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Efficient synthesis of polycycles bearing prenylated, geranylated, and farnesylated citrans: application to 3′-prenylrubranine and petiolin D regioisomer

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ABSTRACT

Efficient synthetic routes for biologically interesting polycycles with prenylated, geranylated, and farnesylated citrans were developed from several trihydroxybenzenes with prenyl, geranyl, and farnesyl groups on the benzene rings. Ethylenediamine diacetate-catalyzed cyclization by a domino aldol-type/electrocyclization/H-shift/hetero Diels–Alder reaction of prenylated, geranylated, and farnesylated trihydroxybenzenes with citral or *trans*,*trans*-farnesal provided a variety of tetracycles bearing prenylated, geranylated, and farnesylated citrans. The mechanistic pathway for regio- and stereochemistry of synthesized polycycles was described. As an application of this methodology, 3′-prenylrubranine and petiolin D regioisomer were first synthesized.

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1. Introduction

Polycycles bearing citrans are common in nature[1] and have a range of biological and pharmacological activities.[2] A pair of tetracyclic monoterpenoid polycycles, desbenzylidenerubramin (**1**) and its regioisomer **2**, have been isolated from *Euodia latifolia* (Fig. 1).[3] This plant has shown desirable medicinal properties and its decoction has been used to treat fever and cramps.[3] Other polycycles with citran and chalcone moieties have been found in nature. Rubranine (**3**) has been isolated from *Aniba rosaeodora*.[4] Essential oils from the extracts of this plant were shown to have antifungal and antimicrobial activities.[5] A pair of monoterpene-chalcone conjugated polycycles, rubraine (or rubranine) (**3**)[6] and isorubraine (**4**),[6] and a pair of sesquiterpene-chalcone conjugated sumadains A (**5**)[7] and B[7] (**6**), with both citran and chalcone moieties were isolated from *Alpinia katsumadai* (Fig. 1). This plant is

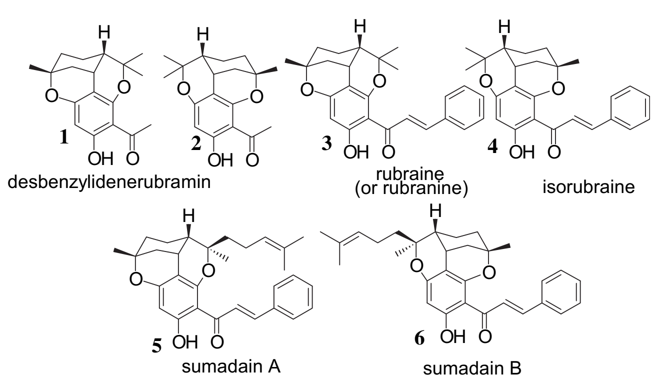

Fig. 1. Naturally occurring polycycles **1**–**6** with citrans.

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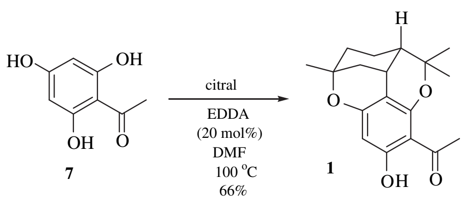
traditionally used as an antiemetic agent in traditional Chinese medicine to treat stomach disorders and has been coded in the Chinese pharmacopeia.[8]

Their wide range of biological activities had promoted research into the development of convenient and efficient syntheses of polycycles with citrans. Recently, we reported a new methodology for synthesizing a variety of benzopyrans by ethylenediamine diacetate-catalyzed reactions of 1,3-dicarbonyls and resorcinols with α,β-unsaturated aldehydes.[9] We also reported a new and useful methodology for preparing a number of polycycles bearing citrans by ethylenediamine diacetate-catalyzed reactions of 2,4,6-trihydroxybenzenes with α,β-unsaturated aldehydes.[10] For example, treatment of 2,4,6-trihydroxyacetophenone (**7**) with citral in the presence of 20 mol % ethylenediamine diacetate at 100 °C for 10 h in DMF afforded tetracyclic monoterpenoid desbenzylidenerubramin (**1**) in 66% yield (Scheme 1).[10]

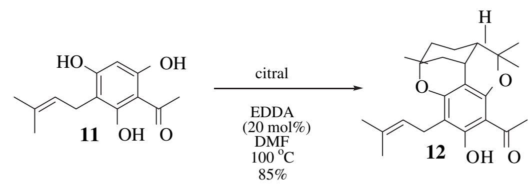


Scheme 1. Reaction of 2,4,6-trihydroxyacetophenone (**7**) and citral for the synthesis of desbenzylidenerubramin (**1**).

Biologically interesting 3′-prenylrubranine (**8**) and petiolin D (**9**) with prenyl or geranyl groups on citran rings were isolated from *Mallotus philippinensis*[11] and *Hypericum pseudopetiolatum* var. *kiusianum*,[12] respectively (Fig. 2). The extract of *Mallotus philippinensis* exhibited bacterial activity.[11b] Members the genus *Hypericum* are traditional medicines for the treatment of burns, bruises, swelling, inflammation, and bacterial and viral infections.[13] Importantly, it was reported that the presence of the prenyl, geranyl or farnesyl group in the natural products leads to a remarkable increase of biological activities.[14] In view of their importance of prenyl, geranyl, and farnesyl groups, further novel work for the synthesis of polycycles with prenylated, geranylated, and farnesylated citrans was attempted. We report herein an efficient and facile synthesis of a variety of biologically interesting polycycles with prenylated, geranylated, and farnesylated citrans. The synthetic methodologies are also employed in the first concise synthesis of 3′-prenylrubranine (**8**) and petiolin D regioisomer (**10**).

