Tetrahedron 65 (2009) 10125–10133

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

EDDA-catalyzed rapid synthetic routes for biologically interesting polycycles bearing citrans and chalcones: the first total synthesis of sumadain A

Xue Wang, Yong Rok Lee *

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Republic of Korea

ARTICLE INFO

Article history:
Received 7 July 2009
Received in revised form 12 October 2009
Accepted 13 October 2009
Available online 15 October 2009

Keywords:
Polycycles
Citran
Chalcone
Rubraine
Sumadain A

ABSTRACT

An efficient and concise synthetic route for biologically interesting polycycles bearing citran and chalcone nuclei was developed starting from a variety of trihydroxybenzenes with substituents on the ring. The key strategies involved an ethylenediamine diacetate-catalyzed cyclization by a domino aldol-type/electrocyclization/H-shift/hetero Diels–Alder reaction of trihydroxybenzenes and citral or *trans*,*trans*-farnesal. This methodology was applied successfully to the synthesis of three natural products, desbenzylidenerubramin, rubraine, sumadain A, and their unnatural derivatives.

1. Introduction

Polycycles bearing citran or cyclol nuclei are widely distributed in nature[1] and have a range of biological and pharmacological properties.[2] Among these, cannabinoids **1**–**4** containing a citran or cyclol moiety have been isolated from *Cannabis sativa*, also known as marijuana or hashish (Fig. 1).[3] This plant contains a group of more than 60 structurally related terpenophenolic compounds and has been used as a psychotomimetic drug since ancient times.[2a] It has also been shown to possess analgesic, antiemetic, psychotropic, and anti-inflammatory properties, and is currently used in traditional medicines for the treatment of asthma and glaucoma.[2a] The increased consumption of this plant has caused worldwide social, legal, and medical problems. However, the biological importance of this plant was realized only after the discovery of the endogenous cannabinoid system. With the

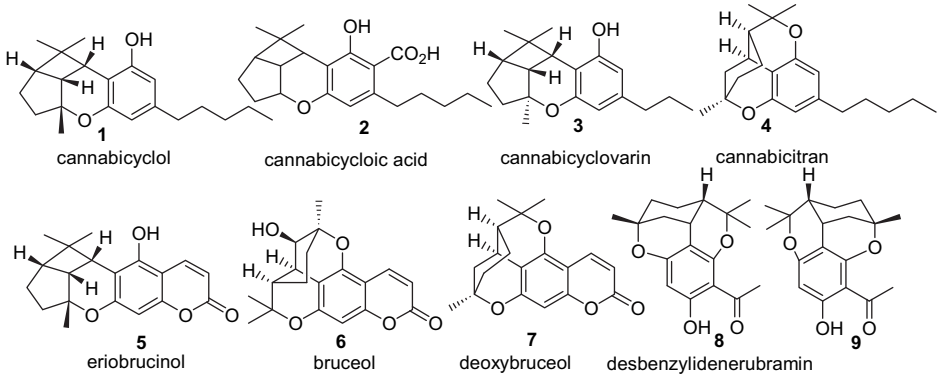


Figure 1. Biologically active and naturally occurring polycycles **1**–**9** with a citran and a cyclol nucleus.

* Corresponding author. Tel.: +82 53 810 2529; fax: +82 53 810 4631.
E-mail address: yrlee@yu.ac.kr (Y.R. Lee).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.10.045

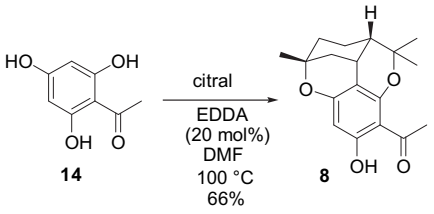
discovery of the two cannabinoid receptors, CB1 and CB2, a new era of research into the pharmacology of these compounds was ushered in.[4] As other polycycles bearing these citran or cyclol moieties, eriobrucinol (**5**), bruceol (**6**), and deoxybruceol (**7**) were isolated from *Eriostemon brucei* and their structures were determined by spectral and X-ray analysis.[5] Desbenzylidenerubramin (**8**) and its isomer **9** of the tetracyclic monoterpenoid were also isolated from *Euodia latifolia*.[6] This plant has shown to possess desirable medicinal properties and its decoction has been used as a remedy for fever and cramps.[6]

Novel polycycles with unique monoterpene–chalcone conjugates have been found in nature. Rubranine (**10**) was already isolated from *Aniba rosaeodora* (Fig. 2).[7] Importantly, the essential oils obtained from the extracts of this plant were shown to have antifungal and antimicrobial activities.[8] Very recently, as part of an ongoing research program to isolate bioactive compounds from Chinese medicinal plants, monoterpene–chalcone conjugated rubraine (or rubranine) (**10**),[9] isorubraine (**11**),[9] and sesquiterpene–chalcone conjugated sumadains A (**12**)[10] and B (**13**)[10] with citran and chalcone moieties were isolated from *Alpinia katsumadai* (Fig. 2). This plant is traditionally used as an antiemetic agent in traditional Chinese medicine to treat stomach disorders and has been coded in the Chinese pharmacopeia.[11]

reported for a variety of biologically interesting polycycles bearing these citran and chalcone moieties. As an application of these methodologies, this paper reports the concise one or two-step synthesis of desbenzylidenerubramin (**8**), rubraine (or rubranine) (**10**), sumadain A (**12**), and their unnatural derivatives.

2. Results and discussion

A reaction of 2,4,6-trihydroxyacetophenone (**14**) with citral in the presence of 20 mol% ethylenediamine diacetate was first examined (Scheme 1). Treatment of **14** with 1.2 equiv of citral at 100 °C for 10 h in DMF afforded tetracyclic monoterpenoid desbenzylidenerubramin (**8**) in 66% yield, without any formation of its regioisomer **9**. The assignment of **8** was easily defined by observing the chemical shifts of the characteristic protons and by comparison with reported data and known X-ray structure in the literature.[6] The ^{1}H NMR spectrum of **8** showed an aromatic peak at δ=6.04 ppm as a singlet and a methine proton of the benzylic position at δ=2.73 ppm as a broad singlet.



Scheme 1.

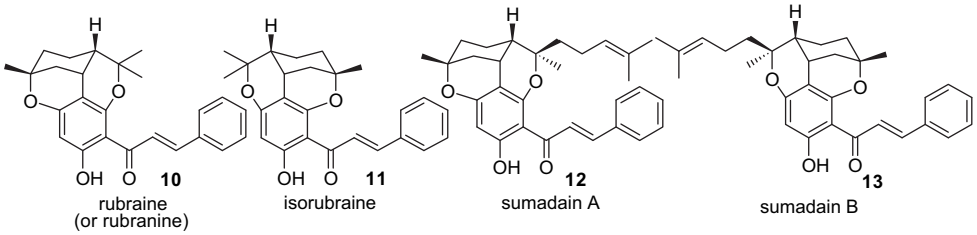


Figure 2. Naturally occurring polycycles **10**–**13** with a citran, cyclol, and chalcone nucleus.

