Efficient Syntheses of Yuehchukene and β-(Dehydroprenyl)indole

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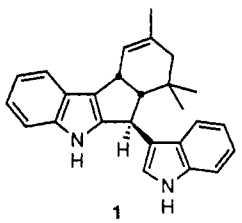
Yuehchukene (1) has been synthesized by one-step transformations of both alcohols (*E*)-β-(3-hydroxy-3-methylbutenyl)indole (3) and β-(1-hydroxy-3-methylbut-3-enyl)indole (4) under various reaction conditions. Alcohol 3 can be prepared efficiently from indole-3-carboxaldehyde (8) via a two-step reaction sequence. Alcohol 4, an isomer of 3, can be obtained from the same starting material 8 in only one step. Alcohol 4 can be converted directly into β-(dehydroprenyl)indole (2) in high yield under mild conditions via a base-induced dehydration. However, alcohol 3 does not give diene 2 under the same reaction conditions. Since diene 2 has been used as the key intermediate for the syntheses of yuehchukene (1), analogues of 1, and a cytotoxic compound, murrapanine (7), our present work also completes formal total syntheses of these bioactive compounds.

The bis-indole natural product, yuehchukene (1), has been isolated from the roots of *Murraya Paniculata* (L.) Jack[1] and from other species[2] in racemic form in trace quantities. Yuehchukene has been characterized as the structurally unusual dimer of β-(dehydroprenyl)indole (2). This compound has been shown to exhibit strong anti-implantation activity in rats[1,3] and mice[4] and moderate activity in guinea pigs[5] and is thought to be a potential fertility-regulating agent. Yuehchukene has been previously synthesized by the Diels–Alder reaction of diene 2, under both acidic[6] and neutral[7] conditions. Other approaches to yuehchukene have also been published.[8] We report here the full details of our efforts toward the efficient synthesis of yuehchukene, employing (*E*)-β-(3-hydroxy-3-methylbutenyl)indole (3)[9] and β-(1-hydroxy-3-methylbut-3-enyl)indole (4) as key intermediates.



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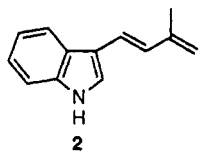

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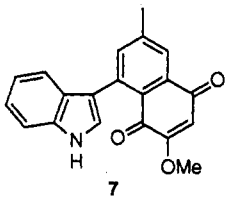
Our approach to the synthesis of 1 is based on the concept that alcohols 3 and 4 are synthetic equivalents of diene 2 and cation 5. Thus, treatment of 3 or 4 with acid was expected to induce the formation of diene 2 and its N-protonated dienophilic tautomer 5 and trigger a Diels–Alder reaction followed by the cyclization of the intermediate 6 to 1 *in situ* (Scheme I). To achieve an efficient synthesis of 1, we needed to design effective synthetic routes to alcohols 3 and 4. Because diene 2 has been used to synthesize 1 and its analogues[6,7,10] and because the other bioactive indole natural product, murrapanine (7),[11] which also contains the functionality of diene 2, has been synthesized via the reaction of 2 and the corresponding quinone, a reinvestigation of the efficient preparation of 2 was also undertaken.



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Results and Discussion

The compound chosen as the starting material for the preparation of both alcohols 3 and 4 was indole-3-carboxaldehyde (8). The Horner–Emmons reaction[12] of 8 with the anion of triethyl phosphonoacetate in refluxing THF gave (*E*)-β-(2-carboethoxyethenyl)indole (9) in 81% yield. Addition of a large excess of methyllithium (5.0 equiv) to the THF solution of 9 under reflux afforded