2. Results and discussion

The reaction of 3-prenyl-2,4,6-trihydroxyacetophenone (**11**) with citral in the presence of 20 mol % ethylenediamine diacetate was first examined (Scheme 2). The starting material **11** was prepared with 65% yield by reacting 2,4,6-trihydroxyacetophenone with prenyl bromide in methanolic KOH at room temperature for 24 h. Treatment of **11** with 1.2 equiv citral at 100 °C for 10 h in DMF afforded tetracyclic adduct **12** in 85% yield, which was easily assigned by observing the chemical shifts of a benzylic methine proton at δ 2.69 ppm as a broad singlet, and a methyl peak of acetyl group at δ 2.59 ppm, and a vinyl peak of prenyl groups at δ 5.20–5.25 ppm as multiplets. The exact structure and stereochemistry of **12** were also confirmed by X-ray single crystal analysis (Fig. 3).



Scheme 2. Reaction of 3-prenyl-2,4,6-trihydroxyacetophenone (**11**) and citral for the synthesis of tetracycle **12**.

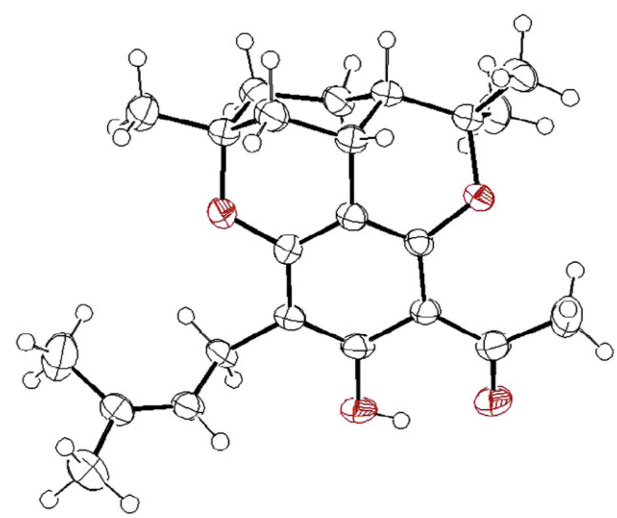


Fig. 3. X-ray structure of compound **12**.

Further reactions of several substituted trihydroxybenzenes **13**–**17** containing prenyl, geranyl, and farnesyl groups with citral or *trans*,*trans*-farnesal were examined in the presence of 20 mol % of EDDA in DMF (Table 1). Reactions of 3-geranyl-2,4,6-trihydroxyacetophenone (**13**) with citral or *trans*,*trans*-farnesal gave adducts **18** and **19** in 83 and 75% yields, respectively. Similarly, treatment of 3-farnesyl-2,4,6-trihydroxyacetophenone (**14**) with citral or *trans*,*trans*-farnesal afforded adducts **20** and **21** in 86 and 76% yields, respectively. The reactions of 3-prenyl-2,4,6-trihydroxybenzopheneone (**15**), 3-geranyl-2,4,6-trihydroxybenzophenone (**16**), and 3-farnesyl-2,4,6-trihydroxybenzophenone (**17**) were also successful. With 3-prenyl-2,4,6-trihydroxybenzopheneone (**15**), the desired adduct **22** was produced in 88% yield. Similarly, reaction of 3-geranyl-