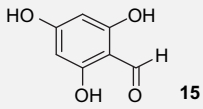
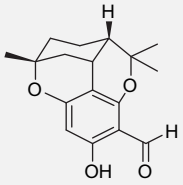
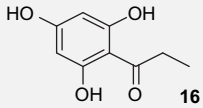
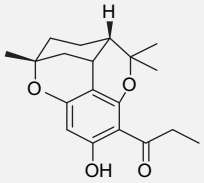
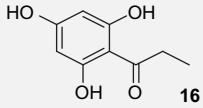
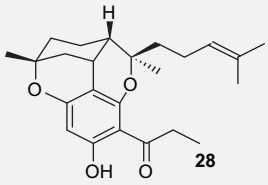
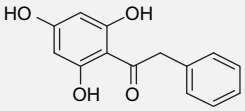
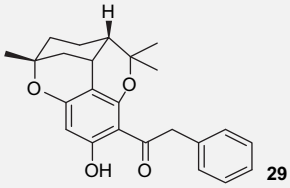
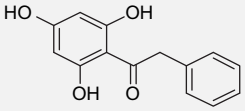
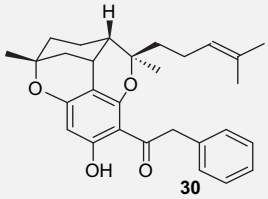
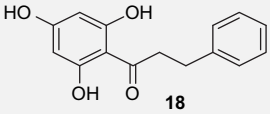
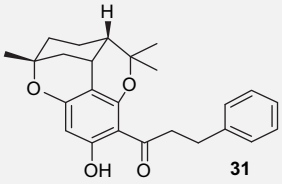
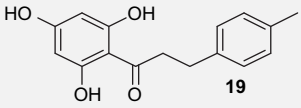
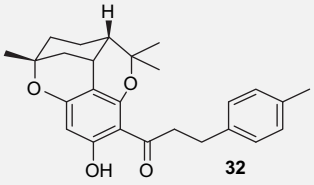
The range of biological activities and properties has stimulated interest in the synthesis of naturally occurring desbenzylidenerubramin (**8**), rubraine (**10**), sumadain A (**12**), and their unnatural derivatives. The structures of desbenzylidenerubramin (**8**), rubraine (**10**), isorubraine (**11**), and sumadains A (**12**) and B (**13**) were established by NMR spectroscopy and X-ray crystallography.[6,9,10] However, no synthetic approaches to isorubraine (**11**) and sumadains A (**12**) and B (**13**) have been reported.

Although a few syntheses of these types of polycycles have been reported, the known protocol was determined from a reaction of phloroglucinol with citral in pyridine as a catalyst and solvent.[12] Nevertheless, there are the limitations of low yields and capricious product isolation.[12] The necessity for overcoming these problems has prompted research for the development of a new synthetic methodologies for polycycles bearing the citran and chalcone moieties.

Brønsted acid–base combined salt catalyzed reactions are one of the most promising catalysts in organic synthesis.[13] Recently, this lab reported a new methodology for synthesizing a variety of benzopyrans by ethylenediamine diacetate-catalyzed reactions of 1,3-dicarboyls and resorcinols with α,β-unsaturated aldehydes.[14] In the original work, a methodology for the preparation of polycycles using ethylenediamine diacetate (EDDA) as a catalyst was developed.[15] Further work and new methodologies for the synthesis of a variety of polycycles with citran and chalcone moieties were attempted. In this paper, efficient and facile synthetic routes are

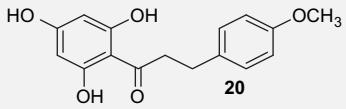
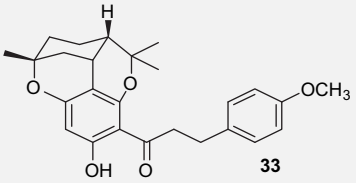
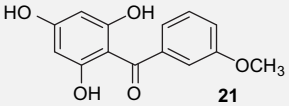
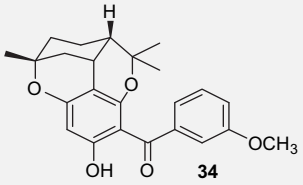
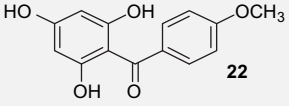
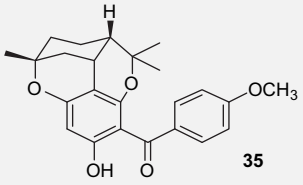
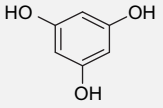
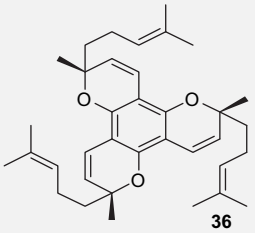
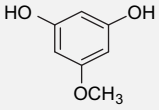
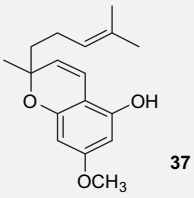
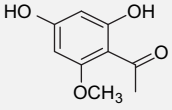
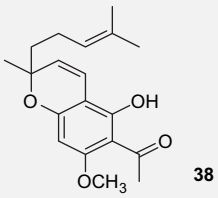
Further reactions of several types of substituted trihydroxybenzenes **15**–**23** and others **24**–**25** with citral or *trans*,*trans*-farnesal were examined (Table 1). Reaction of 2,4,6-trihydroxybenzaldehyde (**15**) with citral in the presence of 20 mol% of ethylenediamine diacetate at 100 °C for 12 h in DMF provided adduct **26** in 45% yield (entry 1). Reactions of 2,4,6-trihydroxypropiophenone (**16**) and 2-phenyl-2′,4′,6′-trihydroxyacetophenone (**17**) with citral afforded adducts **27** and **29** in 65 and 62% yields (entries 2 and 4), whereas those with *trans*,*trans*-farnesal gave desired compounds **28** and **30** in 53 and 52% yields, respectively (entries 3 and 5). With 2′,4′,6′-trihydroxydihydrochalcone (**18**) isolated from *Boesenbergia pandurata*,[16] the cycloaddition reaction was successful. Reaction of **18** with citral for 10 h gave cycloadduct **31** in 55% yield (entry 6). Similarly, treatment of trihydroxydihydrochalcones **19**–**20** with citral for 12 h afforded adducts **32**–**33** in 50 and 57% yield, respectively (entries 7–8). Moreover, reactions of 2,4,6-trihydroxybenzophenones **21**–**22** were also successful. Treatment of **21** with citral provided desired adduct **34** in 45% yield (entry 9), whereas that of **22** gave **35** in 40% yield (entry 10). These reactions provide a rapid route for the synthesis of polycycles with a variety of substituents on the benzopyran ring. To examine further reactions, the commercially available phloroglucinol and pyrogallol were condensed with citral. Interestingly, reaction of phloroglucinol with citral afforded the triple condensation product **36** (22%) as a single C_3-symmetric compound. The structure of **36** was confirmed by comparison with spectral data of the authentic sample, which was produced by phenylboronic acid/

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

Entry	Starting material	Unsaturated aldehyde	Time (h)	Product	Yield (%)
1	 **15**	Citral	12	 **26**	45
2	 **16**	Citral	12	 **27**	65
3	 **16**	*trans*,*trans*-Farnesal	12	 **28**	53
4	 **17**	Citral	10	 **29**	62
5	 **17**	*trans*,*trans*-Farnesal	10	 **30**	52
6	 **18**	Citral	10	 **31**	55
7	 **19**	Citral	12	 **32**	50

