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# A divergent and stereoselective approach for the syntheses of (–)-zeylenol, (+)-6-*O*-benzoylzeylenol, (+)-uvarigranol E and (+)-uvarigranol F

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ABSTRACT

A common, divergent, efficient, and stereoselective approach to the total syntheses of four carbasugars, namely, (–)-zeylenol, (+)-6-*O*-benzoylzeylenol, (+)-uvarigranol E and (+)-uvarigranol F from D-mannose derived key intermediate **14** is described. This intermediate was synthesized using mixed aldol condensation, Grignard reaction and ring closing metathesis as key steps by our previous method in nine steps from D-mannose. From this intermediate, we achieved the syntheses of (+)-6-*O*-benzoylzeylenol, (+)-uvarigranol F in three steps, (+)-uvarigranol E in four steps and improved synthesis of (–)-zeylenol.

## 1. Introduction

Polyoxygenated cyclohexenes are common metabolites of the Annonaceae family. These molecules have common structural features where the polyoxygenated cyclohexene unit has benzoyloxymethyl or hydroxymethyl or acetoxymethyl functionalities on a tertiary carbon. The first example of this class is (–)-zeylenol **1**. Numerous natural products which are having zeylenol skeleton have been isolated from different sources and are showing interesting biological activity [1–3]. (+)-Pipoxide **2**, (–)-tonkinenin A **3**, (–)-6-*O*-benzoylzeylenol **4**, (–)-uvarigranol C **5**, (–)-uvarigranol D **6**, (+)-uvarigranol E **7**, (+)-uvarigranol F **8**, (–)-uvarigranol G **9**, and ferrudiol **10** (Fig. 1) are some examples belong to this class which are isolated from natural sources, whose absolute configuration has been established [1–3]. (–)-Zeylenol **1** was isolated by Cole and Bates [4], in 1981 from the plant *uvaria zeylanica*. Recently, (–)-zeylenol was also isolated from *uvaria* [2d–f,3a–c,5a,b], *kaempferia* [5c] and other species [1b]. Zeylenol related compounds (–)-6-*O*-benzoylzeylenol **4** was isolated from the same *Kaempferia* species [3d], (+)-uvarigranol E **7** and (+)-uvarigranol F **8** isolated from the uvaria [5d] species. (–)-Zeylenol **1** shows anticancer, antifeedant activity [5e] and anti-inflammatory activity (equally active as phenylbutazone) [1b,5a]. For instance (–)-zeylenol **1** exhibits moderate inhibition against PSN-1 [5c], MDA-MB231 (breast) [5a,c] and HepG2 (liver) [5a] cell lines. (–)-Uvagranol C **5** (6-*O*- ethylzeylenol) has shown significant activity as Nav1.7 inhibitor [6], which can be used in the treatment of different pains and the molecule is in preclinical trials at Protheragen [7] company, USA. (+)-Uvarigranol E **7** and also (–)-zeylenol **1** show significant cytotoxicity against P388 cells [2d]. (+)-Uvarigranol F **8** also exhibited inhibition activities against both PSN-1 and MDA-MB231 cell lines [5c]. (–)-Zeylenol **1** and (–)-zeylenone **3** (initially called as (–)-tonkinenin A) have shown α-glucosidase inhibitory activities better than acarbose [2e] (presently in the market for the treatment of diabetes mellitus) and also showed plant root growth inhibitory activity [1e]. In addition (–)-zeylenone **3** also shows strong cytotoxic activity against various tumor cell lines and low toxicity against normal cell lines [1a–d,2f,3e,8]. (–)-Zeylenone **3** is considered as a potential candidate in cancer treatment.

Interesting biological activity of zeylenol and its derivatives, where some are in the developmental stage as drugs prompted us to develop a common approach for this class of compounds. In this connection we are presenting a common strategy for the synthesis of three natural carbasugars and enantiomer of natural product **4**, viz. (–)-zeylenol **1**, (+)-uvarigranol E **7** and (+)-uvarigranol F **8**, and (+)-6-*O*-benzoylzeylenol (*ent*-**4**). Synthesis of analogs of (–)-zeylenol and evaluation of their biological activity is certainly an interesting area of research for finding new leads.

Ogasawara et al. has reported both formal [9a] and total [9b,c] enantiocontrolled synthesis of (–)-zeylenol **1** which has been utilized for the synthesis of (+)-pipoxide **2**, (–)-tonkinenin A **3**, and (–)-uvarigranol G **9** from *meso* ene diol. Palframan [10a] et al. synthesized (+)-zeylenol, as well as its congeners (–)-6-*O*-benzoylzeylenol **4** and (–)-uvaribonol A (*ent*-**8**) from *ipso* and *ortho* diols. Sharma [10b] et al. also synthesized (–)-6-*O*-benzoylzeylenol **4** from diacetone glucose. There were no reports on the synthesis of unnatural enantiomer (+)-6-*O*-benzoylzeylenol

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(*ent*-**4**) and natural (+)-uvarigranol F **6**. And also no report to date on the synthesis of (+)- or (–)-uvarigranol E **7**. We [11] synthesized (–)-zeylenol **1** from D-mannose. (–)-Zeylenol **1** is a basic skeleton for the many natural products of this class. Therefore we planned to synthesize target molecules from the intermediate in our earlier (–)-zeylenol synthesis. The reported synthesis of zeylenol and related structures so far suffer from some drawbacks such as more number of steps, separation of isomers, low yields and mainly lack of generality. Therefore, development of a common approach which can give many of these molecules in good yields and high optical purity will be helpful in generating library in a short possible time.

In our approach, we used Grignard reaction, ring closing metathesis [12], benzoylation and acylation reactions as key steps for the improved synthesis of (–)-zeylenol **1** when compared to our previous synthesis and other related natural products such as *ent*-**4**, **7** and **8** in good overall yields.

## 2. Results and discussion

Based on the retrosynthetic analysis (Scheme 1) we have chosen D-mannose as a starting material which is a cheap and commercially available. D-Mannose was converted to lactol **11** using our previous method [11]. To make the required diene compound for RCM in a better way, we tried vinyl Grignard addition on lactol **11** at different conditions. Interestingly, reversal in diastereoselectivity was observed at different temperatures. Vinyl Grignard addition at room temperature for 6 h yielded the diol as diastereomers **12** and **13** in 1: 2.5 ratio, but at −78 °C it gave 3:1 ratio of **12** and **13** which were separated by column chromatography (See Table 1) (Scheme 2).

Probably at higher temperatures less chelation might be occurring and the nucleophilic addition is taking place via the Felkin-Anh model giving rise to **13** as a major product (Fig. 2).