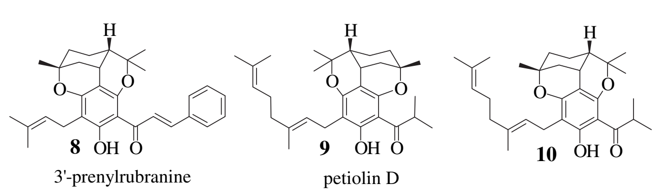
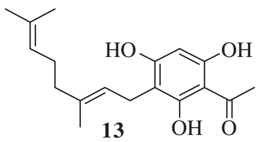
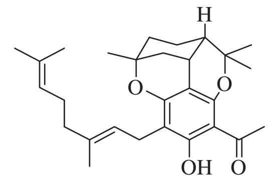
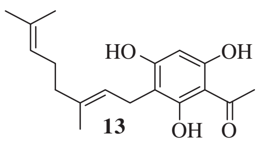
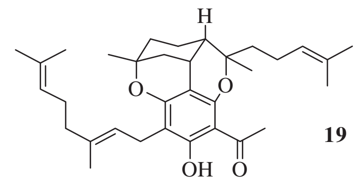
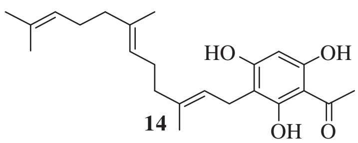
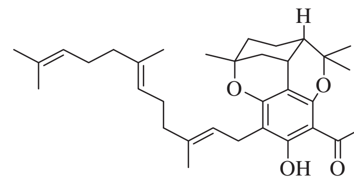
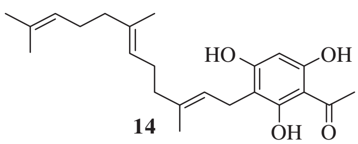
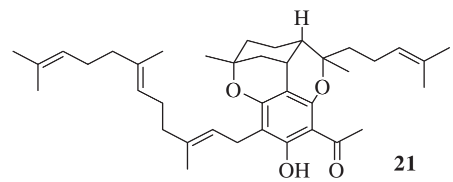
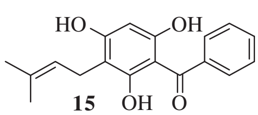
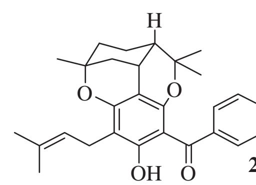
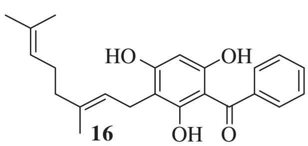
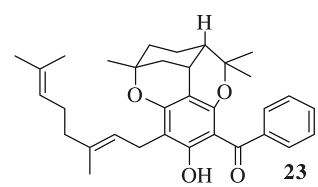
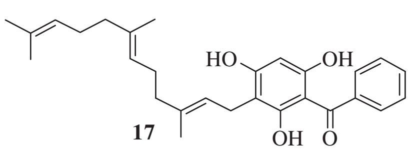
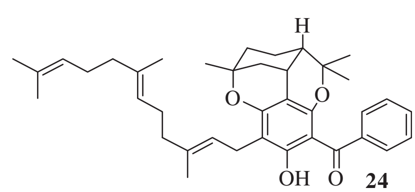


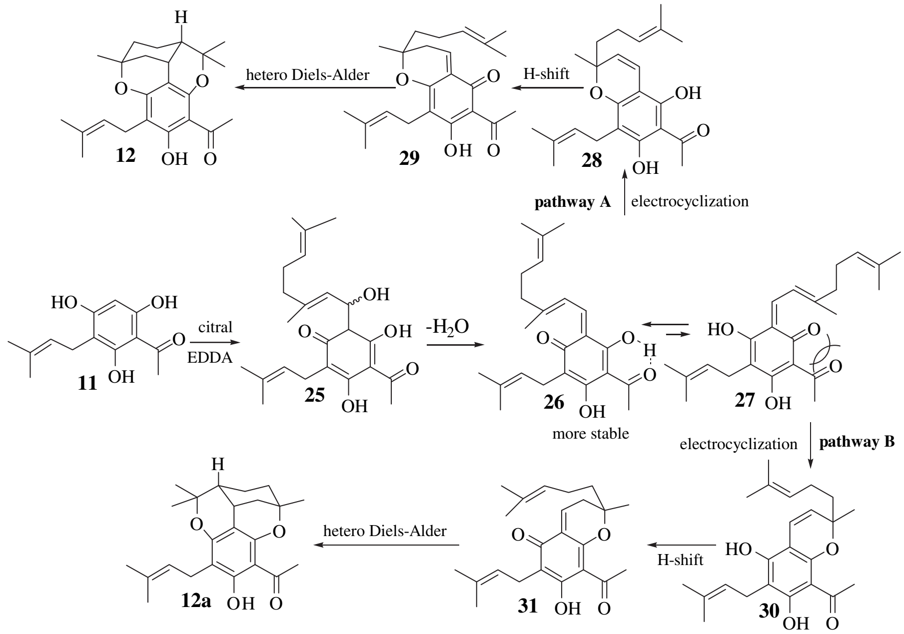
Fig. 2. Naturally occurring 3′-prenylrubranine (**8**), petiolin D (**9**), and unnatural petiolin D regioisomer (**10**).

Table 1
Reactions of several substituted trihydroxybenzenes with citral or *trans*,*trans*-farnesal

Starting material	α,β-Unsaturated aldehyde	Time (h)	Product	Yield (%)
 13	Citral	10	 18	83
 13	*trans*,*trans*-Farnesal	12	 19	75
 14	Citral	12	 20	86
 14	*trans*,*trans*-Farnesal	12	 21	76
 15	Citral	12	 22	88
 16	Citral	12	 23	86
 17	Citral	10	 24	85

2,4,6-trihydroxybenzophenone (**16**) with citral in the presence of 20 mol % of EDDA at 100 °C for 12 h in DMF provided adduct **23** in 86% yield, whereas that of 3-farnesyl-2,4,6-trihydroxybenzophenone (**17**) afforded tetracyclic compound **24** in 85% yield. These reactions provide a rapid route for the synthesis of polycycles with prenyl, geranyl, and farnesyl groups on the benzopyran ring.

