The First Total Synthesis of Tarennane, a Potent Antioxidant Chalcone Constituent from Tarenna Attenuate or Magnolia Officinalis

Jincheng Yang[†,a,b], Tao Yang[†,a], Youfu Luo[a], Jun He[b], Jianyou Shi[c] and Aihua Peng*[,a]

[a]*State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan 610041, P.R. China*

[b]*West China School of Pharmacy, Sichuan University, Chengdu, 610041, P.R. China*

[c]*Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, 610041, P.R. China*

Received September 10, 2010: Revised February 17, 2011: Accepted February 21, 2011

Abstract: The convergent total synthesis of tarennane has been accomplished in six steps starting from commercially available phloroglucinol and guaiacol; the key step of the synthesis relies on a highly regioselective Heck reaction applying iodophenol and $PdCl_2(PPh_3)_2$.

Keywords: Tarennane, total synthesis, heck reaction, antioxidant activity.

INTRODUCTION

A variety of important biological compounds with the central scaffold of aromatic ketone are known collectively as chalcones. It is shown that these compounds possess antifungal, antitumor and anti-inflammatory properties [1]. Cardamonin (**2**, Fig. **1**), isolated from *Alpinia rafflesiana*, inhibits pro-inflammatory mediators in activated RAW 264.7 cells and whole blood [2]. Cochinchinenone **3** from *Dracaena cochinchinensis* shows growth inhibitory effects against *Helicobacter pylori* (ATCC43504) [3]. Compound **4**, an analogue of chalcones from trunk exudates of *Dalbergia sissoo* is one of the most potent NO production inhibitors [4].

Tarennane **1**, a novel chalcone constituent whose ring A was converted to a quinol ether moiety, was first isolated in 2007 from the whole plants of *Tarenna attenuata* (Voigt) Hutchins [5]. Xian-Wen Yang *et al*. reported its potent antioxidant activities against H_2O_2-induced impairment in PC12 cells *in vitro* [5]. In 2009, Chien-Chang Shen *et al*. isolated tarennane in minor quantities from the bark of *Magnolia officinalis* [6]. Therein it was wrongly regarded as a novel compound and named as Magnolianone for its special plant origin. To further investigate the broad biological activities, efficient chemical syntheses of tarennane will be necessary for both *in vitro* and *in vivo* test.

However, none of the synthetic routes reported for chalcones and the analogues [7] is probably practicable for the type of Tarennane. To the best of our knowledge, it is noteworthy that the connection of one aromatic ring with another non-aromatic ring has rarely been investigated. We speculate that the absence of tarennane in the literature compared to the hundreds of synthesized chalcones is due to the lack of a facile synthetic access to this type of compounds, since their indirect potent antioxidant effects as well as other biological activities could be of interest in medical and pharmaceutical science.

In this letter, we describe a facile synthesis of tarennane. Retrosynthetic analysis for tarennane (Scheme **1**) scaffold can be divided into three parts: (i) ring B with one phenolic hydroxyl group at the para-position and a methoxy group next to it; (ii) ring A with one carbonyl group at the para-position and three methoxy groups; (iii) one propylene chain as the connection part.

Our synthesis started with etherification of phloroglucinol **7** with Me_2SO_4 and K_2CO_3 in methanol to produce 1,3,5-Trimethoxybenzene (**8**; Scheme **2**). Then **8** was oxidized by 30% H_2O_2 in the presence of $K_4Fe(CN)_6$ and AcOH at room temperature to get **9** **[**8**]**. Allyltrimethylsilane **10** was added into the CH_2Cl_2 solution of **9** at -80°C to produce **11** in less than half an hour [9]. Experimentally, the low temperature is advantageous for the formation of the target intermediate **11** without or with little production of byproduct_ (4-allyl-2,6-dimethoxy-4-hydroxyl-cyclohexa-2,5-dienone). However, at this step the major isomer of **11** did not need to be separated. Then **11** was methylated directly with Me_2SO_4 in the mixture of sodium hydroxide aqueous solution, toluene and tetrabutylammonium bromide at room temperature to afford the key intermediate **12** [10]. At this stage, the methylation step made the minor isomer of **11** can be easily removed by column chromatography and thus **12** was obtained in an overall yield of 48% over two steps from **9**.