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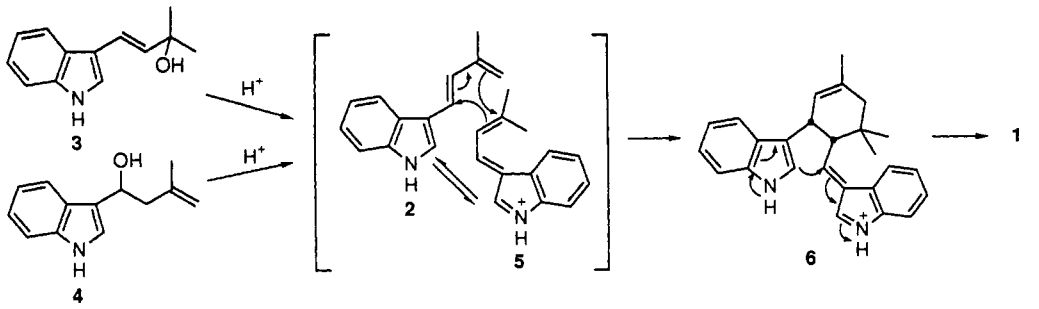
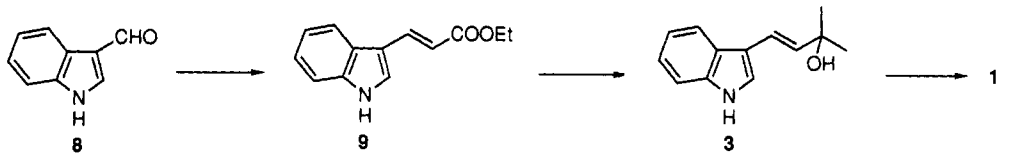
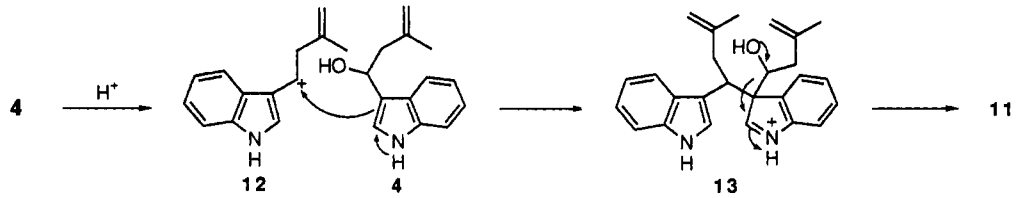
Scheme I



Scheme II

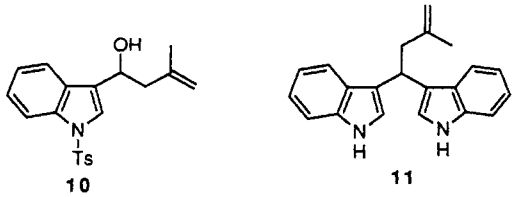


Scheme III



alcohol **3** in quantitative yield. Alcohol **3** is unstable, thus without further purification, it was immediately treated with silica gel and a catalytic amount of TFA in refluxing benzene for 2 h to give yuehchukene (**1**) in 10% yield. The yield of **1** could be raised to 25% if the reaction mixture was stirred at room temperature for 30 min and then at 52 °C for 1 h. Our synthesis of **1** is illustrated in Scheme II. The overall yield of yuehchukene from aldehyde **8** is 20%.

It seemed that β-(1-hydroxy-3-methylbut-3-enyl)indole (**4**), an isomer of **3**, could also be transformed into **1** by using the acid-induced reaction, based on the assumption illustrated by Scheme I. Alcohol **4** was expected to arise from the reaction of **8** and the proper Grignard reagent. Although all of the previous reports indicated that the nitrogen atom of **8** had to be protected for the elaboration of the β-dehydroprenyl group,[6,11] we found that aldehyde **8** could react with an excess of isobutenylmagnesium chloride at room temperature to give alcohol **4** in quantitative yield. The structure of **4** was confirmed by comparison of its ^{1}H NMR spectrum with that of its N-tosylated derivative **10**[6] and by MS (M^+, 201). A benzene solution of alcohol **4** was then treated with TFA under the conditions described above. However, the product of this reaction turned out to be the bis-indole 1,1-di-β-indolyl-3-methylbut-3-ene (**11**, 10%) and no trace of yuehchukene was found. Treatment of alcohol **4** with



acid in benzene at room temperature again gave only indole **11** in 50% yield. Addition of TFA to a dichloromethane solution of **4** also gave **11** (43%) as the sole product. On the basis of previous studies,[13] the mechanism of this transformation could be formulated as shown in Scheme III.