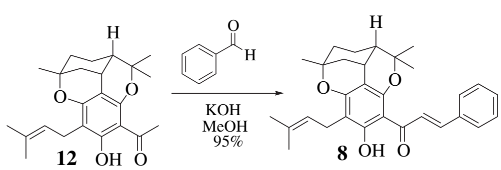
The mechanism for regio- and stereochemistry of synthesized **12** can be explained as shown in Scheme 3. Citral is first protonated by EDDA to give protonated aldehyde, which is then attacked by 3-prenyl-2,4,6-trihydroxypropiophenone (**11**) in the presence of EDDA to yield intermediate **25**. The method of producing aldol-type products by the $Ca(OH)_2$-mediated reaction of resorcinol to enals was already suggested by Shigemasa.[15] Dehydration of **25** in the presence of EDDA gives two possible *o*-quinone methides **26** and **27**. Intermediate **26**, with intramolecular hydrogen bonding, is probably more stable than **27**, with dipole–dipole repulsions. It is at this stage that the observed regioselectivity of **12** can be determined. Electrocyclization of the more stable intermediate **26**



Scheme 3. The mechanism for the formation of compound **12**.

gives benzopyran **28** that undergoes H-shift to produce another quinine methide **29** by pathway A instead of by pathway B.[16] The stereochemistry of **12** can be explained by the pseudoequatorial conformation of the methyl group of *o*-quinone methide **29** in the chair-like transition state.[17] During the hetero Diels–Alder reaction of **29**, the *exo*-transition state must be more energetically favorable than the *endo*-transition state. This is in good agreement with Marino, who reported the synthesis of hexahydrocannabinol through the intramolecular hetero Diels–Alder cycloaddition of *o*-quinone methide.[18]

This methodology was applied in one-step synthesis of natural 3′-prenylrubraine (**8**) from synthesized adduct **12** by aldol condensation (Scheme 4). The reaction of **12** with benzaldehyde in the presence of KOH in ethanol at 50 °C for 48 h gave 3′-prenylrubraine (**8**) in 95% yield. The exact structure and stereochemistry of **8** was confirmed by X-ray analysis (Fig. 4).



Scheme 4. Synthesis of 3′-prenylrubranine (**8**).

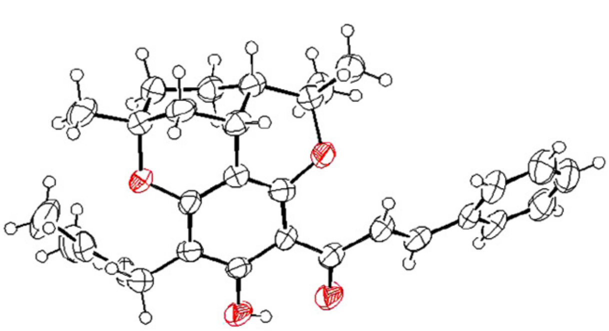


Fig. 4. X-ray structure of synthesized 3′-prenylrubranine (**8**).

This methodology was also applied in the first synthesis of unnatural petiolin D regioisomer (**10**) (Scheme 5). Reaction of **32** with geranyl bromide in the presence of *N*,*N*-diisopropylethylamine in DMF at room temperature for 48 h gave **33** in 55% yield. Treatment of **33** with citral in the presence of 20 mol % ethylenediamine diacetate in DMF at 100 °C for 12 h afforded adduct **10** in 81% yield. The structure and stereochemistry of **10** were confirmed by comparison of its spectral data with those previously reported for petiolin D.[12]

A new synthetic route for biologically interesting polycycles bearing prenylated, geranylated, and farnesylated citrans was developed starting from substituted trihydroxybenzenes with prenyl, geranyl, and farnesyl groups on the benzene ring. The strategy relied on domino aldol-type reaction/electrocyclization/H-migration/hetero Diels–Alder reaction. This methodology was applied to the synthesis of biologically interesting 3′-prenylrubranine (**8**) and petiolin D regioisomer (**10**).

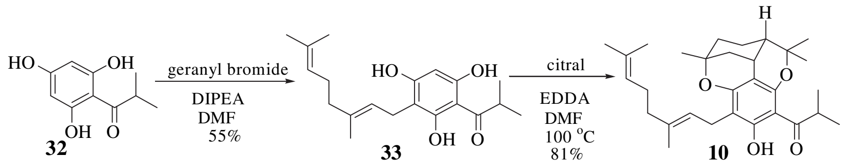
3. Experimental section

3.1. General

All experiments were carried out in a nitrogen atmosphere. Merck, pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^1H and ^{13}C NMR spectra were recorded on a Varian-VNS (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS and MS spectra were carried out at the Korea Basic Science Institute. The HRMS were carried out at the Korea Basic Science Institute on a Jeol JMS 700 spectrometer.

3.2. Typical procedure for compounds 12 and 18–24

To a solution of substituted trihydroxybenzenes (1.0 mmol) and citral or *trans*,*trans*-farnesal (1.2 mmol) in DMF (10 mL) was added ethylenediamine diacetate (36 mg, 0.2 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 10–12 h and then cooled to room temperature. After completion of reaction as indicated by TLC, the reaction mixture was quenched with water



Scheme 5. Synthesis of petiolin D regioisomer (**10**).

(30 mL) and extracted with ethyl acetate (50 mL×3). The combined organic layer was dried over $MgSO_4$ and concentrated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 20:1) to afford products.