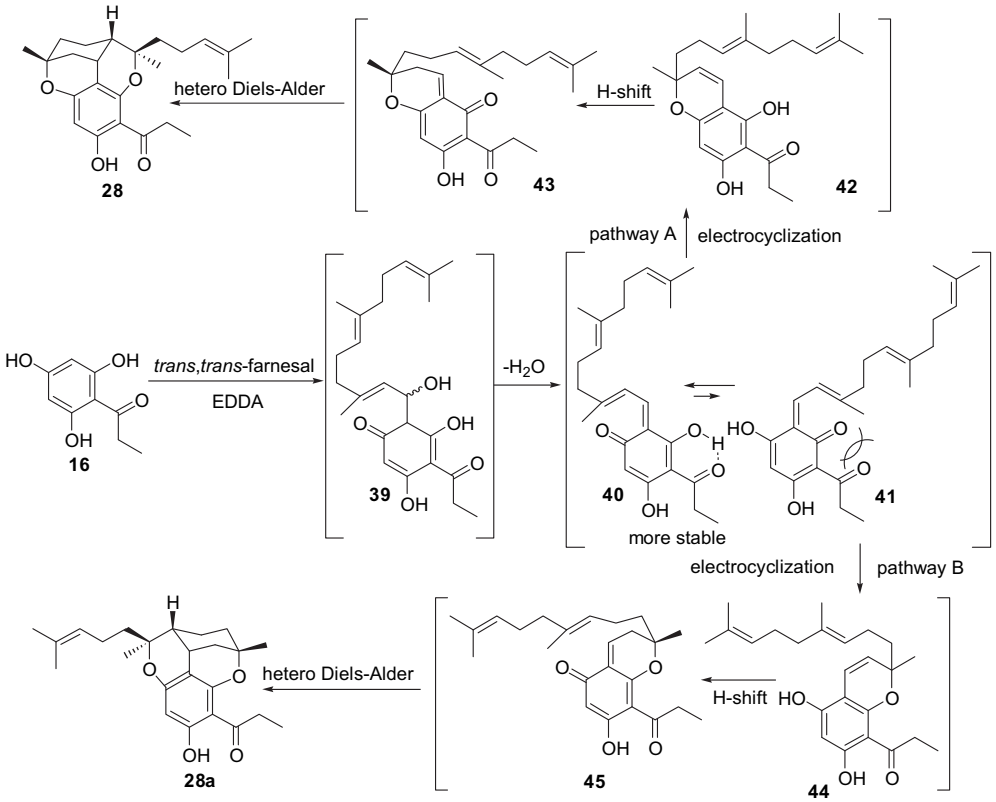
(*continued on next page*)

Table 1 (*continued*)

Entry	Starting material	Unsaturated aldehyde	Time (h)	Product	Yield (%)
8	 **20**	Citral	12	 **33**	57
9	 **21**	Citral	12	 **34**	45
10	 **22**	Citral	12	 **35**	40
11	 **23**	Citral	12	 **36**	22
12	 **24**	Citral	12	 **37**	43
13	 **25**	Citral	12	 **38**	62

propionic acid promoted cycloaddition.[17] However, reaction of pyrogallol with citral provided only polymeric gummy materials without the isolation of any cycloadducts. Next, we employed other compounds **24**–**25** containing two hydroxyl groups on the benzene ring for a cyclization. In these cases, benzopyrans **37** and **38** were produced in 43 and 62% yield, respectively, instead of the formation of the desired polycycles. The structural assignment of **38** was done on the base of ^{1}H NMR data. The ^{1}H NMR spectrum of **38** showed two vinylic protons on the pyranyl ring at δ 6.67 (J=9.9 Hz) and 5.37 (J=9.9 Hz). In particular, the signal for the proton of one hydroxyl group in the benzene ring was observed as a singlet associated with a hydrogen bond to a carbonyl group at δ 14.30 ppm.

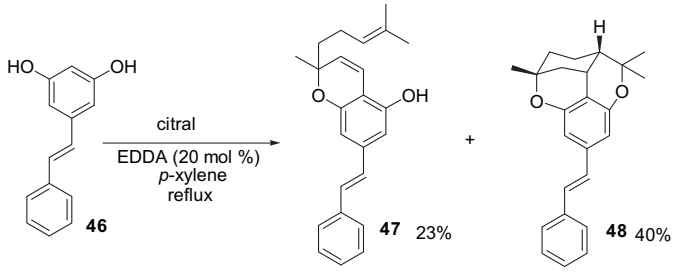
The mechanism for regio- and stereochemistry of synthesized **28** in Table 1 can be explained as shown in Scheme 2. *trans*,*trans*-Farnesal is first protonated by EDDA to give protonated aldehyde, which is then attacked by 2,4,6-trihydroxypropiophenone (**16**) in the presence of EDDA to yield intermediate **39**. Such a process for producing aldol-type products by a $Ca(OH)_2$-mediated reaction of resorcinol to enals was suggested by Shigemasa.[18] The dehydration of **39** in the presence of EDDA gives two possible *o*-quinone



Scheme 2. The mechanism for the formation and stereochemistry of compound **28**.

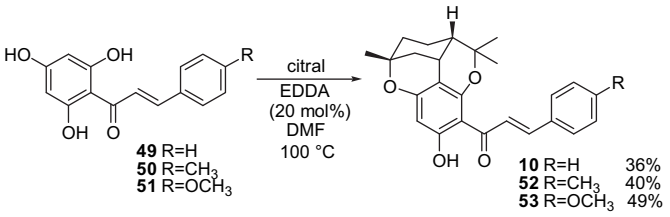
methides **40** and **41** through a tautomerism. Intermediate **40** with intramolecular hydrogen bonding is probably more stable than **41** with dipole–dipole repulsions. It is at this stage that the observed regioselectivity of **28** can be determined. Electrocyclization of much more stable intermediate **40** gives benzopyran **42** that undergoes a H-shift to furnish another quinine methide **43** by pathway A instead of pathway B.[19] The stereochemistry of **28** can be explained by the pseudoequatorial conformation of methyl group of *o*-quinone methide **43** in the chair-like transition state.[20] In the process of the hetero Diels–Alder reaction of **43**, 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 using the intramolecular hetero Diels–Alder cycloaddition of *o*-quinone methide.[21]

To extend the utility of this methodology, further reaction with pinosylvin (**46**) was examined (Scheme 3). Reaction of pinosylvin (**46**) with citral using 20 mol % ethylenediamine diacetate in refluxing *p*-xylene for 10 h provided both benzopyran **47** (23%) and tetracycle **48** (40%). The two compounds were easily separated by column chromatography and assigned by spectroscopic analyses based on reported data in the literature.[22] The ^{1}H NMR spectrum of **47** showed two vinyl protons on pyranyl ring at δ 6.59 (1H, d, J=10.0 Hz) and 5.49 (1H, d, J=10.0 Hz) ppm, whereas that of compound **48** showed a benzylic methine proton at δ 2.83 ppm as a broad singlet. Further support for the structural assignment of **48** was obtained from its ^{13}C NMR spectrum, which clearly showed the expected two quaternary carbons on two tetrahydropyranyl rings at δ 83.8 and 74.7 ppm.



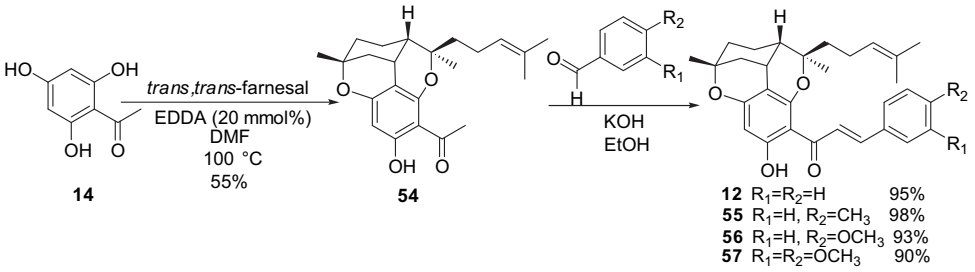
Scheme 3. Reaction of pinosylvin (**46**) with citral in the presence of EDDA.

A one-step synthesis of natural product rubraine (**10**) and its derivatives **52**–**53** was next investigated (Scheme 4). This lab has already reported on the synthesis of rubranine (**10**) starting from desbenzylidenerubramin (**8**), described above through a two-step aldol reaction. As another synthetic approach, reaction of 2′,4′,6′-trihydroxychalcone (**49**) with citral in the presence of 20 mol % ethylenediamine diacetate in DMF at 100 °C for 10 h produced rubraine (**10**) in 36% yield. The spectroscopic data of synthetic material **10** were identical to the values reported in the literature.[7,9,23] Similarly, treatment of **50** and **51** with citral gave unnatural rubraine derivatives **52** and **53** in 40 and 49% yields, respectively.



Scheme 4.