It became apparent that alcohol **4** could not be converted into yuehchukene in acidic solutions of nonprotic solvents such as benzene and dichloromethane. The failure of this reaction might arise from the facile nucleophilic attack of indole **4** on cation **12** to form the intermediate **13**, which would be transformed into **11** as shown in Scheme III. If the nucleophilic attack of **4** on **12** could be prevented, then cation **12** could possibly be transformed into diene **2** and dienophile **5**. These two intermediates would react further to give yuehchukene. Thus we postulated that alcohol **4** might be converted into yuehchukene if the cation **12** were solvated, since the surrounding solvent molecules could deter the nucleophilic attack by molecules of **4**, rendering the conversion of **4** into **2** and **5** more favorable. On the basis of this analysis, we chose ethylene glycol as the medium for the reaction, since cation **12** was expected to be highly solvated by the glycol hydroxyl groups. We found that treatment of **4** with TFA in ethylene glycol at 55–60 °C gave yuehchukene (**1**) in 21% yield.

Since Wenkert and co-workers have achieved the synthesis of **1** by heating diene **2** in a solution of ethylene glycol and water under neutral conditions,[7] we attempted to synthesize **1** by heating alcohol **4** under similar conditions. This approach is based on the assumption that alcohol **4** could be dehydrated at high temperature to form diene **2** and its tautomer which would react further to give **1** (Scheme IV). We found that addition of an ethylene glycol solution of **4** to a mixture of ethylene glycol and water at 135–155 °C, followed by heating for 1 h, afforded yuehchukene in 9–15% yield, depending on the

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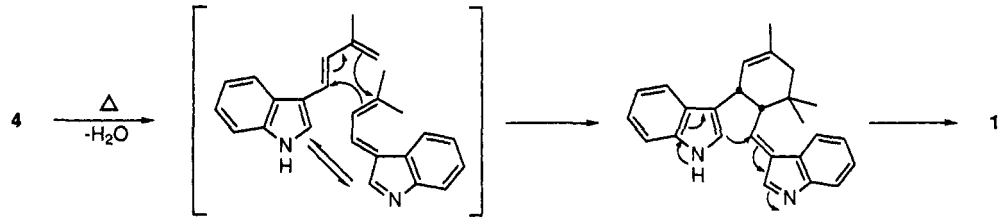
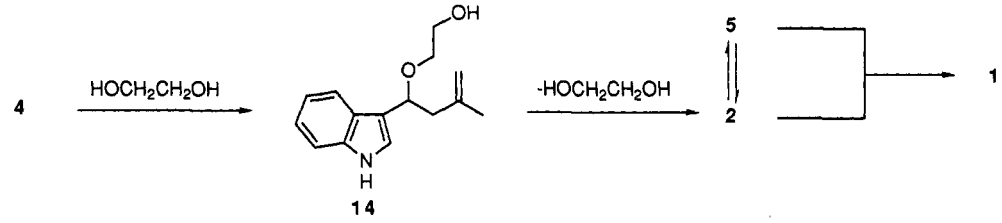
Scheme IV



Scheme V



length of time utilized for the complete addition of the ethylene glycol solution of 4. The longer the time period, the lower the yield of yuehchukene. We also observed that when the reaction temperature was higher, yuehchukene could be obtained in better yield.