*3.2.1. Compound **12**.* Reaction of **11** (236 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **12** (315 mg, 85%) as a solid: mp 180–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.57 (1H, s), 5.25–5.20 (1H, m), 3.23 (2H, d, *J*=7.2 Hz), 2.69 (1H, br s), 2.59 (3H, s), 2.19–2.05 (2H, m), 1.82 (2H, d, *J*=13.5 Hz), 1.75 (3H, s), 1.65 (3H, s), 1.54 (3H, s), 1.48–1.41 (1H, m), 1.38 (3H, s), 1.33–1.21 (1H, m), 1.07 (3H, s), 0.86–0.69 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 161.3, 160.3, 157.2, 130.8, 122.9, 108.9, 107.2, 107.1, 86.1, 75.7, 46.4, 37.6, 34.8, 32.1, 29.9, 28.8, 27.7, 25.8, 24.3, 21.9, 21.2, 17.8; IR (KBr) 3457, 2973, 2917, 1604, 1463, 1423, 1370, 1292, 1223, 1173, 1081, 854, 731 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{23}H_{30}O_4$: 370.2144. Found: 370.2146.

*3.2.2. Compound **18**.* Reaction of **13** (304 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **18** (364 mg, 83%) as a solid: mp 158–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.59 (1H, s), 5.26–5.21 (1H, m), 5.08–5.03 (1H, m), 3.24 (2H, d, *J*=6.9 Hz), 2.70 (1H, br s), 2.60 (3H, s), 2.18–2.12 (1H, m), 2.02–1.94 (4H, m), 1.82 (2H, d, *J*=13.5 Hz), 1.75 (3H, s), 1.66–1.60 (1H, m), 1.62 (3H, s), 1.55 (6H, s), 1.49–1.44 (1H, m), 1.38 (3H, s), 1.34–1.17 (1H, m), 1.08 (3H, s), 0.86–0.71 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 161.3, 160.4, 157.2, 134.3, 131.0, 124.5, 122.7, 109.0, 107.2, 107.1, 86.1, 75.6, 46.4, 39.8, 37.6, 34.8, 32.1, 29.9, 28.8, 27.7, 26.7, 25.7, 24.3, 21.9, 21.1, 17.6, 16.1; IR (KBr) 3544, 2924, 1608, 1435, 1375, 1291, 1175, 1106, 856 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{28}H_{38}O_4$: 438.2770. Found: 438.2768.

*3.2.3. Compound **19**.* Reaction of **13** (304 mg, 1.0 mmol) with *trans*,*trans*-farnesal (264 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **19** (380 mg, 75%) as a solid: mp 96–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.55 (1H, s), 5.25–5.21 (1H, m), 5.20–5.14 (1H, m), 5.08–5.04 (1H, m), 3.25 (2H, d, *J*=7.2 Hz), 2.73 (1H, br s), 2.59 (3H, s), 2.28–2.20 (1H, m), 2.16–2.08 (3H, m), 2.04–1.92 (6H, m), 1.80 (2H, br d, *J*=13.2 Hz), 1.75 (3H, s), 1.70 (3H, s), 1.63 (6H, s), 1.56 (3H, s), 1.49–1.42 (1H, m), 1.38 (3H, s), 1.29–1.19 (1H, m), 1.03 (3H, s), 0.86–0.72 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 161.3, 160.3, 156.8, 134.3, 132.1, 131.0, 124.5, 123.8, 122.7, 109.0, 107.5, 107.4, 88.3, 75.7, 45.7, 42.1, 39.8, 37.7, 34.7, 32.2, 28.8, 27.6, 26.7, 25.7, 22.7, 21.9, 21.1, 21.0, 17.7, 17.6, 16.1; IR (KBr) 3481, 2926, 2368, 1613, 1465, 1430, 1376, 1296, 1227, 1176, 1108, 1022, 981, 862, 832, 802, 733 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{33}H_{46}O_4$: 506.3396. Found: 506.3395.

*3.2.4. Compound **20**.* Reaction of **14** (372 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **20** (436 mg, 86%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.57 (1H, s), 5.26–5.21 (1H, m), 5.10–5.02 (2H, m), 3.25 (2H, d, *J*=7.5 Hz), 2.70 (1H, br s), 2.60 (3H, s), 2.20–2.12 (1H, m), 2.06–1.88 (9H, m), 1.82 (2H, d, *J*=13.2 Hz), 1.75 (3H, s), 1.65 (3H, s), 1.55 (9H, s), 1.48–1.40 (1H, m), 1.38 (3H, s), 1.32–1.20 (1H, m), 1.07 (3H, s), 0.86–0.69 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 161.3, 160.4, 157.1, 134.7, 134.2, 131.1, 124.4, 124.3, 122.7, 109.0, 107.1, 107.0, 86.0, 75.6, 46.4, 39.8, 39.7, 37.6, 34.8, 32.1, 29.9, 28.8, 27.7, 26.7, 26.6, 25.7, 24.2, 21.9, 21.1, 17.6, 16.1, 15.9; IR (neat) 3436, 2923, 2358, 1610, 1427, 1370, 1293, 1218, 1177, 1116, 1085, 1017, 984, 855, 737 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{33}H_{46}O_4$: 506.3396. Found: 506.3398.

