterium acnes* also demonstrates the potential of flavan-3-ol 1 as an anti-acne agent[7].The methanol extract of *merbau* stem exhibits a potent inhibitor of lipase (IC_{50} 4.1 μg/mL) as well as a strong antioxidant (IC_{50} 3.87 μg/mL) that acts as a free-radicals scavenger[8,9].

Merbau (ironwood, mirabow) is a medium-sized to large tree that grows up to 45 m in height with a bole that grows up to 150-cm in diameter[10]. It is a good general-purpose timber, due to its favorable physical and mechanical properties, combined with an attractive appearance. *Merbau* is applied in construction work in houses and buildings, especially for high-class exterior joinery. It is also particularly useful in water works constructions such as bridges, wharves, sluices, and sheet piles[11].

The superior quality of *merbau* has evoked a massive illegal logging industry, which makes this wood species increasingly scarce nowadays[12]. Physiological studies on germination and seedling development have been carried out[13]. Although the growth of *merbau* seedlings is initially fast (40–55 cm in3 months), it gradually slows down (5–6 cm from 3 to 10 months). The rotation age of stands is expected to be over 60 years[10,11].

To explore the beneficial activities of (–)-robidanol**1** and the structure-activity relationship, a synthesis should be attempted. There are only two reports concerning the total synthesis of (–)-robidanol 3-gallateexist [14,15]. This derivative has an *O*-gallyl group at C-3 and shows different bioactivities from the parent compound. We developed a

synthetic method for this compound by modifying the approaches previously reported in catechin synthesis[16-19].

We followed the retrosynthetic analysis shown in scheme 1. We aimed to obtain (–)-robidanol 1 from the epimerization of benzyl-protected (+)-epirobidanol 4, after deprotection of all benzyl protecting groups. Compound 4 was obtained via functional group modifications from intermediate 3, a benzyl-protected flav-3-ene, which is a reductive cyclization product of enone 2, a benzyl ether-protected chalcone robtein.

In this paper, we report the synthesis of enone 2. Our effort to obtain intermediate 3 from enone 2is also discussed. However, we were unsuccessful to convert the highly unstable intermediate 3 into compound 4. In addition, wepresent our attempts to deprotect enone 2 into chalcone robtein. Chalcones have numerous interesting bioactivities[20], one of which is as an anticancer[21]. Whether the pentahydroxychalcones, such as robtein possess this anticancer activity as well.

Material and Methods

Several reagent grade chemicals were purchased fromSigma-Aldrich® [benzyl bromide (BnBr), methyl gallate, lithium aluminum hydride ($LiAlH_4$), tetrahydrofuran (THF), pyridinium chlorochromate (PCC), and sodium hydride (NaH) (60% dispersed in mineral oil)]. Other chemicals were purchased from Merck®: [resacetophenone, potassium carbonate (K_2CO_3), potassium iodide (KI), acetone,methanol, sodium hydroxide (NaOH), aluminum chloride ($AlCl_3$), 37% hydrochloric acid (HCl), sodium hydrogen sulfite ($NaHSO_3$), dichloromethane (DCM), Celite® 545, *N*,*N*-dimethylformamide (DMF), silica gel 60 (0.040–0.063 mm, 0.063–0.200 mm, and 0.2–0.5 mm) for column chromatography, silica gel 60 G and 60 GF_{254} for thin layer chromatography (TLC), and silica gel 60 aluminum sheets 20 cm × 20 cm].

Technical grade chemicals used were: sodium sulfate (Na_2SO_4), copper (II) sulfate ($CuSO_4$) and technical solvents (*n*-hexane, DCM, ethyl acetate [EtOAc], acetone, methanol, and 95% ethanol). These solvents were distilled once without further purification.

The synthetic products were characterized spectroscopically using a Shimadzu®ultraviolet-visible UV-1601 machine,a Bruker®Fourier transform infrared (FTIR)Tensor 37 machine, and a Jeol®^{1}H (500 MHz) and ^{13}C (125 MHz) nuclear magnetic resonance (NMR) ECA 500spectrometer. The melting point was determined in a Mel-Temp Model 1202D Barnstead® melting point apparatus. All reactions were carried out under N_2 atmosphere.

The starting materials, resacetophenone 5 and methyl gallate 6 were protected as the monobenzyl resacetophenone 7 and methyl tribenzylgallate 8 respectively. A reduction of the latter with $LiAlH_4$ gave tribenzylgallyl alcohol 9, which was then oxidized using PCC to afford tribenzylgallaldehyde 10. Finally, Claisen-Schmidt condensation between acetophenone 7 and aldehyde 10 was catalyzed by NaH to produce enone 2 (Scheme 2).