Through careful analysis, we found that alcohol 4 was converted not only to 1, but also to indole 14 in the above reaction. We found also that alcohol 4 could be converted into indole 14 at room temperature by the reaction of 4 with ethylene glycol. Thermal reaction of ether 14 in a solution of ethylene glycol and water at 155 °C was found to afford 1 in only poor yield (6–9%). Based on the above, and on the results of monitoring the thermal reaction of alcohol 4 in ethylene glycol by TLC over time, we concluded that 4 reacts via two different pathways. By one route, 4 dehydrates to give 2 and 5 which react further to give 1. By the second route, 4 reacts with ethylene glycol to afford 14 which transforms into 1 as shown in Scheme V, but only in much lower yield. The first pathway is more favorable to the formation of yuehchukene and proceeds most efficiently at higher temperature, since 14 is the main product of this reaction at lower reaction temperature. Thus, in order to prevent the formation of 14, the reaction was carried out by rapid addition of a freshly prepared solution of 4 in ethylene glycol into a hot solution (155 °C) of ethylene glycol and water. The reaction was continued at 150–155 °C for 1 h and provided 1 in 26% yield. The overall yield of 1 is 26% in this two-step reaction sequence starting from 8. This is the shortest synthesis of 1 reported to date.

Although yuehchukene (1) can be synthesized efficiently via the synthetic routes described above, the direct transformation of alcohol 3 or 4 gives 1 in only 20–26% yields under a variety of conditions. Wenkert has pointed out that the Diels–Alder reaction of diene 2 and dienophile 5 could not only give the endo intermediate 6 but also the exo isomer of 6 with an approximate ratio of 1:1.[7] Since the exo intermediate might undergo polymerization immediately upon formation, he postulated that a reaction of this type could only give yuehchukene in 50% yield at best. Our results are consistent with Wenkert's prediction.

Earlier approaches to diene 2 are not very satisfactory in terms of yield and length. We hoped that base-induced dehydrations of 3 and 4 would provide more efficient pathways for the preparation of 2. We found that treatment of alcohol 3 with potassium hydroxide in ethanol failed to give the desired diene 2. However, β-(dehydroprenyl)indole 2 could be obtained in satisfactory yield (81%) by treatment of alcohol 4 with potassium hydroxide in ethanol at 50 °C. This reaction gave diene 2 in only two steps starting from aldehyde 8 and is the most efficient pathway so far reported.[6-8a,10a,11] Since β-(dehydroprenyl)-indole has been previously transformed into murrapanine,[11] our present work completes a synthetic route to this natural product.

In summary, β-(3-hydroxy-3-methylbutenyl)indole (3) can be converted into yuehchukene (1) via an acid-catalyzed dimerization. β-(1-Hydroxy-3-methylbut-3-enyl)indole (4) can also be converted into 1 under acidic or neutral conditions when ethylene glycol is used as solvent. Also, 4 can be transformed into diene 2 via a base-promoted dehydration. The main advantages of our syntheses are (1) the N-protection and the subsequent deprotection used in previous work for the elaboration of the β-dehydroprenyl group of indole are not required, so that compounds 1 and 2 are synthesized more efficiently; (2) alcohols 3 and 4 can be used as precursors of β-(dehydroprenyl)indole (2) in our reactions, being converted directly into yuehchukene and making the transformation of the two isomeric alcohols into diene 2 unnecessary.

Experimental Section

General. Unless otherwise indicated, all starting compounds were obtained from commercial suppliers and used without further purification, CH_2Cl_2 was distilled under N_2 from CaH_2, and THF was distilled under N_2 from sodium/benzophenone prior to use. All reactions were carried out under a N_2 atmosphere unless otherwise described. Preparative column chromatography used Merck Kieselgel 60 (70–230 mesh) silica gel. Reactions and chromatography fractions were analyzed using Merck silica gel 60 F-254 TLC plates. ^1H NMR spectra were measured at 90 or 300 MHz unless otherwise indicated. ^{13}C NMR spectra were obtained at 75 MHz. Melting points were uncorrected and were determined using a Fischer-Johns melting point apparatus. Low-resolution mass spectra were recorded at the Department of Chemistry, National Sun Yat-Sen University. High-resolution mass spectra (HRMS) were measured at the Department of Chemistry, National Tsing-Hua University.