Ring closing metathesis [12] reaction was carried out on **12** using Grubbs II generation catalyst (10 mol%) to give key intermediate **14** [11]. Synthesis of (+)-6-*O*-benzoylzeylenol *ent*-**4**, (+)-uvarigranol E **7** and (+)-uvarigranol F **8** can be obtained from **14** by benzoylation, deprotection of the acetonide and silyl ether groups. For this, different reactions were carried out on **14** to obtain *ent*-**4**, **7** and **8**. All these compounds differ only with number and position of the benzoyl groups, whereas **7** has acetyl group also.

Cleavage of TBDPS ether in **14** with TBAF resulted in the formation of triol **15** [11]. The triol compound **15** converted to tri benzoyl ester **16** [11] with triethylamine, benzoyl chloride and DMAP (cat.). Deprotection of acetonide under acidic conditions gave the target molecule (+)-6-*O*-benzoylzeylenol ***ent*-4** in 80% yield (Scheme 3).

Both allylic hydroxyl groups in **14** were converted to benzoyl ester **17** with triethylamine, benzoyl chloride and DMAP (cat.). Cleavage of TBDPS ether in **17** with TBAF in THF for a period of 4h at room temperature gave regioisomers **18** and **19** in ratio of 1: 2 in 30% and 60% yields respectively (Scheme 4). Compound **19** was a precursor in our earlier synthesis of (–)-zeylenol **1**, whose spectral data [11] matched with the previously synthesized compound. This synthesis of compound **19** is shorter when compared to our previous one and can be obtained from compound **14** in just three steps. Cleavage [13] of TBDPS ether in **17** was carried out using AcOH, TBAF in THF for a period of 1 h at 0 °C to give compound **18** as a sole product in 80% yield. The primary hydroxyl group in **18** was converted to acyl ester **20** with triethylamine, acetic anhydride and DMAP (cat.). Finally, the deprotection of acetonide group in ester **20** was carried out under acidic conditions with TFA/$H_2O$ to give (+)-uvarigranol E **7** (Scheme 4).

To synthesize (+)-uvarigranol F **8**, only the deprotection of acetonide groups and TBDPS ether in **17** was needed. This can be achieved in a single step under strongly acidic conditions but migration of benzoyl groups from one hydroxyl position to another hydroxyl position was previously observed with similar structures [3d,10a,14]. To minimize the formation of undesired reaction products, It was thought to deprotect the acetonide group first then the TBDPS group in compound **17**. For this purpose, compound **17** was treated with TFA/$H_2O$ for a period of 1h at 0 °C to give the diol **21** in 82% yield. Finally, the diol **21** was treated with TBAF in presence of AcOH to remove the silyl group to give (+)-uvarigranol F **8** as a sole product (Scheme 5). Deprotection of silyl and other protecting groups, in cyclic poly hydroxyl acetates or benzoates is tricky, under normal conditions, which results in migration of acyl (benzoyl) groups, probably because of their close proximity. We have really studied and optimized reaction conditions to prevent migration, at the final stages of our synthesis.

## 3. Conclusions

We have successfully developed a common strategy for the synthesis of (–)-zeylenol **1** and their analogs *ent*-**4**, **7**, and **8** using mixed aldol condensation, Grignard addition, ring-closing metathesis, and benzoylation reactions. This is the first report on synthesis of unnatural *ent*-**4**, natural **7** and **8** isomers. Compound **1** is also a common intermediate for making **2**, **3** and **9**. Therefore our approach is general in nature for the synthesis of zeylenol and its related natural products and their analogs in good yields and with high optical purity.

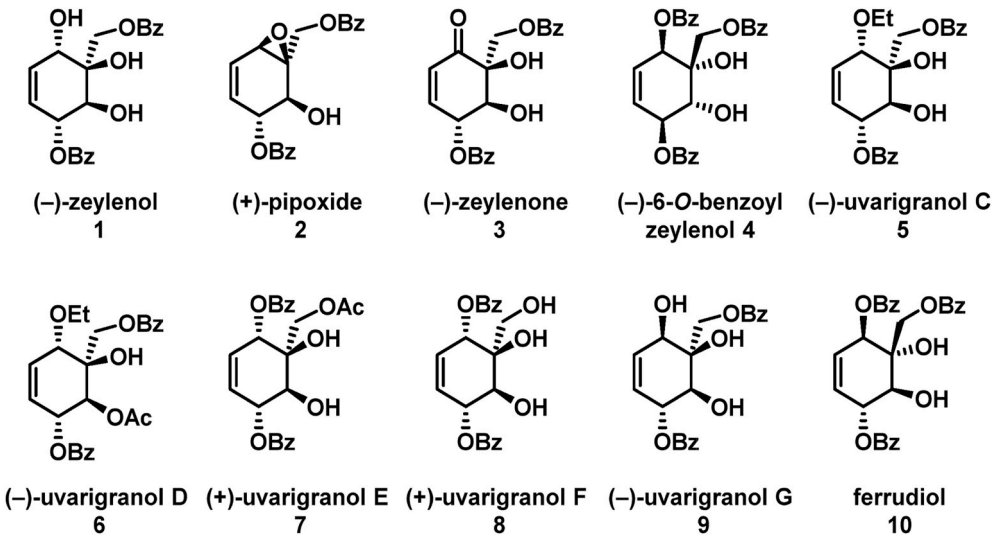
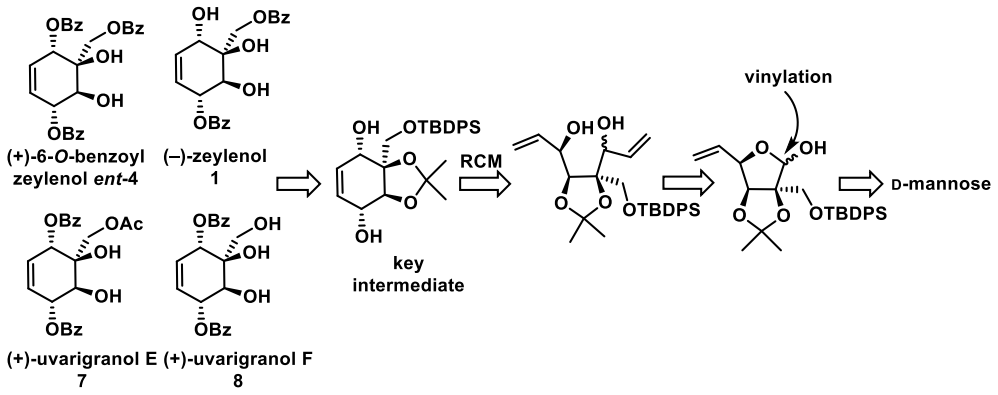



**Fig. 1.** Example of some naturally occurring compounds that belong to the zeylenol family.




**Scheme 1.** Retrosynthetic analysis of (–)-zeylenol **1**, (+)-6-*O*-benzoylzeylenol *ent*-**4**, (+)-uvarigranol E **7** and (+)-uvarigranol F **8**.