4'-Benzyloxy-2'-hydroxyacetophenone (7)[22]: Resacetophenone 5, K_2CO_3 (1.1 eq), KI (0.11 eq) and acetone (3 mL/mmol of 5) were stirred in a two-necked flask. Three different BnBr equivalents (1.1, 2.2 and 3.3 eq) were investigated. The reagent was dissolved in acetone (ca. 2 mL) and added dropwise. The reaction mixture was then heated for 3 h. The basic residue was filtered and the filtrate was evaporated *in vacuo* to give an oily liquid mixture of mono- and diprotected products. Preparative TLC (*n*-hexane-DCM 2:3) separated both products: **7** (R_f ~0.54) and 2′,4′-dibenzyloxyacetophenone (R_f ~0.29).

Product 7 was purified by recrystallization from *n*-hexane to give pale yellow needles (85%): m.p. 100–102°C; UV-Vis:λ_{max}^{MeOH} = 212.2, 274.6, 313.2, 359.6, $\lambda_{max}^{MeOH + NaOH}$ = 201.8, 228.4, 274.6, 322, $\lambda_{max}^{MeOH + AlCl_3}$ = 210.4, 277, 298.6, 353.2; IR (KBr):$\overline{\upsilon}_{max}$ = 3839, 1607; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.55 (s, 3H), 5.09 (s, 2H), 6.50–6.53 (m, 2H), 7.33–7.42 (m, 5H), 7.63 (d, 1H,*J*= 8.45 Hz), 12.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.3, 70.3, 102.0, 108.2, 114.2, 127.6, 128.4, 128.8, 136.0, 132.5, 165.3, 202.7.

Methyl 3,4,5-tribenzyloxybenzoate (8)[17]: Methyl gallate 6, K_2CO_3 (3.3 eq) and acetone (4 mL/mmol of 6) were stirred in a two-neck flask. BnBr (3.3 eq) in acetone (ca. 2 mL) was added dropwise, and the mixture was then heated for 3 h. Distilled water was added to the cooled mixture to dissolve the base residue. The crude products were then extracted with several portions of EtOAc. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Recrystallization from 95% ethanol produced a white needle-like product 8 (98%): R_f ~0.68 (*n*-hexane-EtOAc 4:1); m.p. 94–96°C; UV-Vis: λ_{max}^{MeOH} = 215, 265.8, $\lambda_{max}^{MeOH + NaOH}$ = 205.4, 265;IR (KBr):$\overline{\upsilon}_{max}$ = 2948, 1716.

3,4,5-Tribenzyloxybenzyl alcohol (9)[18]: A two-neck flask containing suspension of $LiAlH_4$ (1 eq) in THF (1 mL/mmol of $LiAlH_4$), ester 8 was added dropwise in THF (2 mL/mmol of 8) while stirring. The mixture was stirred for another 6 h, and the reaction was then quenched by the careful addition of distilled water, 15% (w/v) NaOH and more distilled water, respectively. A portion of DCM was then added, and the mixture was refluxed for 30 min. The hot mixture was poured into a separating funnel and the organic layer was collected. The aqueous layer was mixed with the second portion of DCM and refluxed again. This extraction was repeated as needed, until all the products were extracted (monitored by TLC). The solvent was then removed and product 9 was obtained as white solids (98%): R_f ~0.67 (*n*-hexane-EtOAc 3:2); m.p. 94–97°C; UV-Vis: λ_{max}^{MeOH} = 209.4; IR (KBr):$\overline{\upsilon}_{max}$ =3311, 2865.

3,4,5-Tribenzyloxybenzaldehyde (10)[23]: A mixture of alcohol **9**, PCC (1.4 eq), and DCM (5 mL/mmol of 9) were stirred in a two-neck flask for 6 h at room temperature. The excess of PCC was removed by washing the mixture with several portions of 10% (v/v) $NaHSO_3$ and filtrating the organic layer through a Celite® 545 pad. The filtrate was further washed with distilled water, 10% (w/v) $CuSO_4$, and more distilled water respectively, before the solvent was removed. The crude products were purified through a silica gel column chromatography. Product 10 was eluted with *n*-hexane-DCM 1:2 as yellowish white solids (93%):R_f ~0.59 (*n*-hexane-EtOAc 4:1); m.p. 98–101ºC; UV-Vis:λ_{max}^{MeOH} = 209.8, 277.6; IR (KBr):$\overline{\upsilon}_{max}$ =3029, 1692; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.16 (s, 6H), 7.18 (s, 2H), 7.32–7.45 (m, 15H), 9.18 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 71.5, 76.9, 109.0, 127.6, 128.2, 128.6, 136.5, 131.9, 143.9, 153.3, 191.0.