As other applications of this methodology, first total synthesis of sumadain A (**12**) was investigated. Scheme 5 shows a concise synthetic approach to sumadain A (**12**) and its derivatives **55**–**57**. A



Scheme 5. Synthesis of sumadain A (**12**) and its derivatives **55**–**57**.

reaction of 2,4,6-trihydroxyacetophenone (**14**) with *trans*,*trans*-farnesal using 20 mol % ethylenediamine diacetate in DMF at 100 °C for 10 h afforded adduct **54** in 55% yield. The conversion of **54** to sumadain A (**12**) and its derivatives **55**–**57** was attempted by aldol condensation. Reaction of **54** with benzaldehyde in the presence of KOH in ethanol at room temperature for 48 h gave sumadain A (**12**) in 95% yield. The spectroscopic data of synthetic material **12** were the same as the values reported in the literature.[10] Similarly, treatment of **54** with 4-methylbenzaldehyde, 4-methoxybenzaldehyde, and 3,4-dimethoxy benzaldehyde in the presence of ethanolic KOH for 48 h gave **55**–**57** in 98, 93, and 90% yields, respectively.

In conclusion, an efficient and concise synthetic route for biologically interesting polycycles with citran dihydrochalcone, and chalcone nuclei was developed starting from substituted trihydroxybenzenes. Using this methodology, polycycles with a variety of substituents on the pyranyl rings were synthesized. The key strategy in these synthetic routes was the domino aldol-type reaction/electrocyclization/H-migration/hetero Diels–Alder reaction, which led to the successful synthesis of three natural products, desbenzylidenerubramin (**8**), rubraine (**10**) and sumadain A (**12**), and their unnatural derivatives.

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). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The HRMS and MS (EI) spectra were carried out at the Korea Basic Science Institute on a Jeol JMS 700 spectrometer.

3.2. Typical procedure for compounds 8 and 26–30

To a solution of 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. Water (30 mL) was added and the solution was extracted with ethyl acetate (30 mL×3). Evaporation of solvent and purification by column chromatography on silica gel gave products.

*3.2.1. Desbenzylidenerubramin (**8**).* Reaction of **14** (168 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **8** (200 mg, 66%) as a solid: mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.42 (1H, s), 6.04 (1H, s), 2.73 (1H, br s), 2.65 (3H, s), 2.22–2.06 (2H, m), 1.90 (2H, d, J=13.5 Hz), 1.62 (3H, s), 1.56–1.42 (1H, m), 1.41 (3H, s), 1.39–1.23 (1H, m), 1.15 (3H, s), 0.94–0.76 (1H, m); IR (KBr) 2976, 2932, 1612, 1427, 1366, 1292, 1219, 1163, 1084, 1047, 1026, 1010, 974, 893, 825, 734 cm^{-1}; HRMS m/z (M^+) calcd for $C_{18}H_{22}O_4$: 302.1518. Found: 302.1520; EIMS m/z 302 (M^+, 23), 287 (7), 259 (5), 221 (11), 220 (12), 219 (100), 201 (5), 69 (5).

*3.2.2. Compound **26**.* Reaction of **15** (154 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **26** (130 mg, 45%) as a solid: mp 66–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.69 (1H, s), 9.96 (1H, s), 5.97 (1H, s), 2.77 (1H, br s), 2.25–2.14 (1H, m), 2.08–2.03 (1H, m), 1.84 (2H, d, J=13.5 Hz), 1.55 (3H, s), 1.49–1.42 (1H, m) 1.37 (3H, s), 1.34–1.23 (1H, m), 1.10 (3H, s), 0.86–0.73 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 164.8, 162.9, 160.8, 108.0, 107.4, 96.3, 86.6, 76.6, 45.8, 37.4, 34.6, 29.4, 28.6, 27.2, 24.0, 21.8; IR (KBr) 2934, 1640, 1443, 1370, 1294, 1163, 1140, 1076, 909, 797 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{20}O_4$: 288.1362. Found: 288.1364.

*3.2.3. Compound **27**.* Reaction of **16** (182 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **27** (205 mg, 65%) as a solid: mp 100–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.42 (1H, s), 6.01 (1H, s), 3.15–3.06 (1H, m), 3.04–2.87 (1H, m), 2.69 (1H, br s), 2.18–2.11 (1H, m), 2.08–2.05 (1H, m), 1.82 (2H, d, J=13.2 Hz), 1.55 (3H, s), 1.50–1.34 (1H, m), 1.35 (3H, s), 1.31–1.20 (1H, m), 1.13 (3H, t, J=7.2 Hz), 1.08 (3H, s), 0.87–0.73 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 164.2, 162.3, 159.3, 107.5, 107.1, 96.9, 86.6, 76.0, 46.1, 37.4, 36.5, 34.8, 29.9, 28.7, 27.5, 24.4, 21.8, 8.4; IR (KBr) 3455, 2976, 2932, 1637, 1583, 1485, 1458, 1356, 1263, 1236, 1163, 1140, 1071, 1010, 889, 825, 733 cm^{-1}; HRMS m/z (M^+) calcd for $C_{19}H_{24}O_4$: 316.1675. Found: 316.1675.

*3.2.4. Compound **28**.* Reaction of **16** (182 mg, 1.0 mmol) with *trans*,*trans*-farnesal (264 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **28** (204 mg, 53%) as a solid: mp 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.39 (1H, s), 6.00 (1H, s), 5.16 (1H, t, J=6.9 Hz), 3.17–3.04 (1H, m), 2.97–2.84 (1H, m), 2.71 (1H, br s), 2.28–1.95 (5H, m), 1.81 (2H, d, J=13.2 Hz), 1.73–1.63 (1H, m), 1.69 (3H, s), 1.63 (3H, s), 1.49–1.37 (1H, m), 1.35 (3H, s), 1.29–1.22 (1H, m), 1.13 (3H, t, J=7.5 Hz), 1.04 (3H, s), 0.92–0.77 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 164.1, 162.3, 158.9, 132.2, 123.7, 108.0, 107.2, 96.9, 88.8, 76.0, 45.4, 42.0, 37.5, 36.6, 34.7, 28.6, 27.4, 25.7, 22.6, 21.8, 21.2, 17.7, 8.5; IR (KBr) 3484, 2924, 1611, 1482, 1352, 1429, 1379, 1352, 1230, 1153, 1081, 1040, 1000, 893, 819, 762, 709 cm^{-1}; HRMS m/z (M^+) calcd for $C_{24}H_{32}O_4$: 384.2301. Found: 384.2302.

*3.2.5. Compound **29**.* Reaction of **17** (244 mg, 1.0 mmol) with citral (183 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **29** (234 mg, 62%) as a solid: mp 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.25 (1H, s), 7.35–7.23 (5H, m), 6.05 (1H, s), 4.54 (1H, d, J=16.5 Hz), 4.22 (1H, d, J=16.5 Hz), 2.74 (1H, br s), 2.21–2.05 (2H, m), 1.85 (2H, d, J=13.5 Hz), 1.65 (3H, s), 1.51–1.38 (1H, m), 1.38

(3H, s), 1.35–1.25 (1H, m), 1.08 (3H, s), 0.93–0.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 164.5, 162.8, 159.2, 135.4, 129.7, 128.3, 126.6, 107.7, 107.1, 97.0, 87.1, 76.2, 49.3, 46.1, 37.4, 34.7, 29.9, 28.6, 27.5, 24.3, 21.8; IR (KBr) 3418, 2976, 1622, 1479, 1429, 1350, 1258, 1163, 1140, 1073, 1009, 893, 824, 770 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{24}H_{26}O_4$: 378.1831. Found: 378.1834.