**Table 1**
Vinyl Grignard addition on compounds **11**.

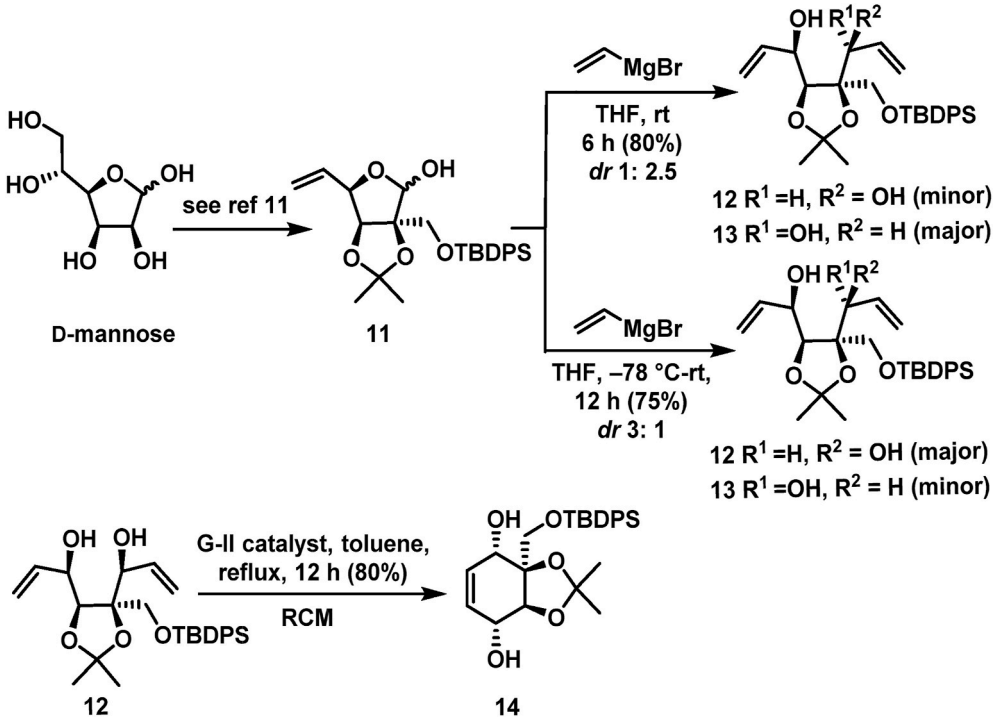
| Entry | Vinyl Grignard (equivalents) | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | 4 | rt | 6 | 80% (*dr*: 1: 2.5) |
| 2 | 4 | −78 °C-rt | 12 | 75% (*dr*: 3: 1) |

## 4. Experimental section

**General Information:** Moisture- and oxygen-sensitive reactions were carried out under nitrogen. All solvents and reagents were purified by standard techniques. All other reagents were obtained from commercial sources and used without further purification. TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness: 0.25 mm). Column chromatography was performed on silica gel (Acme, 60–120 mesh) by using ethyl acetate, hexane, chloroform, and MeOH as eluents. Organic solutions were dried over anhydrous $Na_2SO_4$ and concentrated below 40 °C under reduced pressure. IR spectra were recorded on a Perkin–Elmer RX-1and JASCO FT/IR-5300 FTIR system. NMR spectra were recorded at 300, 400, 500 MHz (H) and 75, 100, 125, 176 MHz (C), respectively. Chemical shifts ($\delta$) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: $\delta = 7.26$ and C: $\delta = 77.16$ ppm) as internal standard, and coupling constants (*J*) are given in Hz. Optical rotations were measured on JASCO P-2000 polarimeter at 20 °C using 50 mm cell of 1 mL capacity. Accurate mass measurements were performed on a Q STAR mass spectrometer (Applied Biosystems, USA).

### 4.1. Procedures for the Grignard reaction

**Procedure A:** To the solution of lactol **11** (0.5 g, 2.17 mmol) in THF (10 mL), 1.0 M THF solution of vinyl magnesium bromide (4.4 mL) was added over 30 min at room temperature under nitrogen. After stirring 2.5 h at room temperature, the mixture was poured into saturated $NH_4Cl$ (20 mL) and extracted with ethyl acetate (50 mL × 3). The collected organic layers were combined, washed with water, brine, then dried over $Na_2SO_4$, concentrated under reduced pressure and purified by column chromatography (hexane: ethyl acetate = 12:1) to afford the corresponding alcohols **12** (0.12 g, 23%) and **13** (0.3 g, 57%) as a yellow