Another key intermediate **14** was obtained from iodization of guaiacol **13** with NaI, NaOH, NaClO in methanol at -5°C [11]. Here the temperature control was the one of the key factors for this reaction. Otherwise, the undesired regioisomer 2-iodo-6-methoxyphenol and 2,4-diiodo-6-methoxyphenol would take a heavy ratio in the products. For instance, if the reaction was taken at room

*Address correspondence to this author at the State Key Laboratory of Biotherapy, Chengdu, 610041, P.R. China; Tel: +862880366761; Fax: +862885164060; E-mail: Peng_aihua@163.com

[†]These authors corresponding equally to this work.

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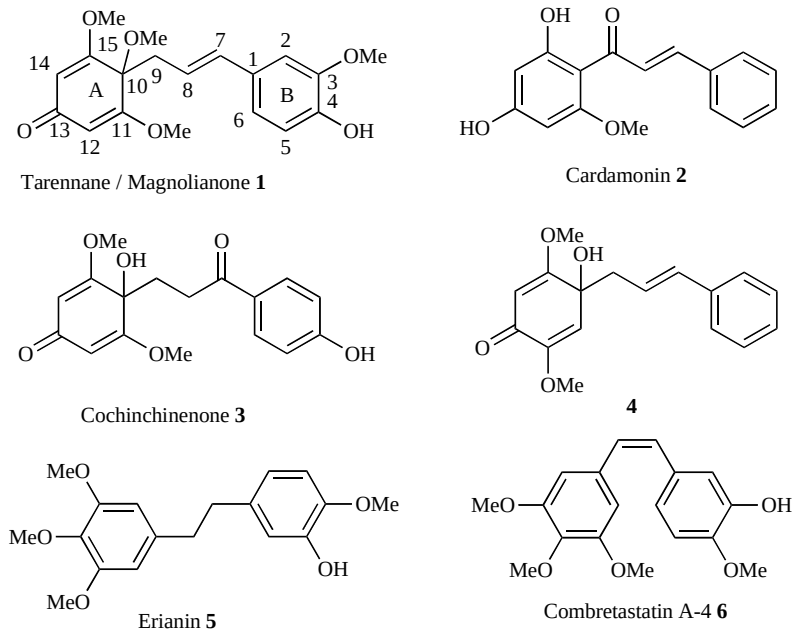
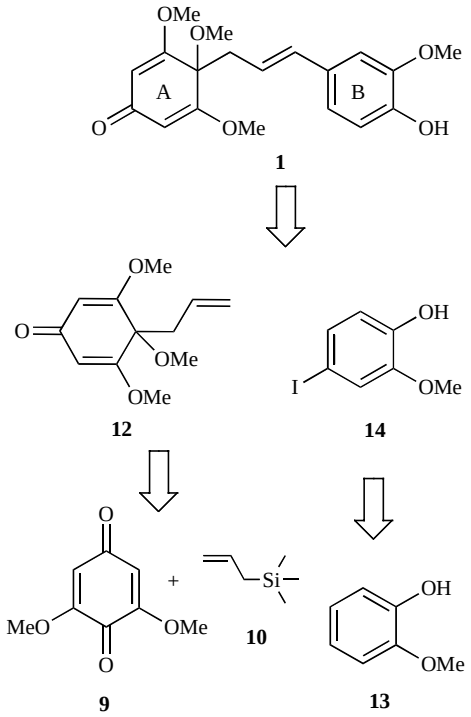


Fig. (1). Tarennane **1** and its analogues.

temperature, the ratio of 2-iodo-6-methoxyphenol might rise up to 30%.



Scheme 1. Retrosynthetic analysis.

At the final connection **12** and **14**, we tried several Heck coupling conditions (Table **1**). Finally, the target tarennane **1** was constructed with triethylamine, $PdCl_2(PPh_3)_2$ and lithium chloride anhydrous in DMF at 90°C for 50 h under argon [12].

Since the structural similarity of tarennane **1** with erianin **5** and combretastatin A-4 **6**, tarennane synthesized in this strategy was evaluated for the antitumor effects compared with **5** and **6** in HepG2 cell lines and A549 cell lines. However, it did not exhibited inhibition in a certain degree with IC_{50}>100μM.

EXPERIMENTAL SECTION

Material and Methods

All commercial chemicals and solvents are reagent grade and were used without further treatment unless otherwise noted. Analytical thin-layer chromatography was performed on GF 254; Qingdao Haiyang company. Melting points were obtained in open capillary tubes and are not corrected. The ^{1}H NMR (400 MHz) spectra were recorded on a Varian Mercury- 400 High Performance Digital FT-NMR with TMS as internal standard, chemical shifts were reported in parts per million (ppm, d) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). HRMS was carried out on Waters Q-TOF Premier mass spectrometry which coupled with an electrospray ionization source. The electrospray ionization source was operated in positive/negative ion mode with a spray voltage of 2.8 kV. Source temperature was set at 90°C. Nitrogen was used as vacuum gas and maintained at 0.36 Bar. In the analysis, the sample was directly injected into mass spectrometry at a flow rate of 3μl/min.