3, 4, 4', 5-Tetrabenzyloxy-2'-hydroxychalcone (2)[19]: A suspension of NaH (60% dispersed in mineral oil) in DMF (1 mL/mmol of NaH) was stirred for 10 min at 0ºC.The amount of NaH was varied: 2.2, 3.3, 5, 7.5, 10, and 12.5 eq. Compound **7** in DMF (3 mL/mmol of **7**) was then added dropwise, and the mixture was stirred for 30 min. Subsequently, compound 10 in DMF (4 mL/mmol of 10) was added dropwise, and the mixture was further stirred for another 10 minutes. The mixture was allowed to warm, and then stirred at room temperature for two reaction times, namely, 2 and 24 h. Distilled water was added to dissolve the base, and afterwards, 0.05 N HCl drops were added carefully while stirring to bring the mixture to pH 4. The stirring continued until all precipitates formed no longer adhered to the container wall. These precipitates were vacuum-filtered, washed by cold distilled water, and then allowed to air-dry by vacuum suction. Flash column chromatography was applied to purify the crude product. The benzyl-protected robtein chalcone 2 was eluted with *n*-hexane-DCM (3:2) as yellow solids (61%):R_f~0.36 (*n*-hexane-EtOAc 9:1); m.p. 157–158 ºC; UV-Vis:λ_{max}^{MeOH} = 208.8, 366, $\lambda_{max}^{MeOH + NaOH}$ = 204.2, 332.6, $\lambda_{max}^{MeOH + AlCl_3}$ = 203.8, 372;^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.12 (s, 4H), 5.16 (s, 4H), 6.55 (d, 1H,*J* =1.95 Hz), 6.58 (dd, 1H,*J* = 2.6, 10.4 Hz), 6.91 (s, 2H), 7.27–7.44 (m, 20H), 7.39 (d, 1H,*J* = 14.95 Hz), 7.70 (d, 1H,*J* = 14.95 Hz), 7.76 (d, 1H,*J* = 9.1 Hz), 13.43 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 70.4, 71.6, 75.5, 102.2, 108.4, 108.6, 114.4, 119.7, 127.7, 127.6, 128.4, 128.8, 128.9, 136.9, 136.0, 141.1, 144.6, 153.3, 165.4, 166.8, 191.8.

Results and Discussion

The synthesis of polyhydroxychalcones typically takes place in basic conditions. The acidic phenolic groups in acetophenone and benzaldehyde starting materials are normally protected. Otherwise, they are deprotonated more readily than the alpha-hydrogen. Hence, the condensation does not occur, and the expected chalcone does not form. Ether protecting groups are common for this situation due to their resistance against base. Benzyl protecting groups were chosen in this study because they are inert in most of the acidic, basic, oxidizing, and reducing conditions employed[24]. Consequently, this group was expected to persist in the synthetic route used (Scheme 2).

The experimental results demonstrated a selective mono protection of 4′-OHin resacetophenone 5. Intramolecular hydrogen bonding between 2′-OH and *ortho*-carbonyl groups hinder etherification at 2′-OH. As shown in figure 1, the *O*-monobenzyl product **7**is consistently 3.5 to 4.5 times higher yield than that of the *O*, *O*-dibenzyl product. A series of experiments varying the equivalents of BnBr resulted in 2.2 eq of BnBr offering the highest yield of **7,** compared with 1.1 and 3.3 eq. Potassium iodide was used as a nucleophilic catalyst; it converts BnBr into the more active BnI. The iodide leaving group will be released more readily when being attacked by the phenoxide ion.

The highest yield of product 7 was 85%, which was obtained in benzylation of 20 mmol of resacetophenone 5 with 2.2 eq of BnBr. The yield is higher than the previous reports. Manners and Jurd[22]proved 78.5% of product 7 from 26 mmol of 5 by using 3.3 eq of BnCl, whilst Ayabe and Furuya[25] acquired 63% from 0.43 mmol of 5 with 1 eq of BnCl.

Resacetophenone 5 shows two –OH stretch peaks in the FTIR spectrum: the free –OH peak at 3294 cm^{-1}, and the hydrogen-bonded one at 3839 cm^{-1} (Figure 2). In the FTIR spectrum of product **7**, the first peak disappears, while the latter persists. This phenomenon proves that monoprotection occurs at the 4′-OH position, leaving the 2′-OH unprotected. The typical ^{1}H NMR signal at 12.73 ppm confirms the existence of this free 2′-OH. Intramolecular hydrogen-bonding creates a strong electron-withdrawing effect which shifts the signal far downfield. The presence of the benzyl protecting group is shown by a 5H multiplet signal at 7.33–7.42 ppm and a downfield methylene signal at 5.09 ppm.

Gallaldehyde (3,4,5-trihydroxybenzaldehyde) is an expensive chemical (SGD249.50 per gram; 98% [Aldrich®]). Therefore, we employed a 3-step approach from methyl gallate (methyl 3,4,5-trihydroxybenzoate) 6 to get aldehyde 10, the tri-*O*-benzyl-protected form of gallaldehyde. Methyl gallate is common in nature and is thus less expensive and more readily available (SGD 166.00 per 100 grams; 98% [Aldrich®]). Initially, all phenolic groups in this ester were protected to give ester 8. Afterwards, the ester group was reduced to benzyl alcohol 9, which was then oxidized to give aldehyde 10.