(*E*)-β-(2-carboethoxyethenyl)indole (9). A solution of 10.1 g (45 mmol) of triethyl phosphonoacetate in 50 mL of dry THF was added dropwise, over a 30-min period, to a stirred mixture of 1.20 g (50 mmol) of sodium hydride in 20 mL of dry THF at 0 °C. The stirring was continued at room temperature for 2 h. Thereafter, a solution of 2.90 g (20 mmol) of indole-3-carboxaldehyde (8) in 50 mL of dry THF was added dropwise over a

20-min period and the mixture was heating under reflux for 8 h. The mixture was poured into 30 mL of water and extracted with ether. The extract was washed with brine, dried, and evaporated. Chromatography of the residue on silica gel and elution with a 6:1 hexane–ethyl acetate mixture afforded 3.48 g (81%) of ester 8 as a white powdery solid: mp 121 °C; IR (KBr) NH 3288 (m), C=O 1674 (s), C=C 1618 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7.2 Hz, CH_3), 4.27 (2 H, q, J = 7.2 Hz, OCH_2), 6.47 (1 H, d, J = 16 Hz, olefinic H), 7.21–7.92 (5 H, m, aryl Hs), 7.98 (1 H, d, J = 16 Hz, olefinic H), 8.91 (1 H, brs, NH); ^{13}C NMR ($CDCl_3$) δ 14.39, 60.18, 111.84, 113.15, 113.41, 120.38, 121.42, 123.23, 125.25, 129.03, 137.14, 138.42, 168.54; MS, m/e (rel inten) 215 (M^+, 100), 170 (23). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.36; H, 6.11; N, 6.47.

(*E*)-β-(3-Hydroxy-3-methylbutenyl)indole (3). A 1.6 M ethereal methyllithium solution (6.3 mL, 10 mmol) was added to a stirring solution of 0.43 g (2 mmol) of ester 9 in 50 mL of dry THF, and the mixture was heated under reflux for 5 h under nitrogen. The solution was then poured into 40 mL of water and extracted with ether. The extract was washed with brine, dried (anhydrous $MgSO_4$), and evaporated to give 0.41 g (100%) of alcohol 3 as an orange oil: ^1H NMR ($CDCl_3$) δ 1.43 (6 H, s, 2 CH_3), 2.68 (1 H, brs, OH), 6.33 (1 H, d, J = 16 Hz, olefinic H), 6.73 (1 H, d, J = 16 Hz, olefinic H), 7.03–7.85 (5 H, m, aryl Hs), 8.80 (1 H, brs, NH); MS m/e (rel inten), 201 (M^+, 41), 186 (80), 183 (51), 168 (86), 167 (100), 142 (29), 116 (24), 115 (98).

Yuehchukene (1) from Acid-Catalyzed Reaction of Indole 3. To a stirred mixture of the freshly prepared alcohol 3 (0.41 g, 2 mmol) and 4 g of silica gel in 50 mL of benzene was added a catalytic amount of TFA. The mixture was stirred at room temperature under N_2 for 30 min and then heated at 52–55 °C for 1 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue which resulted was chromatographed on silica gel. Elution with a 10:1 petroleum ether–ether mixture afforded 92 mg (25%) of yuehchukene (1) as a pale yellow, amorphous powder: mp, ^1H NMR, and MS were identical with those reported previously:[1] ^{13}C NMR ($CDCl_3$) δ 24.05, 28.90, 29.09, 33.50, 37.61, 38.32, 41.02, 60.80, 111.21, 111.68, 118.25, 118.50, 119.34, 119.50, 119.50, 120.52, 120.52, 122.06, 122.27, 122.95, 124.23, 126.78, 130.20, 136.48, 140.22, 145.15.