*3.2.6. Compound **30**.* Reaction of **17** (244 mg, 1.0 mmol) with *trans*,*trans*-farnesal (264 mg, 1.2 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **30** (232 mg, 52%) as a solid: mp 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.22 (1H, s), 7.35–7.22 (5H, m), 6.06 (1H, s), 5.17 (1H, t, *J*=6.9 Hz), 4.54 (1H, d, *J*=16.8 Hz), 4.23 (1H, d, *J*=16.8 Hz), 2.78 (1H, br s), 2.29–2.14 (3H, m), 2.04–1.99 (2H, m), 1.85 (2H, d, *J*=13.5 Hz), 1.80–1.67 (1H, m), 1.70 (3H, s), 1.62 (3H, s), 1.53–1.44 (1H, m), 1.39 (3H, s), 1.34–1.26 (1H, m), 1.07 (3H, s), 0.97–0.82 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 164.5, 162.7, 158.8, 135.3, 132.2, 129.8, 128.3, 126.6, 123.6, 108.2, 107.4, 97.1, 89.4, 76.2, 49.2, 45.2, 42.1, 37.5, 34.6, 28.6, 27.4, 25.7, 22.8, 21.8, 21.3, 17.7; IR (KBr) 3032, 2927, 1615, 1483, 1451, 1380, 1262, 1155, 1084, 999, 896, 844, 712 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{29}H_{34}O_4$: 446.2457. Found: 446.2459.

3.3. Typical procedure for compounds 10, 31–38, and 52–53

To a solution of trihydroxybenzenes (0.5 mmol) or resorcinols (0.5 mmol) and citral (0.6 mmol) in DMF (10 mL) was added ethylenediamine diacetate (18 mg, 0.1 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 10–12 h and then cooled to room temperature. Water (30 mL) was added and the solution was extracted with ethyl acetate (30 mL×3). Evaporation of solvent and purification by column chromatography on silica gel gave products.

*3.3.1. Compound **31**.* Reaction of **18** (129 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **31** (108 mg, 55%) as a solid: mp 74–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.37 (1H, s), 7.26–7.16 (5H, m), 6.04 (1H, s), 3.55–3.44 (1H, m), 3.30–3.12 (1H, m), 3.01 (2H, t, *J*=7.6 Hz), 2.72 (1H, br s), 2.20–2.13 (1H, m), 2.10–2.03 (1H, m), 1.85 (2H, d, *J*=13.2 Hz), 1.55 (3H, s), 1.50–1.41 (1H, m), 1.38 (3H, s), 1.32–1.25 (1H, m), 1.07 (3H, s), 0.89–0.74 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 164.3, 162.2, 159.2, 141.6, 128.3, 128.2, 125.8, 107.7, 107.1, 97.0, 86.8, 76.1, 46.1, 44.5, 37.4, 34.7, 30.4, 29.9, 28.6, 27.5, 24.4, 21.7; IR (KBr) 3447, 2974, 2934, 1601, 1481, 1448, 1360, 1301, 1258, 1219, 1160, 1140, 1071, 975, 894, 822 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{25}H_{28}O_4$: 392.1988. Found: 392.1990.

*3.3.2. Compound **32**.* Reaction of **19** (136 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **32** (102 mg, 50%) as an solid: mp 105–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.37 (1H, s), 7.14 (2H, d, *J*=8.1 Hz), 7.09 (2H, d, *J*=8.1 Hz), 6.04 (1H, s), 3.53–3.42 (1H, m), 3.26–3.15 (1H, m), 2.96 (2H, t, *J*=7.6 Hz), 2.72 (1H, br s), 2.31 (3H, s), 2.21–2.16 (1H, m), 2.10–2.03 (1H, m), 1.84 (2H, d, *J*=13.2 Hz), 1.55 (3H, s), 1.50–1.41 (1H, m), 1.37 (3H, s), 1.33–1.24 (1H, m), 1.07 (3H, s), 0.89–0.74 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 164.4, 162.5, 159.2, 138.5, 135.3, 128.9, 128.2, 107.7, 107.1, 97.0, 86.8, 76.0, 46.2, 44.6, 37.4, 34.8, 30.0, 29.9, 28.7, 27.5, 24.5, 21.8, 21.0; IR (KBr) 3443, 2971, 1618, 1473, 1438, 1363, 1225, 1219, 1150, 1066, 817, 717 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{26}H_{30}O_4$: 406.2144. Found: 406.2142; EIMS *m*/*z* 406 (M^+, 7), 323 (19), 302 (22), 220 (14), 219 (100), 201 (5), 69 (5).

*3.3.3. Compound **33**.* Reaction of **20** (144 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **33** (120 mg, 57%) as a solid: mp 109–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.36 (1H, s), 7.15 (2H, d, *J*=8.7 Hz), 6.82 (2H, d, *J*=8.7 Hz), 6.03 (1H, s), 3.77 (3H, s), 3.51–3.40 (1H, m), 3.24–3.14 (1H, m), 2.94 (2H, t, *J*=7.6 Hz), 2.71 (1H, br s), 2.20–2.12 (1H, m), 2.09–2.02 (1H, m), 1.84 (2H, d, *J*=13.2 Hz), 1.55 (3H, s), 1.50–1.40 (1H, m), 1.37 (3H, s), 1.33–1.24 (1H, m), 1.07 (3H, s), 0.88–0.76 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 164.4, 162.5, 159.2, 157.7, 1337, 129.2, 113.7, 107.6, 107.2, 97.0, 86.8, 76.0, 55.2, 46.2, 44.8, 37.4, 34.8, 30.0, 29.6, 28.6, 27.5, 24.4, 21.8; IR (KBr) 3454, 2932, 1614, 1466, 1442, 1359, 1310, 1247, 1156, 1039, 828, 723 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{26}H_{30}O_5$: 422.2093. Found: 422.2090; EIMS *m*/*z* 422 (M^+, 44), 340 (22), 339 (100), 219 (48), 177 (14), 129 (21), 121 (30), 69 (20).

*3.3.4. Compound **34**.* Reaction of **21** (130 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **34** (89 mg, 45%) as a solid: mp 149–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.59 (1H, s), 7.26 (1H, t, *J*=7.5 Hz), 7.09 (1H, d, *J*=7.5 Hz), 7.04 (1H, s), 6.98 (1H, d, *J*=7.5 Hz), 6.10 (1H, s), 3.92 (3H, s), 2.65 (1H, br s), 2.21–2.14 (1H, m), 1.93–1.87 (1H, m), 1.80 (2H, d, *J*=13.2 Hz), 1.45–1.33 (1H, m), 1.37 (3H, s), 1.22–1.08 (1H, m), 1.08 (3H, s), 0.78–0.65 (1H, m), 0.62 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 164.3, 163.4, 159.3, 158.8, 143.3, 128.4, 120.4, 116.6, 112.4, 107.9, 107.3, 97.3, 85.6, 76.3, 55.4, 45.8, 37.6, 34.8, 29.1, 28.6, 27.5, 23.5, 21.7; IR (KBr) 3446, 2931, 1615, 1581, 1466, 1305, 1250, 1156, 1067, 982, 894, 819, 786 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{24}H_{26}O_5$: 394.1780. Found: 394.1778; EIMS *m*/*z* 394 (M^+, 24), 379 (6), 313 (8), 312 (19), 311 (100), 203 (14), 135 (7), 69 (5).

*3.3.5. Compound **35**.* Reaction of **22** (130 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **35** (79 mg, 40%) as a solid: mp 155–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.43 (1H, s), 7.59 (2H, d, *J*=8.0 Hz), 6.85 (2H, d, *J*=8.0 Hz), 6.11 (1H, s), 3.85 (3H, s), 2.70 (1H, br s), 2.22–2.16 (1H, m), 1.95–1.87 (1H, m), 1.82 (2H, d, *J*=13.2 Hz), 1.45–1.37 (1H, m), 1.37 (3H, s), 1.25–1.15 (1H, m), 1.14 (3H, s), 0.78–0.65 (1H, m), 0.63 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 163.9, 162.7, 162.1, 158.8, 134.2, 130.8, 112.5, 108.0, 107.6, 97.6, 85.6, 76.1, 55.4, 46.1, 37.6, 34.9, 29.2, 28.7, 27.7, 23.6, 21.8; IR (KBr) 3497, 2932, 1604, 1454, 1303, 1253, 1156, 1037, 952, 877, 825 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{24}H_{26}O_5$: 394.1780. Found: 394.1777; EIMS *m*/*z* 394 (M^+, 40), 313 (9), 312 (21), 311 (100), 203 (34), 148 (10), 135 (11), 69 (18).