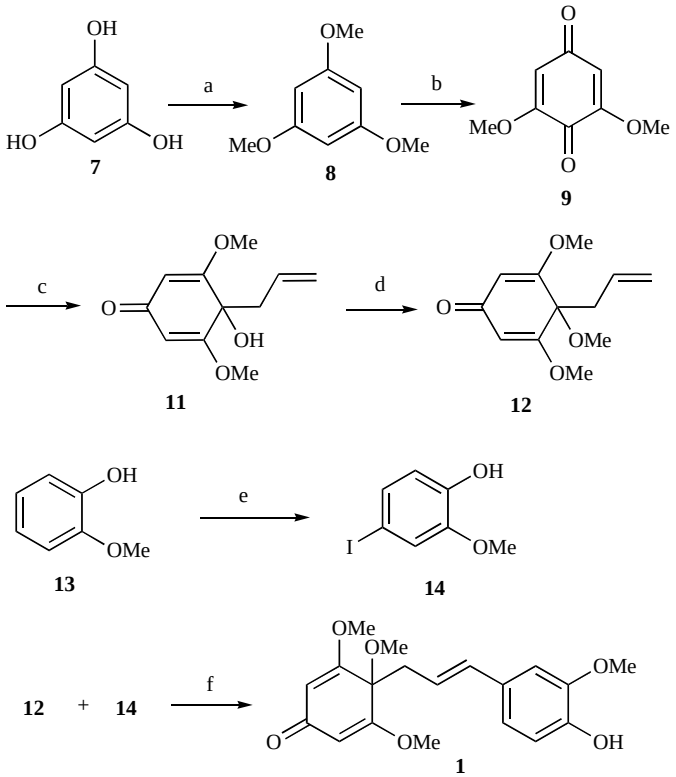
General Synthetic Procedure

Synthesis of 1, 3, 5-trimethoxybenzene (8)

Phloroglucinol dehydrate **7** (27g, 166.67mmol) was mixed with K_2CO_3 (73.6g, 533.33mmol) in the solvent of acetone (ca 300mL). At room temperature, the dimethyl sulfate (50.5mL, 533.33mmol) was dropped into the reaction bottle. When adding over, the reaction temperature was kept

Table 1. The Optimization for the Last Step of Heck Coupling Reaction

Entry	Catalyst	Alkali	Solvent	Temp (°C)	Yield (%)
1	$Pd(OAc)_2$/ PPh_3	Et_3N	DMF	80	10
2	$Pd(OAc)_2$/PPh_3	piperidine	DMF	100	15
3	$Pd(OAc)_2$ /PPh_3	K_2CO_3	DMF	100	8
4	$Pd(OAc)_2$/$(o\text{-}tol)_3P$	K_2CO_3	DMF	100	20
5	$Pd(OAc)_2$/$(o\text{-}tol)_3P$	Et_3N	Toluene	110	12
6	$Pd_2(dBa)_3$ / TBAB	-----	THF/EtOH	25	0
7	$PdCl_2(PPh_3)_2$/LiCl	Et_3N	DMF	90	54



Scheme 2. Reagents and conditions: (a)Me_2SO_4, MeOH, K_2CO_3, ref 90%; (b)H_2O_2, $K_4Fe(CN)_6$, AcOH, rt 60%; (c) allyltrimethylsilane **10**, $TiCl_4$, DCM, -78°C to rt 80%; (d) Me_2SO_4, NaOH, n-Bu_4NBr, tol, rt 60%; (e)NaI, NaOH, NaClO, MeOH, -5°C 70%.;(f) $PdCl_2(PPh_3)_2$ 10mol%, LiCl, Et_3N, DMF, 90°C 54%.

at 60°C for 24 h. Then the mixture was filtered, the filtrate was concentrated and washed with basic water (3×100mL) to obtain **8** (25.3g, 90.2%) as a light yellow solid. TLC: R_f = 0.5 (petroleum/acetone 3:1) mp. 49-50°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 6.08 (s, 3H), 3.77 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 161.5, 92.8, 55.3; MS (EI) *m/z* 168 (M+); HRMS (EI+) m/z calculated for $C_9H_{12}O_3$ 168.0786, found 168.0784.