**Scheme 2.** Synthesis of key intermediate **14**.

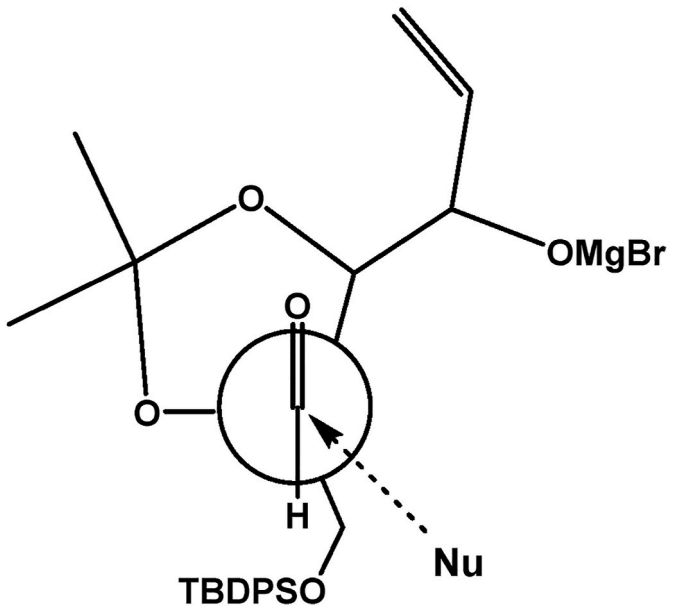



**Fig. 2.** Felkin-Anh model where nucleophile is vinyl Grignard.

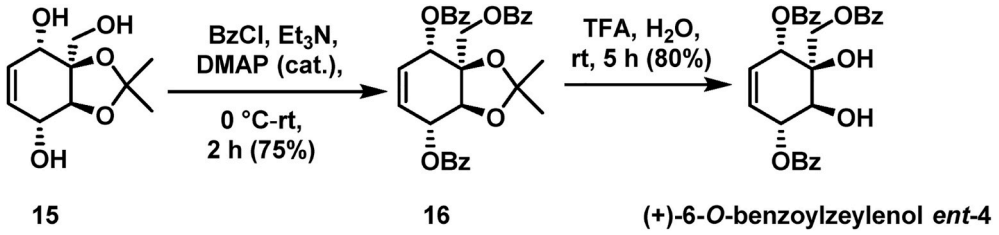
oil in the ratio of 1: 2.5. **Procedure B:** To the solution of lactol **11** (0.5 g, 2.17 mmol) in THF (10 mL), 1.0 M THF solution of vinyl magnesium bromide (4.4 mL) was added over 30 min at −78 °C under nitrogen. After stirring 12 h at room temperature, the mixture was poured into saturated $NH_4Cl$ (20 mL) and extracted with ethyl acetate (50 mL × 3). The collected organic layers were combined, washed with water, brine, then dried over $Na_2SO_4$, concentrated under reduced pressure and purified by column chromatography (hexane: ethyl acetate = 12:1) to afford the corresponding alcohols **12** (0.3 g, 56%) and **13** (0.1 g, 19%) as a yellow oil in the ratio of 3: 1.

**(*S*)-1-((4*R*,5*S*)-4-(((tert-Butyldiphenylsilyl)oxy)methyl)-5-((*R*)-1-hydroxyallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (12):** [11] $[\alpha]_D^{28}$ : +78.2 (*c* 1.5, $CHCl_3$); IR (neat) $\nu_{max}$ : 3391, 2932, 1716, 1427, 1216, 1108, 700 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) : $\delta$ 7.73–7.60 (m, 4H), 7.46–7.36 (m, 6H), 6.06–5.95 (m, 1H), 5.89–5.78 (m, 1H), 5.38 (dt, 1H *J* = 17, 1.2 Hz), 5.28 (dt, 1H *J* = 17, 1.2 Hz), 5.23 (dt, 1H *J* = 10.5, 1.0 Hz), 5.16 (dd, 1H, *J* = 10.3, 1.0 Hz), 4.71–4.64 (m, 1H), 4.47 (d, 1H, *J* = 7.6 Hz), 4.27 (d, 1H, *J* = 2.1 Hz), 3.67 (d, 1H, *J* = 10.3 Hz), 3.51 (d, 3H, *J* = 10.3 Hz), 1.55 (s, 3H), 1.30 (s, 3H), 1.07 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) : $\delta$ 138.2, 135.6, 135.5, 132.5, 132.1, 129.9, 129.8, 127.8, 127.7, 118.3, 116.6, 108.5, 84.4, 83.8, 73.0, 70.0, 67.5, 29.6, 26.8, 26.1, 19.1; ESI-MS (*m/z*) : 505 $(M+Na)^+$; HRMS calcd for $C_{28}H_{38}O_5NaSi$ 505.2380 $(M+Na)^+$, found 505.2389.

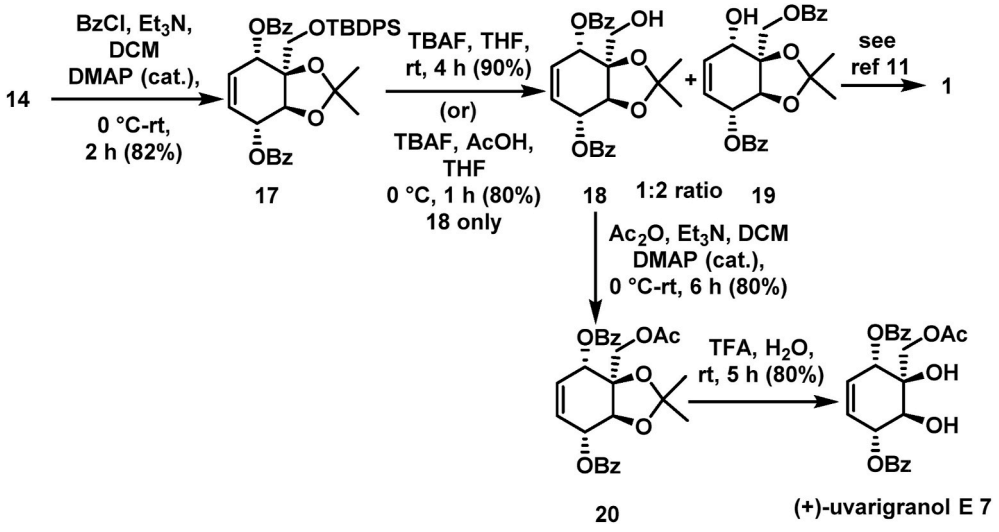
**(1*R*,1′*R*)-1,1′-((4*R*,5*S*)-4-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(prop-2-en-1-ol) (13):** [11] $[\alpha]_D^{28}$ : +38.2 (*c* 1.2, $CHCl_3$); IR (neat) $\nu_{max}$ : 3362, 2932, 1717, 1427, 1216, 1109, 701 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) : $\delta$ 7.73–7.69 (m, 4H), 7.49–7.39 (m, 6H), 6.17–6.01 (m, 2H), 5.49–5.38 (m, 2H), 5.28–5.20 (m, 2H), 4.65 (d, 1H, *J* = 4.6 Hz), 4.56 (s, 1H), 4.30 (m, 1H, *J* = 2.1 Hz), 3.97 (d, 1H, *J* = 11.2 Hz), 3.76 (dd, 1H, *J* = 11.2, 2.5 Hz), 1.52 (s, 3H), 1.38 (s, 3H), 1.09 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) : $\delta$ 138.1, 135.9, 135.5, 135.4, 134.7, 132.3, 132.2, 129.8, 129.7, 129.4, 127.6, 127.5, 115.8, 115.8, 107.6, 83.6, 80.4, 71.9, 69.1, 63.7, 28.1, 26.7, 26.3, 19.0; ESI-MS (*m/z*) : 505 $(M+Na)^+$; HRMS calcd for $C_{28}H_{38}O_5NaSi$ 505.2383 $(M+Na)^+$, found 505.2380.