The protection step occurred successfully with an almost quantitative yield (98%). It is only slightly less than the yield reported by Zaveri et al[17] and higher than the results reported by Ahmed[18] (91%) and Oi et al[26] (70%). The reduction of the ester group gave the corresponding benzyl alcohol in an excellent yield (98%), higher than that in previous reports (95%[17] and 87%[18]). Finally, the oxidation of thebenzyl

alcohol group to the aldehyde gave a93% yield, which is also better than the previous reports (92%[17]and 87%[18]). The overall yield of aldehyde 10 is 89% in three steps from methyl gallate 6.

The FTIR spectra were used to follow the functional group conversion in this three-stepwork (Figure 3): (1) Protection with benzyl ether is indicated by the disappearance of the phenolic O–H stretch frequency at 3323 cm^{-1}, accompanied with the appearance of a methylene C–Hsp^3 stretch of the benzyl groups at 2948 cm^{-1}. (2) Following the reduction, the C=O stretch at 1716 cm^{-1}frequency disappears while the O–H stretch re-appears at 3311 cm^{-1}. (3) Subsequently, oxidation removes the O–H stretch frequency, and at the same time recovers the C=O stretch at 1692 cm^{-1}frequency.

The structure of product 10 is ascertained from the ^1H and ^{13}C NMR spectra. A singlet signal of aldehyde is found at 9.80 ppm. Three benzyl ether groups give a 15H second-order multiplet signal at 7.32 δ 7.45 ppm along with an apparent singlet signal at 5.16 ppm from 6 methylene protons. The ^{13}C NMR spectrum is in accordance with these results. The aldehyde carbonyl group gives a signal at 191.0 ppm, and signals at 71.5 ppm (2C) and 76.9 ppm (1C) come from 3 methylene carbons.

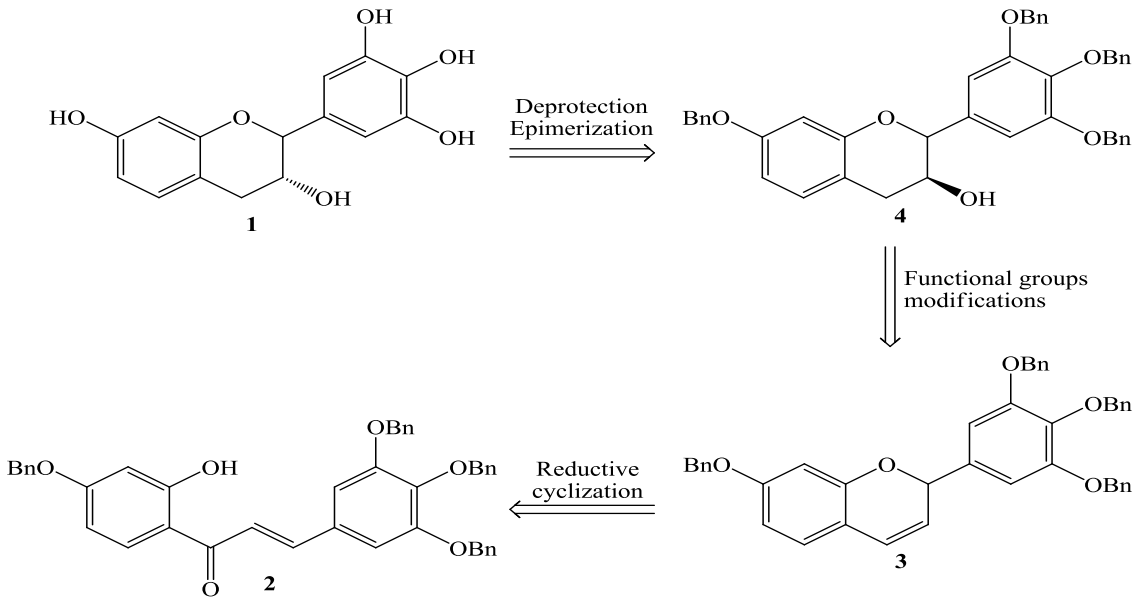
Benzyl-protected robtein (2) was then synthesized via condensation between acetophenone 7 and aldehyde 10. As shown in figure 4, the prolonged reaction consistently produces a higher yield.

Increasing the amount of NaH from 2.2 to 3.3 eq with a 24 h reaction time significantly increased the yield of chalcone **2**. However, the yield fluctuated when higher equivalents of NaH were used. A different trend was observed with a 2 h reaction time. The yield increased steadily from 11% (2.2 eq NaH) up to 57% (12.5 eq NaH). Overall, 10 eq NaH and 24 h reaction time produced the highest yields (61%). However, only slightly less yields were obtained with 3.3 and 5 eq NaH: 59 and 60% respectively. Therefore, 3.3 eq of NaH and a 24 h reaction time was chosen as the most efficient reaction condition for the synthesis of chalcone 2.