*3.2.5. Compound **21**.* Reaction of **14** (372 mg, 1.0 mmol) with *trans*,*trans*-farnesal (264 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **21** (436 mg, 76%) as a solid: mp 62–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.55 (1H, s), 5.26–5.21 (1H, m), 5.16–5.14 (1H, m), 5.08–5.04 (1H, m), 3.25 (2H, d, *J*=6.9 Hz), 2.72 (1H, br s), 2.59 (3H, s), 2.29–2.20 (1H, m), 2.16–2.08 (3H, m), 2.04–1.89 (11H, m), 1.80 (2H, br d, *J*=13.2 Hz), 1.75 (3H, s), 1.70 (3H, s), 1.63 (6H, s), 1.56 (6H, s), 1.49–1.42 (1H, m), 1.38 (3H, s), 1.27–1.19 (1H, m), 1.03 (3H, s), 0.86–0.71 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 161.3, 160.3, 156.8, 134.7, 134.3, 132.1, 131.1, 124.4, 124.3, 123.8, 122.7, 109.0, 107.5, 107.4, 88.3, 75.7, 45.7, 42.1, 39.8, 39.7, 37.7, 34.7, 32.2, 28.8, 27.6, 26.7, 26.6, 25.7, 22.7, 21.9, 21.1, 21.0, 17.7, 17.6, 16.1, 16.0; IR (KBr) 2923, 2357, 1611, 1428, 1373, 1294, 1228, 1176, 1110, 1019, 982, 842, 737 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{38}H_{54}O_4$: 574.4022. Found: 574.4025.

*3.2.6. Compound **22**.* Reaction of **15** (298 mg, 1.0 mmol), with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **22** (380 mg, 88%) as a solid: mp 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.87 (1H, s), 7.49–7.47 (2H, m), 7.43–7.33 (3H, m), 5.31–5.26 (1H, m), 3.31 (2H, d, *J*=6.9 Hz), 2.65 (1H, br s), 2.21–2.14 (1H, m), 1.88–1.84 (2H, m), 1.78 (3H, s), 1.68 (3H, s), 1.60–1.52 (1H, m), 1.44–1.32 (1H, m), 1.38 (3H, s), 1.18–1.10 (1H, m), 1.02 (3H, s), 0.72–0.59 (1H, m), 0.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 161.4, 161.1, 157.1, 142.5, 131.0, 130.0, 127.7, 127.2, 122.9, 109.6, 107.5, 107.1, 85.1, 75.9, 46.1, 37.8, 34.8, 29.0, 28.8, 27.8, 25.9, 23.4, 21.9, 21.4, 17.8; IR (KBr) 3449, 2976, 2926, 1600, 1567, 1451, 1422, 1367, 1307, 1219, 1113, 1083, 1048, 909, 830, 741 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{28}H_{32}O_4$: 432.2301. Found: 432.2303.

*3.2.7. Compound **23**.* Reaction of **16** (366 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **23** (430 mg, 86%) as a solid: mp 103–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.87 (1H, s), 7.51–7.48 (2H, m), 7.44–7.31 (3H, m), 5.31–5.26 (1H, m), 5.10–5.06 (1H, m), 3.31 (2H, d, *J*=6.9 Hz), 2.65 (1H, br s), 2.21–2.14 (1H, m), 2.07–1.95 (4H, m), 1.88–1.85 (2H, m), 1.78 (3H, s), 1.71–1.66 (1H, m), 1.64 (3H, s), 1.57 (3H, s), 1.44–1.32 (1H, m), 1.38 (3H, s), 1.17–1.10 (1H, m), 1.02 (3H, s), 0.71–0.59 (1H, m), 0.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 161.4, 161.2, 157.1, 142.5, 134.4, 131.1, 130.0, 127.7, 127.2, 124.5, 122.8, 109.6, 107.5, 107.1, 85.1, 75.9, 46.1, 39.8, 37.8, 34.9, 29.0, 28.8, 27.8, 26.8, 25.7, 23.3, 21.8, 21.3, 17.7, 16.1; IR (KBr) 3446, 2975, 2928, 2368, 1606, 1553, 1452, 1421, 1366, 1301, 1142, 1118, 1082, 1051, 910, 853, 818 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{33}H_{40}O_4$: 500.2927. Found: 500.2925.

*3.2.8. Compound **24**.* Reaction of **17** (434 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **24** (484 mg, 85%) as a solid: mp 72–73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.89 (1H, s), 7.50–7.48 (2H, m), 7.41–7.31 (3H, m), 5.31–5.27 (1H, m), 5.11–5.04 (2H, m), 3.31 (2H, d, *J*=7.2 Hz), 2.65 (1H, br s), 2.20–2.13 (1H, m), 2.08–1.93 (9H, m), 1.89–1.84 (2H, m), 1.81 (3H, s), 1.66 (3H, s), 1.57 (6H, s), 1.44–1.32 (1H, m), 1.38 (3H, s), 1.17–1.09

(1H, m), 1.02 (3H, s), 0.71–0.61 (1H, m), 0.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 161.3, 161.2, 157.0, 142.4, 134.7, 134.4, 131.2, 130.0, 127.7, 127.2, 124.4, 124.3, 122.7, 109.6, 107.5, 107.0, 85.1, 75.9, 46.1, 39.9, 39.7, 37.7, 34.8, 29.0, 28.8, 27.7, 26.7, 26.6, 25.7, 23.3, 21.8, 21.3, 17.7, 16.1, 16.0; IR (KBr) 3471, 2919, 2369, 1715, 1590, 1450, 1430, 1420, 1367, 1268, 1222, 1165, 1142, 1080, 1050, 950, 823, 735 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{38}H_{48}O_4$: 568.3553. Found: 568.3554.