**(3a*R*,4*S*,7*R*,7a*S*)-3a-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d] [1,3] dioxole-4,7-diol (14):** [11]

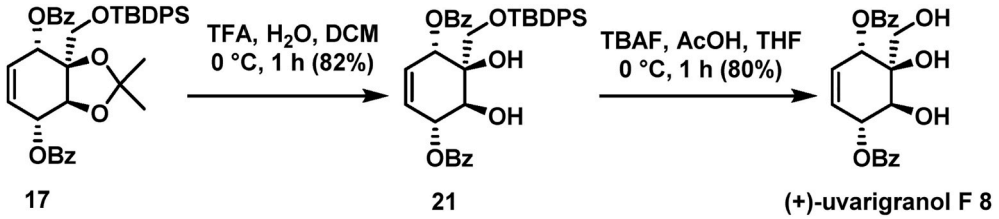
To the solution of diene **12** (1.0 g, 2.0 mmol) in toluene (80 mL), Grubbs' second-generation catalyst (0.176 g, 0.20 mmol) was added at




**Scheme 3.** Synthesis of (+)-6-*O*-benzoylzeylenol ***ent*-4**.




**Scheme 4.** First total synthesis of (+)-uvarigranol E **7**.




**Scheme 5.** Synthesis of (+)-uvarigranol F **8**.

room temperature. Refluxed the reaction mixture for 12 h. Toulene was removed under vacuum, applied for column chromatography (hexane: ethyl acetate = 1:4) to provide cyclohexenol **14** as an oily compound (0.75 g, 80%). $[\alpha]_D^{28}$ : +45.6 (*c* 0.8, $CHCl_3$); IR (neat) $\nu_{max}$ : 3384, 2931, 2857, 1427, 1108 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) : $\delta$ 7.76–7.64 (m, 4H), 7.48–7.37 (m, 6H), 6.14 (dd, 2H, *J* = 3.0, 1.6 Hz), 4.43 (s, 1H), 4.25 (s, 1H), 4.08 (d, 1H, *J* = 3.0 Hz), 4.01 (d, 1H, *J* = 11.2 Hz), 3.87 (d, 1H, *J* = 11.2 Hz), 3.36 (bs 1H), 2.85 (bs 1H), 1.36 (s, 3H), 1.23 (s, 3H), 1.07 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) : $\delta$ 135.8, 135.5, 132.4, 132.2, 132.1, 131.8, 129.9, 127.8, 127.7, 109.6, 84.7, 81.3, 69.8, 68.0, 67.3, 28.0, 27.0, 26.8, 19.1; ESI-MS (*m/z*) : 477 $(M+Na)^+$; HRMS calcd for $C_{26}H_{38}O_5NSi$ 472.2513 $(M+NH_4)^+$, found 472.2515.

**(3a*R*,4*S*,7*R*,7a*S*)-3a-((benzoyloxy)methyl)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*] [1,3] dioxole-4,7-diyl dibenzoate (16):** To a solution of the triol **15** (0.1 g, 0.46 mmol), TEA (0.4 mL, 3 mmol), and a catalytic amount of DMAP in dry $CH_2Cl_2$ (10 mL) was added benzoyl chloride (0.32 mL, 2.7 mmol) at room temperature. The solution was stirred at room temperature for 2 h and poured into saturated aqueous $NH_4Cl$ (10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (30 mL), and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography (hexane: ethyl acetate = 10:1) provided **16** (0.183 g, 75%) as a syrup. $[\alpha]_D^{23}$ : -5.5 (*c* 0.97, $CHCl_3$); IR (neat) $\nu_{max}$ : 2929, 1719, 1248, 1093, 707 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) : $\delta$ 8.13–7.95 (m, 6H), 7.61–7.31 (m, 9H), 6.08–6.00 (m, 2H), 5.95–5.92 (m, 1H), 5.84–5.82 (m, 1H), 4.85 (d, *J* = 12.1 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.65 (d, *J* = 2.0 Hz, 1H), 1.59 (s, 3H), 1.47 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) : $\delta$ 166.05, 165.67, 165.44, 133.36, 133.26, 133.18, 129.81, 129.75, 129.65, 129.61, 129.54, 129.49, 129.40, 128.48, 128.42, 128.34, 126.89, 109.98, 80.80, 78.32, 72.60, 69.75, 63.43, 27.86, 26.86; ESI-MS (*m/z*) : 551 $(M+Na)^+$; HRMS calcd for $C_{31}H_{28}O_8Na$ $[M+Na]^+$ 551.1682 found 551.1677.

**(1*R*,4*S*,5*S*,6*S*)-5-((benzoyloxy)methyl)-5,6-dihydroxycyclohex-2-ene-1,4-diyl dibenzoate (or) (+)-6-*O*-benzoylzeylenol (4):** [10a] To the solution of tribenzoate **16** (0.1 g, 0.19 mmol) in TFA (2 mL) and $H_2O$ (1 mL) was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure to give syrup which was purified by column chromatography (hexane: ethyl acetate = 4:1) to give (+)-6-*O*-benzoylzeylenol **4** in 80% yield (0.073 g) as a white solid. MP : 136-138 °C. {lit [10b]. MP 137-139}; $[\alpha]_D^{23}$ : +58.3 (*c* 0.18, $CHCl_3$). {*enantiomer* lit [10a]. −56 *c* 0.5, $CHCl_3$)}; IR (neat) $\nu_{max}$ : 3464, 2925, 1718, 1264, 1108, 709 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) : $\delta$ 8.13–8.00 (m, 4H), 7.86 (d, *J* = 7.1 Hz, 2H), 7.63–7.30 (m, 9H), 6.14–5.99 (m, 2H), 5.84–5.76 (m, 2H), 4.92 (d, *J* = 12.2 Hz, 1H), 4.63 (d, *J* = 12.2 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$) : $\delta$ 167.19, 167.03, 165.78, 133.62, 133.50, 133.26, 129.86, 129.78, 129.68, 129.36, 129.33, 129.1, 128.54, 128.47, 128.44, 128.33, 126.69, 74.96, 73.40, 71.69, 71.33, 66.79; ESI-MS (*m/z*): 385 $(M+H)^+$, 511 $[M+Na]^+$; HRMS calcd for $C_{28}H_{24}O_8Na$ $[M+Na]^+$ 511.1369 found 511.1351.