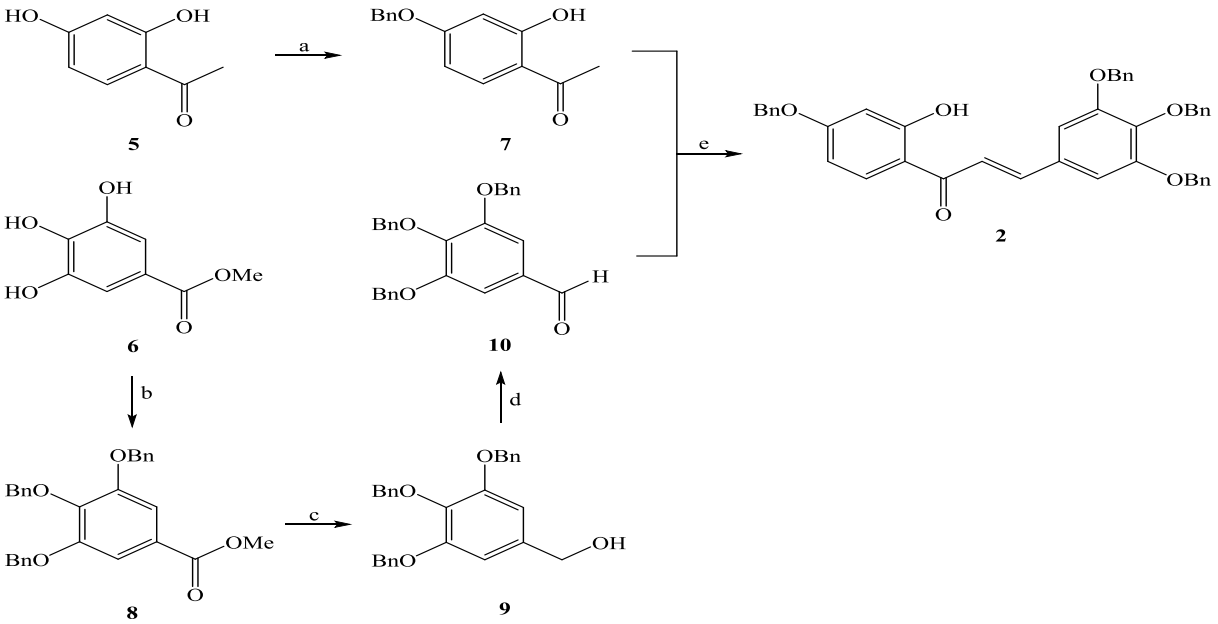
In previous reports, 3,4,4′,6′-tetrabenzyloxy-2′-hydroxychalcone, a precursor of catechin, was synthesized in a 72% yield[18]. A quantitative yield of the same chalcone was reported by using a combination of benzyl with methyl, methoxy-methyl, or *p*-methoxybenzyl protecting groups[19]. Zaveri et al[17]. also reported a 92% yield in the synthesis of 4′,6′-dibenzyloxy-3,4-dimethoxy-2′-hydroxychalcone. In the synthesis of chalcone 2, however, we faced some difficulties in the purification step. The similar R_f value between chalcone 2 and the unreacted 10 could only be separated neatly with the condition we reported herewith.

Preparative TLC, gravitational column chromatography, as well as using other combinations of eluents and recrystallization from diethyl ether[18] all failed to separate the two compounds. Increasing the equivalent of NaH and prolonging the reaction time also failed to complete the reaction of aldehyde 10.

Deprotection of benzyl groups in chalcone 2 would give robtein. Several debenzylation methods have been reported including the most common Pd/C-catalyzed hydrogenolysis[17,18,27], $AlCl_3$-catalyzed substitution with *N*, *N*-dimethylaniline (DMA)[28,29] and acidic deprotection with HCl in acetic acid[22]. The first method was excluded for deprotection of chalcone 2, since the hydrogen also reduces the double bond to give a dihydrochalcone. This was avoided because α,β-unsaturated ketone was predicted to play a primary role in chalcone anticancer bioactivity[21].



Scheme 1: Retrosynthetic analysis of (–)-robidanol 1 from benzyl-protected chalcone robtein 2.



Scheme 2: Synthetic pathway for benzyl-protected chalcone robtein 2. Reagents and conditions: (a) BnBr, KI, K_2CO_3, acetone, reflux, 3 h, 85%; (b) BnBr, K_2CO_3, acetone, reflux, 3 h, 98%; (c) (i) $LiAlH_4$, THF, rt, 6 h, (ii) NaOH, H_2O, 98%; (d) PCC, DCM, rt, 6 h, 85%; (e) NaH, DMF, rt, 24 h, 60%.