*3.3.6. Compound **36**[17].* Reaction of **23** (63 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **36** (58 mg, 22%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (3H, d, *J*=9.9 Hz), 5.35 (3H, d, *J*=9.9 Hz, 5.07) (3H, t, *J*=6.8 Hz), 2.20–2.10 (6H, m), 1.80–1.55 (6H, m), 1.64 (9H, s), 1.48 (9H, s), 1.35 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 131.4, 124.6, 124.0, 117.0, 102.8, 78.4, 40.7, 26.0, 25.5, 22.4, 17.4; IR (neat) 2921, 1631, 1596, 1447, 1370, 1140, 1009, 905, 821, 724 cm^{-1}.

*3.3.7. 7-Methoxy-2-methyl-2-(methylpent-3-enyl)-2H-chromen-5-ol (**37**).* Reaction of **24** (70 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **37** (59 mg, 43%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (1H, d, *J*=9.9 Hz), 5.99 (1H, s), 5.87 (1H, s), 5.39 (1H, d, *J*=9.9 Hz), 5.08 (1H, t, *J*=6.8 Hz), 3.70 (3H, s), 2.15–2.03 (2H, m), 1.82–1.63 (2H, m), 1.64 (3H, s), 1.56 (3H, s), 1.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 155.2, 152.1, 131.7, 125.3, 124.1, 116.6, 103.1, 94.7, 94.6, 78.6, 55.3, 41.0, 26.2, 25.7, 22.7, 17.6; IR (neat) 3415, 2957, 1620, 1490, 1449, 1364, 1262, 1197, 1140, 971, 819, 779 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{17}H_{22}O_3$: 274.1569. Found: 274.1572; EIMS *m*/*z* 274 (M^+, 11), 259 (5), 192 (12), 191 (100), 148 (3), 69 (3).

*3.3.8. 6-Acetyl-7-methoxy-2-methyl-2-(methylpent-3-enyl)-2H-chromen-5-ol (**38**).* Reaction of **25** (91 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 12 h afforded **38** (98 mg, 62%) as a solid: mp 79–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$)

δ 14.30 (1H, s), 6.67 (1H, d, *J*=9.9 Hz), 5.85 (1H, s), 5.37 (1H, d, *J*=9.9 Hz), 5.06 (1H, t, *J*=6.8 Hz), 3.83 (3H, s), 2.57 (3H, s), 2.10–2.02 (2H, m), 1.80–1.64 (2H, m), 1.64 (3H, s), 1.55 (3H, s), 1.38 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 162.9, 161.7, 160.5, 131.8, 124.0, 123.8, 116.4, 105.5, 102.4, 90.8, 80.6, 55.5, 41.6, 32.9, 27.1, 25.6, 22.6, 17.6; IR (KBr) 3476, 2919, 1615, 1438, 1379, 1268, 1213, 1123, 1034, 988, 881, 822 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{24}O_4$: 316.1675. Found: 316.1672; EIMS *m*/*z* 316 (M^+, 10), 234 (14), 233 (100), 215 (12), 191 (16), 69 (6).

*3.3.9. 2-Methyl-2-(4-methylpent-3-enyl)-7-(E)-styryl-2H-chromen-5-ol (**47**) and compound **48**.* A reaction of **46** (106 mg, 0.5 mmol) with citral (91 mg, 0.6 mmol) in refluxing *p*-xylene (10 mL) for 10 h afforded compounds **47** (40 mg, 23%) and **48** (69 mg, 40%) as an oil. Compound **47**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (2H, d, *J*=8.6 Hz), 7.26 (2H, dd, *J*=8.6, 8.4 Hz), 7.18 (1H, d, *J*=8.4 Hz), 6.96 (1H, d, *J*=16.3 Hz), 6.83 (1H, d, *J*=16.3 Hz), 6.59 (1H, d, *J*=10.0 Hz), 6.55 (1H, s), 6.39 (1H, s), 5.49 (1H, *J*=10.0 Hz), 5.10–4.98 (2H, m), 2.18–1.99 (2H, m), 1.75–1.63 (2H, m), 1.60 (3H, s), 1.53 (3H, s), 1.34 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 151.4, 138.3, 137.2, 131.7, 128.9, 128.7, 128.2, 128.1, 127.7, 126.5, 124.1, 116.8, 109.2, 107.1, 106.1, 78.4, 41.1, 26.3, 25.7, 22.7, 17.6; IR (neat) 3409, 2970, 2921, 1613, 1567, 1429, 1343, 1263, 1198, 1143, 1083, 1058, 960, 824, 749 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{24}H_{26}O_2$: 346.1933. Found: 346.1936; EIMS *m*/*z* 346 (M^+, 9), 264 (19), 263 (100), 150 (3), 107 (3), 77 (3), 69 (9), 58 (5). Compound **48**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (2H, d, *J*=7.8 Hz), 7.27 (2H, dd, *J*=7.8, 7.5 Hz), 7.17 (1H, d, *J*=7.5 Hz), 6.94 (2H, s), 6.60 (1H, s), 6.57 (1H, s), 2.83 (1H, br s), 2.20–2.15 (1H, m), 2.02–1.98 (1H, m), 1.878 (2H, d, *J*=13.2 Hz), 1.48 (3H, s), 1.41–1.36 (1H, m), 1.33 (3H, s), 1.25–1.18 (1H, m), 0.98 (3H, s), 0.74–0.61 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 156.9, 137.4, 136.8, 129.2, 128.6, 128.2, 127.3, 126.4, 116.9, 107.8, 107.4, 83.8, 74.7, 46.7, 37.3, 35.2, 29.7, 29.0, 28.3, 23.8, 22.1; IR (neat) 3026, 2975, 2930, 1610, 1578, 1449, 1424, 1352, 1314, 1130, 1065, 997, 963, 909, 883, 827, 733 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{24}H_{26}O_2$: 346.1933. Found: 346.1929; EIMS *m*/*z* 346 (M^+, 30), 331 (7), 303 (5), 265 (10), 264 (22), 263 (100), 151 (10), 123 (7), 109 (5), 91 (7), 69 (31).

*3.3.10. Rubraine (**10**)[7,9,23].* To a solution of 2′,4′,6′-trihydroxychalcone **49** (126 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 10 h afforded rubraine **10** (70 mg, 36%) as a solid: mp 172–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.02 (1H, s), 8.29 (1H, d, *J*=15.7 Hz), 7.80 (1H, d, *J*=15.7 Hz), 7.66–7.57 (2H, d, *J*=7.5 Hz), 7.50–7.40 (3H, m), 6.13 (1H, s), 2.79 (1H, br s), 2.25–2.09 (2H, m), 1.90 (2H, d, *J*=13.2 Hz), 1.68 (3H, s), 1.58–1.45 (1H, m) 1.42 (3H, s), 1.35–1.22 (1H, m), 1.09 (3H, s), 0.93–0.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 165.4, 162.9, 159.0, 141.8, 135.5, 129.9, 128.8, 128.1, 127.1, 108.3, 107.9, 97.4, 86.9, 76.2, 46.0, 37.4, 34.6, 30.0, 28.5, 27.6, 24.2, 21.7; IR (KBr) 3445, 1631, 1479, 1339, 1231, 1163, 1142, 1074, 1017, 826, 731 cm^{-1}.