**(3a*R*,4*S*,7*R*,7a*S*)-3a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*] [1,3] dioxole-4,7-diyl dibenzoate (17):** To a solution of the alcohol **14** (1 g, 2.2 mmol), TEA (1.4 mL, 9.6 mmol), and a catalytic amount of DMAP in dry $CH_2Cl_2$ (10 mL) was added benzoyl chloride (0.64 mL, 5.5 mmol) at room temperature. The solution was stirred at room temperature for 2 h and poured into saturated aqueous $NH_4Cl$ (10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (50 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and filtered. The concentration of the filtrate followed by flash chromatography (hexane: ethyl acetate = 10:1) provided **17** (1.19 g, 82%) as syrup. $[\alpha]_D^{23}$ = +33.9 (*c* 0.41, $CHCl_3$); IR (neat) $\nu_{max}$ : 2930,1720, 1247, 1092, 703 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) : $\delta$ 8.07 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.80 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.69 (ddd, *J* = 8.0, 2.9, 1.3 Hz, 4H), 7.60–7.55 (m, 1H), 7.55–7.50 (m, 1H), 7.42–7.38 (m, 4H), 7.34–7.30 (m, 6H), 6.01–5.96 (m, 1H), 5.96–5.92 (m, 1H), 5.82–5.78 (m, 1H), 5.76 (dd, *J* = 4.1, 2.0 Hz, 1H), 4.86 (d, *J* = 1.4 Hz, 1H), 4.14 (d, *J* = 11.3 Hz, 1H), 3.89 (d, *J* = 11.3 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.02 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) : $\delta$ 165.66, 165.64, 135.67, 133.21, 133.04, 130.04, 129.84, 129.72, 129.70, 128.36, 128.29, 127.70, 127.67, 126.89, 109.33, 82.84, 77.24, 73.02, 70.76, 63.23, 28.02, 27.12, 26.66, 19.17; ESI-MS (*m/z*) : 685 $[M+Na]^+$; HRMS calcd for $C_{40}H_{42}O_7NaSi$ $[M+Na]^+$ 685.2597, found 685.2581.

### 4.2. Procedures for the compounds 18 and 19

**Procedure A:** To an ice cooled stirred solution of silyl compound **17** (0.5 g, 0.75 mmol) in THF (10 mL) was added TBAF (1.1 mL, 1 M solution in THF, 1.13 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 4 h. It was quenched with saturated $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (100 mL). The combined organic fractions were collected and washed with water and brine, then dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane: ethyl acetate = 10:1) to afford compound **18** (96 mg, 30%) & **19** [11] (192 mg, 60%) in overall 90% yield as a viscous liquid. **Procedure B:** To a solution of compound **17** (100 mg, 0.15 mmol) and acetic acid (25 μL, 0.45 mmol) in THF (1.4 mL) was added TBAF (1.0 M solution in THF, 450 μL, 0.45 mmol) at 0 °C. The mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure to give syrup which was purified by column chromatography (hexane: ethyl acetate = 4:1) to give compound **18** in 80% yield (51 mg) as syrup.

**(3a*R*,4*S*,7*R*,7a*S*)-3a-(hydroxymethyl)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*] [1,3] dioxole-4,7-diyl dibenzoate (18):** $[\alpha]_D^{28}$ : -8.7 (*c* 1.35, $CHCl_3$); IR (neat) $\nu_{max}$ : 2927, 1720, 1259, 1097, 708 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) : $\delta$ 8.11–8.02 (m, 4H), 7.63–7.56 (m, 2H), 7.49–7.41 (m, 4H), 6.03–5.99 (m, 1H), 5.98–5.97 (m, 1H), 5.86 (dd, *J* = 4.1, 2.0 Hz, 1H), 5.77–5.75 (m, 1H), 4.64 (dd, *J* = 2.2, 0.7 Hz, 1H), 4.18 (d, *J* = 12.3 Hz, 1H), 3.82 (d, *J* = 12.3 Hz, 1H), 1.57 (s, 3H), 1.47 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) : $\delta$ 165.66, 165.57, 133.62, 133.33, 130.13, 129.83, 129.75, 129.62, 129.57, 129.44, 128.43, 127.32, 109.67, 82.74, 77.34, 72.25, 70.41, 60.86, 27.91, 26.96; ESI-MS (*m/z*) : 447 $[M+Na]^+$; HRMS calcd for $C_{24}H_{24}O_7Na$ $[M+Na]^+$ 447.1420 found 447.1411.

**((3a*R*,4*S*,7*R*,7a*S*)-7-(benzoyloxy)-4-hydroxy-2,2-dimethyl-7,7a-dihydrobenzo[d] [1,3] dioxol-3a(4H)-yl)methyl benzoate (19):** [11] $[\alpha]_D^{28}$ : +122 (*c* 1.6, $CHCl_3$); IR (neat) $\nu_{max}$ : 3392, 2926, 1714, 1249,1023, 709 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) : $\delta$ 8.07–7.98 (m, 4H), 7.58–7.51 (m, 2H), 7.42–7.35 (m, 4H), 6.03 (dt, 1H, *J* = 2.2, 10.2 Hz), 5.83 (dt, 1H, *J* = 2.2, 10.2 Hz), 5.73 (t, 1H, *J* = 2.2 Hz), 4.78 (d, 1H, *J* = 12.4 Hz), 4.52–4.48 (m, 2H), 4.45 (dd, *J* = 4.8, 2.4 Hz, 1H), 1.53 (s, 3H),

1.45 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) : $\delta$ 166.3, 165.5, 133.3, 133.1, 132.4, 129.7, 129.6, 129.2, 128.4, 125.7, 109.9, 82.6, 79.0, 71.6, 71.0, 63.4, 28.2, 26.8; ESI-MS ($m/z$) : 447 $(M+Na)^+$; HRMS calcd for $C_{24}H_{24}O_7$ $(M+H)^+$ 424.3325, found 424.3320.

**(3a*R*,4*S*,7*R*,7a*S*)-3a-(acetoxymethyl)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*] [1,3] dioxole-4,7-diyl dibenzoate (20):** To compound **18** (80 mg, 0.18 mmol) in DCM (2 mL) were added triethylamine (78 μL, 0.56 mmol), acetic anhydride (26 μL, 0.28 mmol) and a few crystals of DMAP (cat.) and the reaction mixture was stirred for 6 h at room temperature. Then methanol (1 mL) was added, and stirring was continued for 15 min. The solution was diluted with HCl (0.1 N, 0.1 mL), the two layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with DCM (10 mL). The total organic extracts were combined and dried using anhydrous $Na_2SO_4$ and concentrated at reduced pressure to give a residue. The residue was purified on column (hexane: ethyl acetate = 5:1) to afford **20** (70 mg, 80%) as a colorless oil. $[\alpha]_D^{28}$ : +128.8 (*c* 0.5, $CHCl_3$); IR (neat) $\nu_{max}$ : 2923, 1723, 1252, 1096, 711 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) : $\delta$ 8.07–8.03 (m, 4H), 7.62–7.56 (m, 2H), 7.48–7.40 (m, 4H), 6.04–5.99 (m, 2H), 5.83–5.81 (m, 1H), 5.78–5.76 (m, 1H), 4.66 (d, $J$ = 12.1 Hz, 1H), 4.52 (d, $J$ = 2.3 Hz, 1H), 4.41 (d, $J$ = 12.1 Hz, 1H), 2.03 (s, 3H), 1.55 (s, 3H), 1.46 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) : $\delta$ 170.49, 165.61, 165.44, 133.39, 129.79, 129.61, 129.54, 129.48, 128.48, 127.30, 110.06, 77.93, 77.56, 72.30, 69.93, 62.97, 27.87, 26.70, 20.79; ESI-MS ($m/z$) : 489 $[M+H]^+$; HRMS calcd for $C_{26}H_{26}O_8Na$ $[M+H]^+$ 489.1525 found 489.1518.