β-(1-Hydroxy-3-methylbut-3-enyl)indole (4). A dry 500-mL two-necked flask was fitted with a reflux condenser, a pressure-equalized dropping funnel, and a magnetic stirrer. In the flask was placed 3.89 g (160 mmol) of magnesium turnings, 100 mL of dry THF, and a crystal of iodine. In the dropping funnel was placed a solution of freshly distilled 3-chloro-2-methylprop-1-ene (14.49 g, 160 mmol) in 60 mL of dry THF. One-quarter of the 3-chloro-2-methylprop-1-ene solution was added into the flask under N_2. The stirred mixture was heated to about 40 °C by a water bath to start the reaction. As soon as the THF began to boil, the water bath was removed and the addition of the remaining 3-chloro-2-methylprop-1-ene solution was continued at a rate such that the solution could boil gently without the external heat source. The mixture was stirred for another 2 h after the addition was completed. A solution of 5.80 g (40 mmol) of aldehyde 8 in 180 mL of dry THF was then added to the mixture at room temperature. The mixture was stirred at room temperature for 30 min and then poured into crushed ice. It was then extracted with ether. The extract was washed with brine, dried (anhydrous $MgSO_4$), and evaporated to afford 8.02 g (100%) of alcohol 9 as a light green oil: ^1H NMR ($CDCl_3$) δ 1.75 (3 H, s, CH_3), 2.45 (1 H, brs, OH), 2.57 (1 H, d, J = 5 Hz, 2-H), 2.60 (1 H, d, J = 9 Hz, 2-H), 4.83 (1 H, s, olefinic H), 4.86 (1 H, s, olefinic H), 5.09 (1 H, dd, J = 5, 9 Hz, 1-H), 6.76 (1 H, d, J = 1.8 Hz, α-H), 7.06–7.70 (4 H, m, aryl Hs), 8.23 (1 H, brs, NH); ^{13}C NMR ($CDCl_3$) δ 22.24, 46.12, 65.60, 111.30, 113.33, 118.29, 119.18, 119.30, 121.43, 121.81, 125.53, 136.31, 142.63; MS m/e (rel inten) 201 (M^+, 8), 183 (13), 146 (100); exact mass 201.1156, calcd for $C_{13}H_{15}ON$ 201.1155. Anal. Calcd for $C_{13}H_{15}ON$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.31; H, 7.69; N, 6.99.

1,1-Di-β-indolyl-3-methylbut-3-ene (11). A stirred mixture of the freshly prepared alcohol 4 (120 mg) in 15 mL of benzene was added with a catalytic amount of TFA. The mixture was stirred at 25 °C under N_2 for 1.5 h. The mixture was washed with aqueous $NaHCO_3$ solution (10%) and water and then extracted with ether. The extract was dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. The residue which resulted was chromatographed on silica gel with a 1:4 ethyl acetate–hexane mixture to give 11 (45 mg, 50%) as pale oil: ^1H NMR ($CDCl_3$) δ 1.76 (3 H, s, CH_3), 2.96 (2 H, d, J = 7.5 Hz, CH_2), 4.69 (2 H, s, olefinic Hs), 4.76 (1 H, t, J = 7.5 Hz, CH), 6.94 (2 H, d, J = 2.1 Hz, α-H), 7.01–7.31 (6 H, m, aryl Hs), 7.60 (2 H, d, J = 7.8 Hz), 7.83 (2 H, brs, NH); ^{13}C NMR ($CDCl_3$) δ 22.4, 32.2, 44.0, 111.1, 111.8, 119.0, 119.5, 119.8, 121.7, 121.7, 127.0, 136.5, 144.5; MS m/e (rel inten) 300 (M^+, 5), 245 (100); HRMS calcd for $C_{21}H_{20}N_2$ 300.1628, found 300.1623.