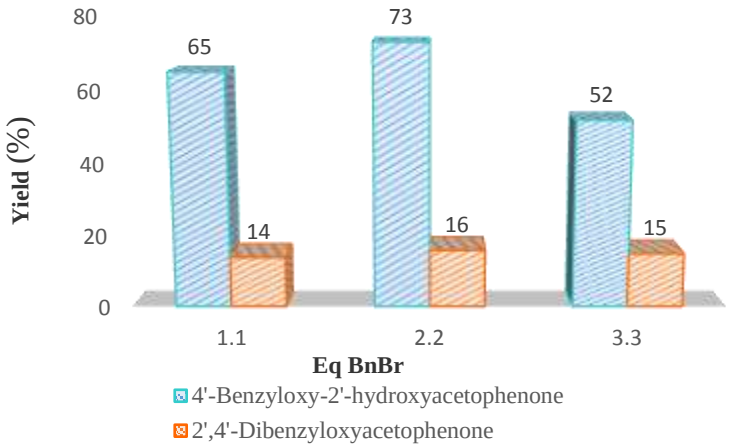


Figure 1: Optimization of benzyl bromide equivalent used in benzylation of resacetophenone 5

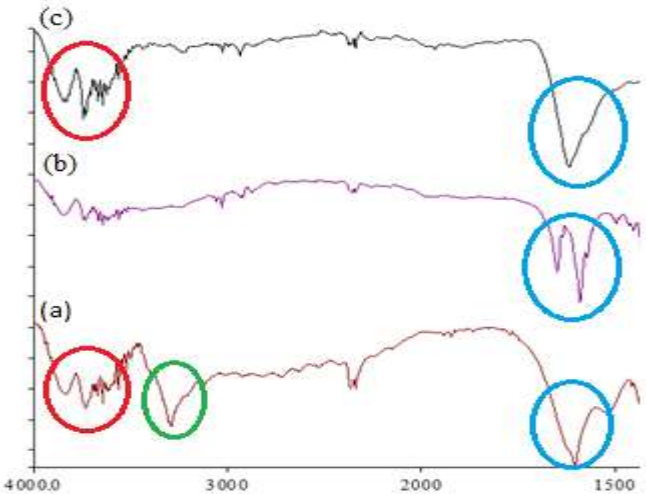


Figure 2: FTIR spectra of (a) resacetophenone 5, (b) 2′,4′-dibenzyloxyacetophenone and (c) 4′-benzyloxy-2′-hydroxyacetophenone 7

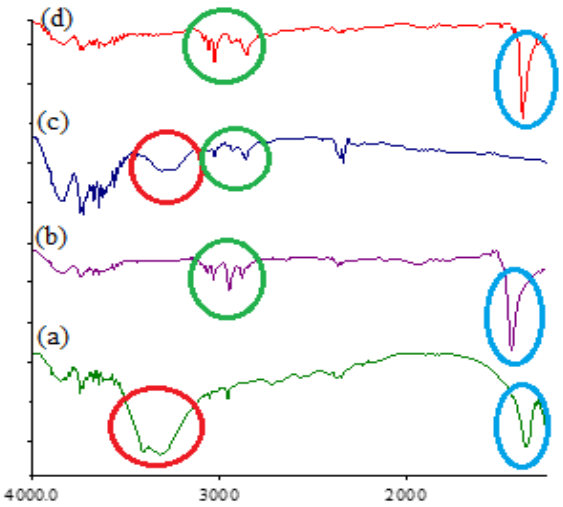


Figure 3: FTIR spectra of (a) methyl gallate 6, (b) methyl tri-*O*-benzyl gallate 8, (c) tri-*O*-benzylgallyl alcohol 9 and (d) tri-*O*-benzylgallaldehyde 10.

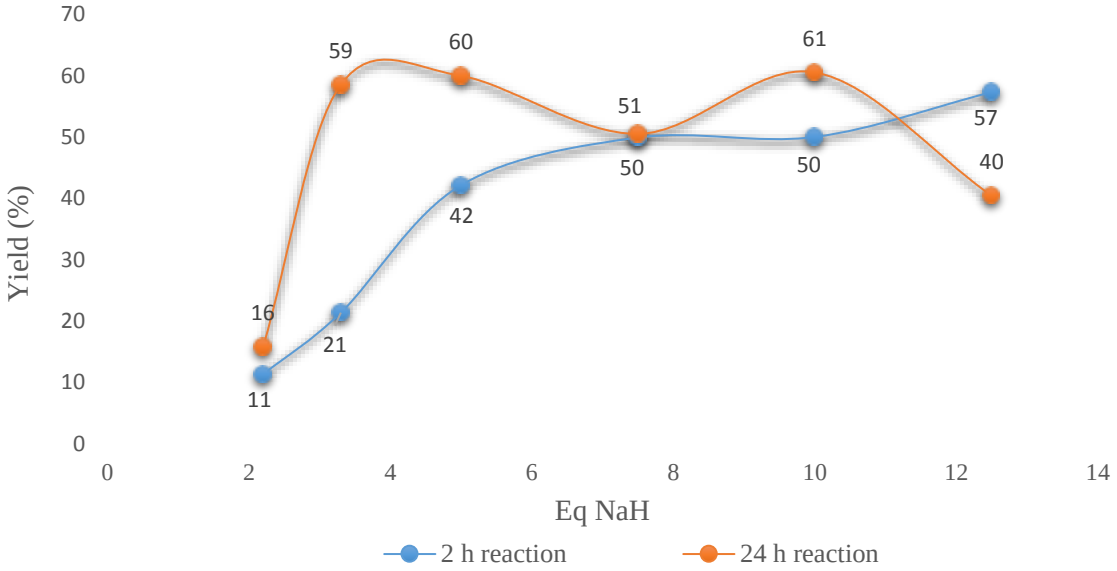


Figure 4: Optimization of reaction time and NaH equivalents in the synthesis of benzyl-protected chalcone 2.