**(1*R*,4*S*,5*S*,6*S*)-5-(acetoxymethyl)-5,6-dihydroxycyclohex-2-ene-1,4-diyl dibenzoate (or) (+)-uvarigranol E (7):** [5d] To compound **20** (50 mg, 0.107 mmol) in TFA (1 mL) and $H_2O$ (0.5 mL) was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure to give syrup which was purified by column chromatography (hexane: ethyl acetate = 4:1) to give (+)-uvarigranol E **7** in 80% yield (36 mg) as a syrup. $[\alpha]_D^{23}$ : +24.6 (*c* 0.1, $CH_3OH$). {lit.[5d] + 23 *c* 0.5, $CH_3OH$)}; IR (neat) $\nu_{max}$ : 3464, 2924, 1718, 1261, 1096, 701 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) : $\delta$ 8.11–8.02 (m, 4H), 7.60 (td, $J$ = 7.3, 1.4 Hz, 2H), 7.47 (td, $J$ = 7.9, 3.1 Hz, 4H), 6.06 (ddd, $J$ = 10.1, 3.8, 1.5 Hz, 1H), 6.00 (dd, $J$ = 10.1, 2.6 Hz, 1H), 5.79–5.75 (m, 1H), 5.68 (d, $J$ = 3.8 Hz, 1H), 4.62 (d, $J$ = 12.2 Hz, 1H), 4.41 (d, $J$ = 12.2 Hz, 1H), 4.24 (d, $J$ = 6.1 Hz, 1H), 1.89 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) : $\delta$ 171.65, 167.02, 165.76, 133.56, 129.87, 129.74, 129.37, 128.64, 128.57, 128.51, 126.55, 74.72, 73.39, 71.64, 71.03, 66.44, 20.53; ESI-MS ($m/z$) : 449 $[M+Na]^+$; HRMS calcd for $C_{23}H_{22}O_8Na$ $[M+Na]^+$ 449.1212 found 449.1209.

**(1*R*,4*S*,5*S*,6*S*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-5,6-dihydroxycyclohex-2-ene-1,4-diyl dibenzoate (21):** Compound **17** (0.1 g, 0.15 mmol) dissolved in DCM (1 mL). To this TFA (2 mL) and $H_2O$ (1 mL) was added at 0 °C stirred for 1 h. The reaction mixture was concentrated under reduced pressure to give syrup which was purified by column chromatography (hexane: ethyl acetate = 5:1) to give diol **21** in 82% yield (0.077 g) as a syrup. $[\alpha]_D^{23}$ : +42.8 (*c* 0.30, $CHCl_3$); IR (neat) $\nu_{max}$ : 2926, 1719, 1262, 1108, 746 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.06 (ddd, $J$ = 7.7, 6.3, 1.5 Hz, 2H), 7.97–7.91 (m, 2H), 7.63–7.54 (m, 4H), 7.47–7.32 (m, 9H), 7.24–7.21 (m, 1H), 7.04 (t, $J$ = 7.7 Hz, 2H), 6.15 (ddd, $J$ = 10.1, 4.5, 2.0 Hz, 1H), 5.97 (dd, $J$ = 10.1, 2.3 Hz, 1H), 5.85 (dt, $J$ = 3.5, 2.0 Hz, 1H), 5.63 (t, $J$ = 4.7 Hz, 1H), 4.15–4.05 (m, 2H), 3.99 (d, $J$ = 10.6 Hz, 1H), 1.00 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) : $\delta$ 167.06, 165.01, 135.49, 135.39, 133.28, 133.18, 130.11, 129.95, 129.86, 129.72, 128.46, 128.37, 127.87, 127.63, 125.52, 75.70, 74.30, 71.36, 70.10, 64.63, 26.74, 19.14; ESI-MS ($m/z$) : 645 $[M+Na]^+$; HRMS calcd for $C_{37}H_{38}O_7SiNa$ $[M+Na]^+$ 645.2284 found 645.2286.

**(1*R*,4*S*,5*S*,6*S*)-5,6-dihydroxy-5-(hydroxymethyl)cyclohex-2-ene-1,4-diyl dibenzoate (or) (+)-Uvarigranol F (8):** [5d,10a] To a solution of compound **21** (60 mg, 0.096 mmol) and acetic acid (16 μL, 0.29 mmol) in THF (1.4 mL) was added TBAF (1.0 M solution in THF, 29 μL, 0.29 mmol) at 0 °C. The mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure to give syrup which was purified by column chromatography (hexane: ethyl acetate = 4:1) to give (+)-uvarigranol F **8** in 80% yield (29 mg) as syrup. $[\alpha]_D^{23}$ : +70.7 (*c* 0.21, $CHCl_3$) {lit [5d]. +58.2 (*c* 0.05, $CHCl_3$)}; IR (neat) $\nu_{max}$ : 3463, 2924, 1716, 1263, 1107, 710 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) : $\delta$ 8.11 (d, $J$ = 7.2 Hz, 2H), 8.04 (d, $J$ = 7.2 Hz, 2H), 7.61 (t, $J$ = 7.3 Hz, 2H), 7.47 (t, $J$ = 7.7 Hz, 4H), 6.05 (m, 2H), 5.83 (d, $J$ = 7.2 Hz, 1H), 5.52 (d, $J$ = 3.5 Hz, 1H), 4.23 (d, $J$ = 7.4 Hz, 1H), 4.10 (d, $J$ = 12.2 Hz, 1H), 3.67 (d, $J$ = 12.2 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) : $\delta$ 167.77, 166.18, 133.68, 133.61, 130.24, 129.95, 129.84, 129.38, 129.17, 128.60, 128.51, 125.64, 74.79, 73.85, 73.34, 71.66, 64.79; ESI-MS ($m/z$) : 385 $[M+H]^+$; HRMS calcd for $C_{21}H_{21}O_7$ $[M+H]^+$ 385.1281, found 385.1285.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