3.3. 3-Prenylrubranine (8)

To a solution of **12** (370 mg, 1.0 mmol) in ethanol (10 mL) were added potassium hydroxide (280 mg, 5.0 mmol) and benzaldehyde (212 mg, 1.0 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 48 h. Addition of water (30 mL) and extraction with ethyl acetate (3×50 mL), washing with 2 N HCl solution and brine, dried over $MgSO_4$, and removal of the solvent followed by flash column chromatography on silica gel gave **8** (462 mg, 95%) as a solid: mp 79–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.20 (1H, s), 8.27 (1H, d, *J*=15.6 Hz), 7.74 (1H, d, *J*=15.6 Hz), 7.61 (2H, d, *J*=7.8 Hz), 7.42–7.33 (3H, m), 5.30–5.25 (1H, m), 3.29 (2H, d, *J*=6.9 Hz), 2.76 (1H, br s), 2.21–2.05 (2H, m), 1.85 (2H, d, *J*=13.2 Hz), 1.78 (3H, s), 1.67 (3H, s), 1.63 (3H, s), 1.54–1.45 (1H, m), 1.40 (3H, s), 1.29–1.21 (1H, m), 1.03 (3H, s), 0.86–0.76 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 162.7, 162.3, 160.7, 156.8, 141.4, 135.8, 130.9, 129.8, 128.9, 128.2, 127.7, 122.8, 109.6, 107.9, 107.8, 86.4, 75.8, 46.4, 37.7, 34.7, 30.2, 28.8, 27.9, 25.9, 24.2, 21.9, 21.3, 17.8; IR (KBr) 3461, 2924, 2672, 1987, 1612, 1447, 1350, 1168, 998, 882, 727 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{30}H_{34}O_4$: 458.2457. Found: 458.2461.

3.4. Compound 33

A mixture of isobutyryl phloroglucinol (1.17 g, 6.0 mmol), geranyl bromide (1.303 g, 6.0 mmol), and *N*,*N*-diisopropylethylamine (2.33 g, 3.1 mL, 18.0 mmol) in DMF (25 mL) was stirred at room temperature for 48 h. Addition of 2 N HCl solution (30 mL), extraction with EtOAc (3×50 mL), and removal of the solvent followed by flash column chromatography on silica gel using hexane/EtOAc (3:1) gave **33** (1.10 g, 55%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.32 (1H, s), 5.95 (1H, s), 5.30–5.20 (1H, m), 5.10–4.95 (1H, m), 3.30 (2H, d, *J*=6.6 Hz), 2.07–1.95 (4H, m), 1.76 (3H, s), 1.63 (3H, s), 1.55 (6H, s), 1.13 (6H, d, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 163.0, 161.3, 160.1, 138.1, 131.8, 123.9, 122.0, 106.0, 104.0, 95.3, 39.7, 30.0, 26.4, 25.6, 21.5, 19.3, 17.6, 16.1; IR (neat) 3360, 2968, 2925, 1620, 1432, 1382, 1236, 1171, 1132, 1097, 1066, 884, 821 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{28}O_4$: 332.1988. Found: 332.1985.

3.5. Compound 10

A mixture of **33** (332 mg, 1.0 mmol), citral (183 mg, 1.2 mmol), and ethylenediamine diacetate (36 mg, 0.2 mmol) in DMF (10 ml) was stirred at 100 °C for 12 h afforded **10** (378 mg, 81%) as a solid: mp 73–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.71 (1H, s), 5.27–5.22 (1H, m), 5.08–5.04 (1H, m), 4.00–3.91 (1H, m), 3.25 (2H, d, *J*=7.2 Hz), 2.73 (1H, br s), 2.19–2.12 (1H, m), 2.07–1.93 (5H, m), 1.83 (2H, dd, *J*=13.2, 1.5 Hz), 1.75 (3H, s), 1.62 (3H, s), 1.56 (3H, s), 1.54 (3H, s), 1.49–1.40 (1H, m), 1.38 (3H, m), 1.30–1.21 (1H, m), 1.15 (3H, d, *J*=6.3 Hz), 1.13 (3H, d, *J*=6.3 Hz), 1.04 (3H, s), 0.90–0.75 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7, 162.1, 160.0, 156.8, 134.2, 131.0, 124.6, 122.9, 109.4, 107.0, 106.3, 85.8, 75.5, 46.6, 39.8, 38.1, 37.7, 35.0, 30.0, 28.9, 27.9, 26.8, 25.6, 24.3, 22.0, 21.2, 20.3, 18.6, 17.7, 16.1; IR (KBr) 2974, 2928, 1612, 1455, 1418, 1381, 1367, 1252, 1179, 1143, 1112, 1080, 1051, 1010, 987, 897, 818, 731 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{30}H_{42}O_4$: 466.3083. Found: 466.3079.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.09.075.