*3.3.11. Compound **52**.* To a solution of **50** (135 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **52** (81 mg, 40%) as a solid: mp 216–217 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.95 (1H, s), 8.19 (1H, d, *J*=15.7 Hz), 7.74 (1H, d, *J*=15.7 Hz), 7.51 (2H, d, *J*=8.1 Hz), 7.17 (2H, d, *J*=8.1 Hz), 6.08 (1H, s), 2.77 (1H, br s), 2.37 (3H, s), 2.24–2.06 (2H, m), 1.86 (2H, d, *J*=13.5 Hz), 1.64 (3H, s), 1.53–1.41 (1H, m), 1.38 (3H, s), 1.32–1.23 (1H, m), 1.05 (3H, s), 0.92–0.77 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 165.5, 162.8, 159.0, 142.1, 140.4, 132.8, 129.6, 128.2, 126.2, 108.3, 108.0, 97.4, 86.8, 76.2, 46.1, 37.5, 34.7, 30.1, 28.6, 27.6, 24.3, 21.8, 21.5; IR (KBr) 3449, 2924, 1618, 1549, 1478, 1235, 1181, 1163, 1142, 1078, 1020, 988, 881, 823 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{26}H_{28}O_4$: 404.1988. Found: 404.1985.

*3.3.12. Compound **53**.* To a solution of **51** (143 mg, 0.5 mmol) with citral (92 mg, 0.6 mmol) in DMF (10 ml) at 100 °C for 10 h afforded **53** (103 mg, 49%) as a solid: mp 208–209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.04 (1H, s), 8.13 (1H, d, *J*=15.6 Hz), 7.74 (1H, d, *J*=15.6 Hz), 7.56 (2H, d, *J*=8.7 Hz), 6.92 (2H, d, *J*=8.7 Hz), 6.08 (1H, s), 3.83 (3H, s), 2.77 (1H, br s), 2.22–2.05 (2H, m), 1.86 (2H, d, *J*=13.2 Hz), 1.64 (3H, s), 1.56–1.40 (1H, m), 1.38 (3H, s), 1.32–1.23 (1H, m), 1.05 (3H, s), 0.91–0.80 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 165.5, 162.7, 161.2, 159.0, 142.0, 130.0, 128.4, 124.9, 114.4, 108.3, 108.1, 97.5, 86.8, 76.1, 55.4, 46.2, 37.6, 34.8, 30.2, 28.7, 27.7, 24.4, 21.8; IR (KBr) 3445, 1622, 1553, 1510, 1480, 1422, 1352, 1233, 1171, 1022, 829 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{26}H_{28}O_5$: 420.1937. Found: 420.1938.

*3.3.13. Compound **54**.* To a solution of 2,4,6-trihydroxyacetophenone (**14**) (168 mg, 1.0 mmol) with *trans*,*trans*-farnesal (264 mg, 1.2 mmol) in DMF (10 ml) at 100 °C. The reaction mixture was stirred at 100 °C for 10 h and then cooled to room temperature. Water was added and the solution was extracted with ethyl acetate. Evaporation of solvent and purification by column chromatography on silica gel gave product **54** (204 mg, 55%) as a solid: mp 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.29 (1H, s), 6.01 (1H, s), 5.18–5.12 (1H, m), 2.72 (1H, br s), 2.58 (3H, s), 2.26–1.94 (5H, m), 1.82 (2H, br d, *J*=13.4 Hz), 1.76–1.69 (1H, m), 1.69 (3H, s), 1.63 (3H, s), 1.50–1.40 (1H, m), 1.36 (3H, s), 1.32–1.23 (1H, m) 1.05 (3H, s), 0.94–0.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 164.2, 162.6, 159.1, 132.1, 123.7, 108.0, 107.7, 96.9, 88.9, 76.1, 45.4, 42.1, 37.5, 34.7, 32.1, 28.6, 27.4, 25.6, 22.7, 21.8, 21.1, 17.7; IR (neat) 2928, 1622, 1485, 1433, 1364, 1294, 1161, 1061, 961, 824, 772, 735 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{23}H_{30}O_4$: 370.2144. Found: 370.2142; EIMS *m*/*z* 370 (M^+, 23), 261 (8), 221 (31), 220 (13), 219 (100), 181 (5), 69 (10).

3.4. Typical procedure for compounds 12 and 55–57

To a solution of **54** (0.5 mmol) in ethanol (5 ml) were added potassium hydroxide (2.5 mmol) and corresponding aldehyde (0.5 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Addition of water (30 mL) and extraction with ethyl acetate (3×50 mL), washing with 2 N-HCl solution and brine, drying over $MgSO_4$, and removal of the solvent followed by flash column chromatography on silica gel gave products.

*3.4.1. Sumadain A (**12**).* To a solution of **54** (185 mg, 0.5 mmol) in ethanol (5 ml) were added KOH (140 mg, 2.5 mmol) and benzaldehyde (53 mg, 0.5 mmol) at room temperature for 48 h afforded **12** (218 mg, 95%) as a solid: mp 172–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.95 (1H, s), 8.16 (1H, d, *J*=15.6 Hz), 7.78 (1H, d, *J*=15.6 Hz), 7.63–7.60 (2H, m), 7.37–7.35 (3H, m), 6.09 (1H, s), 5.22–5.18 (1H, m), 2.79 (1H, br s), 2.41–2.29 (1H, m), 2.29–2.02 (4H, m), 1.85 (2H, br d, *J*=13.5 Hz), 1.79–1.69 (1H, m), 1.73 (3H, s), 1.64 (3H, s), 1.51–1.41 (1H, m), 1.38 (3H, s), 1.30–1.24 (1H, m), 1.01 (3H, s), 0.94–0.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 165.6, 162.9, 158.7, 142.3, 135.5, 132.2, 130.0, 128.8, 128.4, 127.1, 123.6, 108.8, 108.3, 97.6, 89.2, 76.2, 45.6, 42.4, 37.6, 34.7, 28.6, 27.6, 25.7, 23.0, 21.8, 21.1, 17.7; IR (KBr) 3452, 2972, 2925, 1626, 1552, 1478, 1340, 1234, 1161, 1080, 1022, 982, 909, 827, 763, 726 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{30}H_{34}O_4$: 458.2457. Found: 458.2458; EIMS *m*/*z* 458 (M^+, 31), 309 (27), 308 (22), 307 (100), 203 (38), 69 (12).

*3.4.2. Compound **55**.* To a solution of **54** (185 mg, 0.5 mmol) in ethanol (5 ml) were added KOH (140 mg, 2.5 mmol) and *p*-tolualdehyde (60 mg, 0.5 mmol) at room temperature for 48 h afforded **55** (232 mg, 98%) as a solid: mp 160–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.98 (1H, s), 8.12 (1H, d, *J*=15.6 Hz), 7.77 (1H, d, *J*=15.6 Hz), 7.51 (2H, d, *J*=8.1 Hz), 7.16 (2H, d, *J*=8.1 Hz), 6.09 (1H, s), 5.23–5.18 (1H, m), 2.79 (1H, br s), 2.44–2.32 (1H, m), 2.36 (3H, s), 2.28–2.01 (4H, m), 1.84 (2H, d, *J*=13.5 Hz), 1.81–1.69 (1H, m), 1.74 (3H, s), 1.65 (3H, s), 1.50–1.41 (1H, m), 1.38 (3H, s), 1.30–1.21 (1H, m),

1.01 (3H, s), 0.94–0.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 165.6, 162.8, 158.7, 142.5, 140.4, 132.9, 132.3, 129.6, 128.4, 126.1, 123.7, 108.8, 108.4, 97.6, 89.2, 76.2, 45.6, 42.5, 37.7, 34.7, 28.7, 27.7, 25.8, 23.0, 21.9, 21.5, 21.2, 17.7; IR (KBr) 3453, 2928, 2856, 1737, 1624, 1547, 1473, 1342, 1238, 1159, 1079, 1016, 986, 912, 876, 818, 712 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{31}H_{36}O_4$: 472.2614. Found: 472.2617; EIMS *m*/*z* 472 (M^+, 32), 323 (28), 322 (23), 321 (100), 203 (40), 69 (19).