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## References

[1] a) L. Yong-Hong, X. Li-Zhen, Y. Shi-Lin, D. Jie, Z. Yong-Su, Z. Min, S. Nan-Jun, Phytochemistry 45 (1997) 729;
b) S. Hongthong, C. Kuhakarn, T. Jaipetch, S. Prabpai, P. Kongsaeree, P. Piyachaturawat, S. Jariyawat, K. Suksen, J. Limthongkul, A. Panthong, N. Nuntasaen, V. Reutrakul, Fitoterapia 106 (2015) 158;
c) S. Yang, Y. Liao, L. Li, X. Xu, L. Cao, Molecules 23 (2018) 2149;
d) Z. Sun, S. Yang, C. Xu, G. Ma, L. Cao, Y. Tian, J. Lin, Preprints 3 (2019) 1;
e) Y. Takeuchi, Q. Cheng, Q.-W. Shi, T. Sugiyama, T. Oritani, Biosci. Biotechnol. Biochem. 65 (2001) 1395;
f) S. Lallo, S. Lee, D.F. Dibwe, Y. Tezuka, H. Morita, Nat. Prod. Res. 28 (2014) 1754.

[2] a) R. Lekphrom, K. Kanokmedhakul, F. Schevenels, S. Kanokmedhakul, Fitoterapia 127 (2018) 420;
b) S. Awale, J.Y. Ueda, S. Athikomkulchai, D.F. Dibwe, S. Abdelhamed, S. Yokoyama, I. Saiki, R. Miyatake, J. Nat. Prod. 75 (2012) 1999;
c) S. Awale, A.M. Tawila, D.F. Dibwe, J.y. Ueda, S. Sun, S. Athikomkulchai, C. Balachandran, I. Saiki, K. Matsumoto, H. Esumi, Bioorg. Med. Chem. Lett 27 (2017) 1967;
d) W. Kaweetripob, C. Mahidol, H. Prawat, S. Ruchirawat, Phytochem. Lett. 12 (2015) 248;
e) P. Meesakul, S.G. Pyne, S. Laphookhieo, Nat. Prod. Res. 34 (2020) 2495;
f) A.P.G. Macabeo, A.I.G. Flores, R.A.T. Fernandez, S. Budde, C. Faderl, H.-M. Dahse, S.G. Franzblau, Nat. Prod. Res. (2020) 1, 0.

[3] a) D.V. Ho, T. Kodama, H.T.B. Le, K.V. Phan, T.T. Do, T.H. Bui, A.T. Le, N.N. Win, H. Imagawa, T. Ito, H. Morita, H.T. Nguyen, Bioorg. Med. Chem. Lett 25 (2015) 3246;
b) T. Jaipetch, S. Hongthong, C. Kuhakarn, P. Pailee, P. Piyachaturawat, K. Suksen, P. Kongsaeree, S. Prabpai, N. Nuntasaen, V. Reutrakul, Fitoterapia 137 (2019), 104182;
c) C. Auranwiwat, P. Wongsomboon, T. Thaima, R. Rattanajak, S. Kamchonwongpaisan, A.C. Willis, W. Lie, S.G. Pyne, T. Limtharakul, Fitoterapia 120 (2017) 103;
d) O. Pancharoen, P. Tuntiwachwuttikul, W.C. Taylor, Phytochemistry 28 (1989) 1143;
e) L. Zhang, X. Huo, Y. Liao, F. Yang, L. Gao, L. Cao, Sci. Rep. 7 (2017) 1669.

[4] S.D. Jolad, J.J. Hoffmann, K.H. Schram, J.R. Cole, M.S. Tempesta, R.B. Bates, J. Org. Chem. 46 (1981) 4267.

[5] a) P. Seangphakdee, W. Pompimon, P. Meepowpan, A. Panthong, N. Chiranthanut, R. Banjerdpongchai, B. Wudtiwai, N. Nuntasaen, S. Pitchuanchom, Sci. Asia 39

(2013) 610;
b) V.S. Parmar, O.D. Tyagi, A. Malhotra, S.K. Singh, K.S. Bisht, R. Jain, Nat. Prod. Rep. 11 (1994) 219;
c) S. Lallo, S. Lee, D.F. Dibwe, Y. Tezuka, H. Morita, Nat. Prod. Res. 28 (2014) 1754;
d) X.P. Pan, D.Q. Yu, K.H. Lee, Chin. Chem. Lett. 7 (1996) 241;
e) P.C. Stevenson, N.C. Veitch, M.S.J. Simmonds, Phytochemistry 68 (2007) 1579.
[6] Z. Cao, R. Chen, F. Zhao, X. Li, J. Kang, X. Pan, CN 105687180A (2016) and CN 105687180B (2018).
[7] See website. https://www.protheragen.com/available-projects/polyoxygenated-cyclohexene-compound-4.
[8] a) X. Huo, Y. Liao, Y. Tian, L. Gao, L. Cao, RSC Adv. 6 (2016), 114096;
b) L. Zhang, J. Jin, L. Zhang, R. Hu, L. Gao, X. Huo, D. Liu, X. Ma, C. Wang, J. Han, L. Li, X. Sun, L.J. Cao, Proteomics 126 (2015) 279;
c) S. Zeng, B. Zhu, J. Zeng, W. Wu, C. Jiang, Mol. Med. Rep. 18 (2018) 5572.
[9] a) S. Ogawa, T. Takagaki, J. Org. Chem. 50 (1985) 2356;
b) K. Hiroya, K. Ogasawara, Chem. Commun. (1999) 2197.c)K. Hiroya, M. Honzumi, T. Kamikubo, H. Nakashima, T. Taniguchi, K. Ogasawara, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu. 1999, 41,331.
[10] a) M.J. Palframan, G. Kociok-Köhn, S.E. Lewis, Chem. Eur J. 18 (2012) 4766;
b) P.S. Reddy, G.V.M. Sharma, Synthesis 46 (2014) 1532.
[11] A. Vinaykumar, C. Muniraju, B.V. Rao, Tetrahedron Lett. 58 (2017) 1075.
[12] M. Scholl, S. Ding, C.W. Lee, R.H. Grubbs, Org. Lett. 1 (1999) 953.
[13] Y. Yamamoto, T. Itoh, K. Yamamoto, Org. Biomol. Chem. 15 (2017) 8186.
[14] E.J. Corey, A. Guzman-Perez, M.C. Noe, J. Am. Chem. Soc. 117 (1995), 10805.