It was found that debenzylation of chalcone 2 in the $AlCl_3$-DMA system resulted in a major by-product (based on TLC monitoring). This product was thought to result from the conjugate addition of DMA to the α,β-unsaturated ketone. On the other hand, debenzylation of chalcone 2 using the HCl-AcOH system caused isomerization into the more stable flavanone isomer (based on the UV-Vis spectra). The crude products also showed a complex TLC pattern which necessitated a difficult purification. Attempts to perform ring-opening reaction of the flavanone to obtain the expected chalcone robtein are underway. It has been reported that basic conditions in ethanol promote this ring-opening reaction[30].

Some efforts have also been carried out to cyclizechalcone 2 into flav-3-ene 3. However, flav-3-ene3 was highly unstable and any delay for an NMR investigation immediately turned 3 into an inseparable complex mixture. The conversion of crude 3 without further purification through hydroboration-oxidation into a flavan-3-ol or dihydroxylation into flavan-3,4-diol is currently being investigated.

Conclusion

3,4,4′,5-Tetrabenzyloxy-2′-hydroxychalcone 2 as an intermediate of (–)-robidanol 1 was synthesized with an overall yield of 54% over four steps from the methyl gallate 6.

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References

1. Freudenberg K. and Weinges K., Systematik und nomenklatur der flavonoide, *Tetrahedron*, **8(3)**, 336-349 **(1960)**

2. Cronjé A., Steynberg J.P., Brandt E.V., Young D.A. and Ferreira D., Oligomeric flavanoids Part 16: Novel prorobinetinidins and the first A-type proanthocyanidin with a 5-deoxy A- and a 3,4-*cis* C-ring from the maiden investigation of commercial wattle bark extract, *J. Chem. Soc. Perkin Trans. 1*, **(20)**, 2467-2477 **(1993)**

3. Batubara I., Darusman L.K., Mitsunaga T., Aoki H., Rahminiwati M., Djauhari E. and Yamauchi K., Flavonoid from *Intsia palembanica* as skin whitening agent, *J. Biol. Sci*., **11(8)**, 475-480 **(2011)**

4. Roux D.G. and Paulus E., Interrelationships of flavonoid components from the heartwood of *Robinia pseudacacia*, *Biochem. J.*, **82(2)**, 324-329 **(1962)**
5. Rizk A.F.M., The chemical constituents and economic plants of the Euphorbiaceae, *Bot. J. Linn. Soc.*, **94(1)**, 293-326 **(1987)**

6. Yu F., Li N. and Yu S.S., A new diterpenoid glucopyranoside from *Erythrophleum fordii*, *J. Asian Nat. Prod. Res.*, **7(1)**, 19-24 **(2005)**

7. Batubara I., Kuspradini H., Muddathir A.M. and Mitsunaga T., *Intsia palembanica* wood extracts and its isolated compounds as *Propionibacterium acnes* lipase inhibitor, *J. Wood Sci*., **60(2)**, 169-174 **(2014)**

8. Batubara I., Mitsunaga T. and Ohashi H., Screening antiacne potency of Indonesian medicinal plants: antibacterial, lipase inhibition, and antioxidant activities, *J. Wood Sci.*, **55(3)**, 230-235 **(2009)**

9. Batubara I., Darusman L.K., Mitsunaga T., Rahminiwati M. and Djauhari E., Potency of Indonesian medicinal plants as tyrosinase inhibitor and antioxidant agent, *J. Biol. Sci.*, **10(2)**, 138-144 **(2010)**

10. Praciak A., The CABI Encyclopedia of Forest Trees, Centre for Agriculture and Biosciences International (CABI), Wallingford **(2013)**

11. Tong P.S., Chen H.K., Hewitt J. and Affre A., Review of trade in merbau from major range states, TRAFFIC Southeast Asia, Selangor **(2009)**

12. Simangunsong E.M., Riniarti M. and Duryat, Seedling improvement growth of mirabow (*Intsia palembanica*) with shading and fertilization, *J. Sylva Lestari*, **4(1)**, 81-88 **(2016)**

13. Sasaki S., Physiological characteristics of tropical rainforest tree species: A basis for the development of silvicultural technology, *Proc. Jpn. Acad.*, Ser. B, **84(2)**, 31-57 **(2008)**