β-[1-(2-Hydroxyethoxy)-3-methylbut-3-enyl]indole (14). A solution of alcohol 3 (335 mg) in 20 mL of ethylene glycol was stirred at room temperature for 24 h. The mixture was poured into 10 mL of water and extracted with dichloromethane. The extract was washed with brine, dried (anhdrous $MgSO_4$), and evaporated. Chromatography of the residue on silica gel and stepwise elution with the mixture of ethyl acetate–hexane (1/8 → 1/3 → 1/2) afforded ether 14 (278 mg, 68%) as a pale oil: ^1H NMR ($CDCl_3$) δ 1.76 (3 H, s, CH_3), 2.57 (1 H, dd, J = 14.4, 5.4 Hz, 2-H), 2.82 (1 H, dd, J = 14.4, 8.4 Hz, 2-H), 3.40–3.65 (4 H, m, 2 CH_2O), 4.76–4.83 (3 H, m, 1-H and olefinic Hs), 7.06–7.22 (3 H, m, aryl Hs), 7.32 (1 H, d, J = 7.8 Hz, aryl H), 7.76 (1 H, d, J = 7.8 Hz, aryl H), 8.33 (1 H, brs, NH); ^{13}C NMR ($CDCl_3$) δ 22.74, 44.67, 61.93, 69.15, 74.73, 111.34, 112.37, 116.47, 119.52, 119.60, 122.12, 122.40, 125.92, 136.54, 142.98; MS m/e (rel inten) 245 (M^+, 2), 190 (100), 183 (43), 182 (65), 117 (21). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.20; H, 7.87; N, 5.94.

β-(Dehydroprenyl)indole (2). A stirring solution of alcohol 4 (1.01 g, 5 mmol) and KOH (7.0 g, 12.5 mmol) in 100 mL of an ethanol/water (4:1) mixture was heated at 50 °C for 30 min. It was then poured into 100 mL of water and extracted with ether. The extract was washed with brine, dried (anhydrous K_2CO_3), and evaporated to afford the crude product (846 mg) as yellow solid. Rapid chromatography[7] of the freshly obtained product gave diene 2 (746 mg, 81%) as pale, powdery solid: mp, IR and ^1H NMR (200 MHz) were identical with those reported previously.

Acid-Catalyzed Conversion of Alcohol 4 to Yuehchukene (1) Using Ethylene Glcyol as Solvent. The freshly prepared alcohol 4 (100 mg, 0.5 mmol) was added into the stirring mixture of 40 mL of ethylene glycol and a catalytic amount of TFA under N_2 at 55 °C. The mixture was stirred at 55–60 °C for another 1 h. The mixture was then stirred at 25 °C for 10 min. The mixture was added with 20 mL of H_2O and neutralized with a 10% aqueous NaOH solution. It was then extracted with dichloromethane. The extract was dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. By using the same purification procedure as that used in the conversion of alcohol 3 to 1, the residue which resulted was chromatographed to yield yuehchukene (1) (19 mg, 21%) as a pale yellow amorphous powder.

Thermal Conversion of Alcohol 4 to Yuehchukene (1) Under Neutral Conditions. A freshly prepared solution of alcohol 4 (221 mg, 1.1 mmol) in 25 mL of ethylene glycol was added into a stirred mixture of ethylene glycol (100 mL) and water (5 mL) at 155 °C under an air atmosphere. The mixture was then heated at 150–155 °C for 1 h. After cooling, the mixture was poured into water (100 mL), and a 10% aqueous NaOH solution was added slowly up to pH 7. The mixture was then extracted with dichloromethane. The extract was dried (anhydrous $MgSO_4$) and evaporated. By using the same purification procedure as described above, the residue which resulted was chromatographed to yield yuehchukene (1) (52 mg, 26%) as a pale yellow amorphous powder.

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