3.4.3. Compound ***56****.* To a solution of **54** (185 mg, 0.5 mmol) in ethanol (5 ml) were added KOH (140 mg, 2.5 mmol) and *p*-anisaldehyde (68 mg, 0.5 mmol) at room temperature for 48 h afforded **56** (227 mg, 93%) as a solid: mp 175–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.98 (1H, s), 8.05 (1H, d, *J*=15.6 Hz), 7.76 (1H, d, *J*=15.6 Hz), 7.56 (2H, d, *J*=8.7 Hz), 6.87 (2H, d, *J*=8.7 Hz), 6.08 (1H, s), 5.23–5.18 (1H, m), 3.82 (3H, s), 2.78 (1H, br s), 2.44–2.32 (1H, m), 2.30–2.02 (4H, m), 1.85 (2H, d, *J*=13.5 Hz), 1.82–1.70 (1H, m), 1.73 (3H, s), 1.65 (3H, s), 1.52–1.40 (1H, m), 1.37 (3H, s), 1.29–1.21 (1H, m), 1.01 (3H, s), 0.94–0.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 165.6, 162.7, 161.3, 158.6, 142.3, 132.2, 130.1, 128.4, 124.8, 123.7, 114.3, 108.7, 108.4, 97.6, 89.1, 76.1, 55.3, 45.7, 42.5, 37.7, 34.7, 28.6, 27.7, 25.7, 23.0, 21.9, 21.1, 17.8; IR (KBr) 3463, 2930, 1624, 1547, 1510, 1474, 1421, 1348, 1290, 1235, 1166, 1021, 1084, 984, 911, 876, 824, 731 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{31}H_{36}O_5$: 488.2563. Found: 488.2562; EIMS *m*/*z* 488 (M^+, 40), 340 (5), 339 (25), 338 (23), 337 (100), 205 (5), 204 (5), 203 (41), 161 (5), 69 (7).

3.4.4. Compound ***57****.* To a solution of **54** (185 mg, 0.5 mmol) in ethanol (5 ml) were added KOH (140 mg, 2.5 mmol) and 3,4-dimethoxy benzaldehyde (83 mg, 0.5 mmol) at room temperature for 48 h afforded **57** (233 mg, 90%) as a solid: mp 158–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.05 (1H, s), 8.03 (1H, d, *J*=15.6 Hz), 7.76 (1H, d, *J*=15.6 Hz), 7.17 (1H, d, *J*=7.8 Hz), 7.16 (1H, s), 6.94 (1H, d, *J*=7.8 Hz), 6.09 (1H, s), 5.18–5.5.13 (1H, m), 3.91 (3H, s), 3.87 (3H, s), 2.79 (1H, br s), 2.34–1.98 (5H, m), 1.84 (2H, d, *J*=13.5 Hz), 1.84–1.78 (1H, m), 1.71 (3H, s), 1.60 (3H, s), 1.51–1.40 (1H, m), 1.38 (3H, s), 1.29–1.23 (1H, m), 1.02 (3H, s), 0.93–0.78 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 165.6, 162.7, 158.6, 151.0, 149.2, 142.6, 132.5, 128.7, 124.9, 123.5, 111.0, 109.5, 108.7, 108.4, 97.7, 89.1, 76.1, 56.0, 55.7, 45.3, 42.6, 37.7, 34.7, 28.6, 27.7, 25.7, 23.1, 21.9, 21.4, 17.7; IR (KBr) 3410, 2930, 1621, 1547, 1511, 1474, 1420, 1353, 1319, 1260, 1160, 1024, 1083, 1160, 1024, 980, 905, 818, 771 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{32}H_{38}O_6$: 518.2668. Found: 518.2665; EIMS *m*/*z* 518 (M^+, 17), 369 (21), 368 (23), 367 (100), 205 (5), 204 (6), 203 (41), 191 (6), 165 (5), 69 (7).

Acknowledgements

This work was supported by grant no. RTI04-01-04 from the Regional Technology Innovation Program of the Ministry of Knowledge Economy (MKE).

Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.10.045.

References and notes

1. (a) Bukuru, J.; Van, T. N.; 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., Chem. Commun.* **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; (f) Crombie, L.; Ponsford, R. *J. Chem. Soc., Chem. Commun.* **1968**, 894.
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. (a) Crombie, L.; Crombie, W. M. L. *Phytochemistry* **1975**, *14*, 213; (b) Shoyama, Y.; Morimoto, S.; Nishioka, I. *Chem. Pharm. Bull.* **1981**, *29*, 3720; (c) Kane, V.; Martin, A. R.; Peters, J. A. *J. Org. Chem.* **1984**, *49*, 1793; (e) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1971**, *93*, 217.
4. (a) Devane, W. A.; Dysarz, F. A., III; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 606; (b) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561; (c) Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61.
5. (a) Rashid, M. A.; Armstrong, J. A.; Gray, A. I.; Waterman, P. G. *Phytochemistry* **1992**, *31*, 3583; (b) Gray, A. I.; Rashid, M. A.; Waterman, P. G. *J. Nat. Prod.* **1992**, *55*, 681.
6. Goh, S. H.; Chung, V. C.; Sha, C. K.; Mak, T. C. W. *Phytochemistry* **1990**, *29*, 1704.
7. De Alleluia, I. B.; Brez Fo, R.; Gottlieb, O. R.; Magalhaes, E. G.; Marques, R. *Phytochemistry* **1978**, *17*, 517.
8. (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.
9. Hua, S.-Z.; Luo, J.-G.; Wang, X.-B.; Wang, J.-S.; Kong, L.-Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2728.
10. Hua, S.-Z.; Wang, X.-B.; Luo, J.-G.; Wang, J.-S.; Kong, L.-Y. *Tetrahedron Lett.* **2008**, *49*, 5658.
11. Jiangsu New Medicinal College. *The Encyclopedia of Chinese Materia Medica*; Shanghai Science & Technical: Shanghai, 1978; p 1582.
12. (a) Kane, V. V.; Grayeck, T. L. *Tetrahedron Lett.* **1971**, 3991; (b) Crombie, L.; Ponsford, R. *J. Chem. Soc. C* **1971**, 788; (c) Crombie, L.; Redshaw, S. D.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1979**, 628.
13. (a) Hatana, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858; (b) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758; (c) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059; (d) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245; (e) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570.
14. (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) Wang, X.; Lee, Y. R. *Tetrahedron Lett.* **2007**, *48*, 6275; (e) Wang, X.; Lee, Y. R. *Synthesis* **2007**, 3044; (f) Lee, Y. R.; Xia, L. *Synthesis* **2007**, 3240; (g) Lee, Y. R.; Li, X.; Kim, J. H. *J. Org. Chem.* **2008**, *73*, 4313; (h) Lee, Y. R.; Xia, L. *Tetrahedron Lett.* **2008**, *49*, 3283; (i) Xia, L.; Lee, Y. R. *Synlett* **2008**, 1643; (j) Lee, Y. R.; Hung, T. V. *Tetrahedron* **2008**, *64*, 7338.
15. Lee, Y. R.; Kim, J. H. *Synlett* **2007**, 2232.
16. Cheenpracha, S.; Karalai, C.; Ponglimanont, C.; Subhadhirasakul, S.; Tewtrakul, S. *Bioorg. Med. Chem.* **2006**, *14*, 1710.
17. Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 467.
18. Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768.
19. Crombie, L.; Redshaw, S. D.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1979**, 631.
20. Talley, J. J. *J. Org. Chem.* **1985**, *50*, 1695.
21. Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671.
22. Belofsky, G.; French, A. N.; Wallace, D. R.; Dodson, S. L. *J. Nat. Prod.* **2004**, *67*, 26.
23. Combes, G.; Vassort, P. *Tetrahedron* **1970**, *26*, 5981.