References and notes

1. (a) Bukuru, J.; Nguyen, T. V.; Puyvelde, L. V.; He, W.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 5905; (b) Begley, M. J.; Crombie, L.; King, R. W.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2393; (c) Mechoulam, R.; Gaoni, Y. *Fortschr. Chem. Org. Naturst.* **1967**, *25*, 175; (d) Claussen, U.; von Spulak, F.; Korte, F. *Tetrahedron* **1968**, *24*, 1021; (e) Crombie, L.; Ponsford, R.; Shani, A.; Yagnitinsky, B.; Mechoulan, R. *Tetrahedron Lett.* **1968**, 5771.
2. (a) Turner, C. E.; Elsohly, M. A.; Boeren, E. G. *J. Nat. Prod.* **1980**, *43*, 169; (b) Cui, C.-B.; Yan, S.-Y.; Cai, B.; Yao, X.-S. *J. Asian Nat. Prod. Res.* **2002**, *4*, 233.
3. Goh, S. H.; Chung, V. C.; Sha, C. K.; Mak, T. C. W. *Phytochemistry* **1990**, *29*, 1704.
4. De Alleluia, I. B.; Brez Fo, R.; Gottlieb, O. R.; Magalhaes, E. G.; Marques, R. *Phytochemistry* **1978**, *17*, 517.
5. (a) Delespaul, Q.; De Billerbeck, V. G.; Roques, C. G.; Michel, G.; Marquir-Vinuales, C.; Bessiere, J.-M. *J. Essent. Oil Res.* **2000**, *12*, 256; (b) Hammer, K. A.; Carson, C. F.; Riley, T. V. *J. Appl. Microbiol.* **1999**, *86*, 985.
6. Hua, S.-Z.; Luo, J.-G.; Wang, X.-B.; Wang, J.-S.; Kong, L.-Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2728.
7. Hua, S.-Z.; Wang, X.-B.; Luo, J.-G.; Wang, J.-S.; Kong, L.-Y. *Tetrahedron Lett.* **2008**, *49*, 5658.
8. Jiangsu New Medicinal College. *The Encyclopedia of Chinese Materia Medica*; Shanghai Science & Technical: Shanghai, 1978; p 1582.
9. (a) Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett.* **2005**, *46*, 7539; (b) Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853; (c) Lee, Y. R.; Kim, D. H. *Synthesis* **2006**, 603; (d) Lee, Y. R.; Kim, J. H. *Synlett* **2007**, 2232; (e) Wang, X.; Lee, Y. R. *Tetrahedron Lett.* **2007**, *48*, 6275; (f) Wang, X.; Lee, Y. R. *Synthesis* **2007**, 3044; (g) Lee, Y. R.; Xia, L. *Synthesis* **2007**, 3240; (h) Lee, Y. R.; Kim, Y. M. *Helv. Chim. Acta* **2007**, *90*, 2401; (i) Lee, Y. R.; Li, X.; Kim, J. H. *J. Org. Chem.* **2008**, *73*, 4313; (j) Xia, L.; Lee, Y. R. *Synlett* **2008**, 1643; (k) Lee, Y. R.; Hung, T. V. *Tetrahedron* **2008**, *64*, 7338; (l) Lee, Y. R.; Xia, L. *Tetrahedron Lett.* **2008**, *49*, 3283; (m) Lee, Y. R.; Kim, Y. M.; Kim, S. H. *Tetrahedron* **2009**, *65*, 101; (n) Jung, D. H.; Lee, Y. R.; Kim, S. H. *Helv. Chim. Acta* **2010**, *93*, 635.
10. Wang, X.; Lee, Y. R. *Tetrahedron* **2009**, *65*, 10125.
11. (a) Ahluwalia, V. K.; Sharma, N. D.; Mittai, B.; Gupta, S. R. *Indian J. Chem.* **1988**, *27B*, 238; (b) Zaidi, S. F. H.; Yoshida, I.; Butt, F.; Yusuf, M. A.; Usmanghani, K.; Kadowaki, M.; Sugiyama, T. *Biol. Pharm. Bull.* **2009**, *32*, 631.
12. Tanaka, N.; Kubota, T.; Ishiyama, H.; Kashiwada, Y.; Takaishi, Y.; Ito, J.; Mikami, Y.; Shiro, M.; Kobayashi, J. *Heterocycles* **2009**, *79*, 917.
13. (a) Dostalek, M.; Pistovcakova, J.; Jurica, J.; Tomandl, J.; Linhart, I.; Sulcova, A.; Hadasova, E. *Life Sci.* **2005**, *78*, 239; (b) Medina, M. A.; Martinez-Poveda, B.; Amores-Sanchez, M. I.; Quesada, A. R. *Life Sci.* **2006**, *79*, 105; (c) Beerhues, L. *Phytochemistry* **2006**, *67*, 2201.
14. (a) Nguyen, P. H.; Dao, T. T.; Kim, J.; Phong, D. T.; Ndinteh, D. T.; Mbafor, J. T.; Oh, W. K. *Bioorg. Med. Chem.* **2011**, *19*, 3378; (b) Halabalaki, M.; Alexi, X.; Aligiannis, N.; Alexis, M. N.; Skaltsounis, A.-L. *J. Nat. Prod.* **2008**, *71*, 1934; (c) Nikaido, T.; Ohmoto, T.; Kinoshita, T.; Sankawa, U.; Delle Monache, F.; Botta, B.; Tomimori, T.; Miyaichi, Y.; Shirataki, Y.; Yokoe, I.; Komatsu, M. *Chem. Pharm. Bull.* **1989**, *37*, 1392.
15. Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768.
16. Crombie, L.; Redshaw, S. D.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1979**, 630.
17. Talley, J. J. *J. Org. Chem.* **1985**, *50*, 1695.
18. Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671.