14. Dell'Agli M., Bellosta S., Rizzi L., Galli G.V., Canavesi M., Rota F., Parente R., Bosisio E. and Romeo S., A structure-activity study for the inhibition ofmetalloproteinase-9 activity and gene expression byanalogues of gallocatechin-3-gallate, *Cell Mol. Life Sci.*, **62(23)**, 2896-2903 **(2005)**

15. Menegazzi M., Mariotto S., Dal Bosco M., Darra E., Vaiana N., Shoji K., Safwat A.A., Marechal J.D., Perahia D., Suzuki H. and Romeo S., Direct interaction of natural and synthetic catechins with signal transducer activator of transcription 1 affects both its phosphorylation and activity, *FEBS J*., **281(3)**, 724-738 **(2014)**

16. Ding T.J., Wang X.L. and Cao X.P., A fast assembly of (–)-epigallocatechin-3-gallate [(–)-EGCG] via intra- and inter-molecular mitsunobu reaction, *Chin. J. Chem.*, **24(11)**, 1618-1624 **(2006)**

17. Zaveri N., Chao W.R. and Bensari A., Analogs of green tea polyphenols as chemotherapeutic and chemopreventive agents, US 7, 122, 573 B2 **(2006)**

18. Ahmed I., Study of Enantioselective epoxidation, asymmetric reduction and synthesis of bioactive oligomeric flavonoids, der Universitat Paderborn **(2007)**

19. Zhang M., Jagdmann Jr. G.E., van Zandt M., Beckett P. and Schroeter H., Enantioselective synthesis of orthogonally protected (2*R*,3*R*)-(–)-epicatechin derivatives, key intermediates in the *de novo* chemical synthesis of (–)-epicatechin glucuronides and sulfates, *Tetrahedron: Asymmetry*, **24(7)**, 362-373 **(2013)**

20. Singh P., Anand A. and Kumar V., Recent developments in biological activities of chalcones: A mini review, *Eur. J. Med. Chem*., **85**, 758-777 **(2014)**

21. Mai C.W., Yaeghoobi M., Abd-Rahman N., Kang Y.B. and Pichika M.R., Chalcones with electron-withdrawing and electron-donating substituents: Anticancer activity against TRAIL resistant cancer cells, structure-activity relationship analysis and regulation of apoptotic proteins, *Eur. J. Med. Chem*., **77**, 378-387 **(2014)**

22. Manners G.D. and Jurd L., Additional flavanoids in *Gliricidia sepium*, *Phytochemistry*, **18(6)**, 1037-1042 **(1979)**

23. Watanabe M., Awen B.Z. and Kato M., Efficient synthesis of(l*S*,5*S*)-4-alkyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ones from (1*R*,5*S*)-(+)-nopinone and preparation of some chiral buildingblocks suitable for the asymmetric synthesis, *J. Org. Chem.*, **58(15)**, 3923-3927 **(1993)**

24. Kocienski P.J., Protecting Groups, 3rded., Thieme, New York **(2005)**

25. Ayabe S. and Furuya T., Studies on plant tissue cultures, Part 36: Biosynthesis of a retrochalcone, echinatin and other flavonoids in the cultured cells of *Glycyrrhiza echinate*, A new route toa chalcone with transposed A- and B-rings, *J. Chem. Soc. Perkin Trans. 1*, **0**, 2725-2734 **(1982)**

26. Oi H., Matsuura D., Miyake M., Ueno M., Takai I., Yamamoto T., Kubo M., Moss J. and Noda M., Identification in traditional herbal medications andconfirmation by synthesis of factors that inhibitcholera toxin-induced fluid accumulation, Proc. Acad. Natl. Sci. USA, **99 (5)**, 3042-3046 **(2002)**

27. Sato S., Hiroe K., Kumazawa T. and Jun-Ichi O., Total synthesis of two isoflavone *C*-glycosides: genistein and orobol 8-*C*-b-D-glucopyranosides, *Carbohydr Res.*, **341(9)**, 1091-1095 **(2006)**

28. Akiyama T., Hirofuji H. and Ozaki S., $AlCl_3$-*N*,*N*-dimethylaniline: A new benzyl and allyl ether cleavage reagent, *Tetrahedron Lett.*, **32(10)**, 1321-1324 **(1991)**

29. Akiyama T., Hirofuji H. and Ozaki S., $AlCl_3$-*N*,*N*-dimethylaniline: A novel benzyl and allyl ether cleavage reagent, *Bull. Chem. Soc. Jpn.*, **65(7)**, 1932-1938 **(1992)**

30. Miles C.O. and Main L., Kinetics and mechanism of the cyclisation of 2′,6′-dihydroxy-4,4′-dimethoxychalcone; Influence of the 6′-hydroxy group on the rate of cyclisation under neutral conditions, *J. Chem. Soc. Perkin Trans*., **2(10)**,1639-1642 **(1985)**.