Synthesis of 2, 6-dimethoxycyclohexa-2, 5-diene-1, 4-dione (9)

1, 3, 5-trimethoxybenzene **8** (13.12g, 78.10mmol) was dissolved in CH_3COOH (ca. 50mL) and cooled with ice-water. Then 30% H_2O_2 (24mL, 234.30mmol) was added into this black solution, which turned into yellow with a little white bubble on the surface. About 2 h later, this solution was filtered, and the cake was washed with distilled water (2×100 mL) as well as 60-90°C petroleum ether (3×100 mL). The yellow solid was the product. (7.88g, 60%) TLC: R_f = 0.06 (petroleum/acetone 3:1) mp. 254-256°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 5.86 (s, 2H), 3.83 (s, 6H); MS (EI) *m/z* 168 (M+); HRMS (EI+) *m/z* calculated for [MNa^+] $C_8H_8O_4Na^+$ 191.0320, found 191.0308.

Synthesis of 4-allyl-4-hydroxy-3, 5-dimethoxycyclohexa-2, 5-dienone (11)

2, 6-dimethoxycyclohexa-2, 5-diene-1, 4-dione **9** (5g, 29.76 mmol) was added into DCM (*ca*. 20mL) under argon. The reaction mixture was cooled to -78°C. Ten minutes later, the solution was added $TiCl_4$ (2mL, 14.88mmol). At this moment, the solution became blood red. Six minutes later, the allyltrimethylsilane **10** (4.84mL, 30.50mmol) was added. Then the temperature of the solution rised heavily, the

Table 2. The Comparison of the Synthetic Tarennane with Natural Tarennane and Natural Magnolianone

Position	natural magnolianone (acetone-d_6)		natural tarennane (CD_3OD)		synthetic tarennane ($CDCl_3$)	
	^{13}C 125MHz	^{1}H 500MHz	^{13}C 100MHz	^{1}H 500MHz	^{13}C 100MHz	^{1}H 400MHz
3-OCH_3	56.2	3.78	56.3	3.79	56.3	3.87
10-OCH_3	52.3	3.03	53.0	3.08	52.7	3.14
11,15-OCH_3	56.5	3.80	57.0	3.82	55.9	3.80
13	186.4		190.0		187.1	
12,14-CH	105.1	5.54	104.8	5.64	104.4	5.63
11,15	169.6		172.3		169.2	
10	80.0		81.0		79.2	
9-CH_2	40.7	2.78 d(7.5)	41.6	2.79 d(7.6)	40.4	2.88 d(7.2)
8-CH	120.1	5.67 m	119.0	5.57 dt (15.6,7.6)	119.1	5.57 m
7-CH	134.7	6.29d(15.5)	135.8	6.25 d(15.6)	134.0	6.29 d(15.2)
6-CH	120.2	6.73dd (8.0,1.5)	120.8	6.66 d(8.2)	119.9	6.72 m
5-CH	115.7	6.69 d(8.0)	116.6	6.64 d(8.2)	114.3	
4	147.2		149.0		145.4	
3	148.3		149.4		146.5	
2-CH	110.4	6.85 d(1.5)	110.5	6.76	108.2	6.80 m
1	130.3		129.8		129.5	

tempreture was kept under -50°C. Fifiteen minutes later, the bottle was put out to room temperature and added H_2O (30mL). The organic layer was separated and washed with water (3×50mL) and then brine (1×50mL) and dry over anhydrous Na_2SO_4. After the organic layer was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (petroleum/acetone 5:1) to afford **11** (5.04 g, 80.6%) as khaki solid. TLC: R_f = 0.1 (petroleum/acetone 3:1) R_f = 0.4 (petroleum/acetone 1:1) mp. 62-64°C ^{1}H NMR (400 MHz, $CDCl_3$, δ) 5.44 (s, 2H), 5.40 (m, 1H), 5.04 (m, 2H), 3.78 (s, 6H), 2.77 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 186.8, 157.3, 135.2, 125.0, 107.4, 58.5, 32.2; MS (EI) *m/z* 210 (M+); HRMS (EI+) *m/z* calculated for [MNa^+] $C_{11}H_{14}O_4Na^+$ 233.0790, found 233.0780.

Synthesis of 4-allyl-3, 4, 5-trimethoxycyclohexa-2, 5-dienone (12)

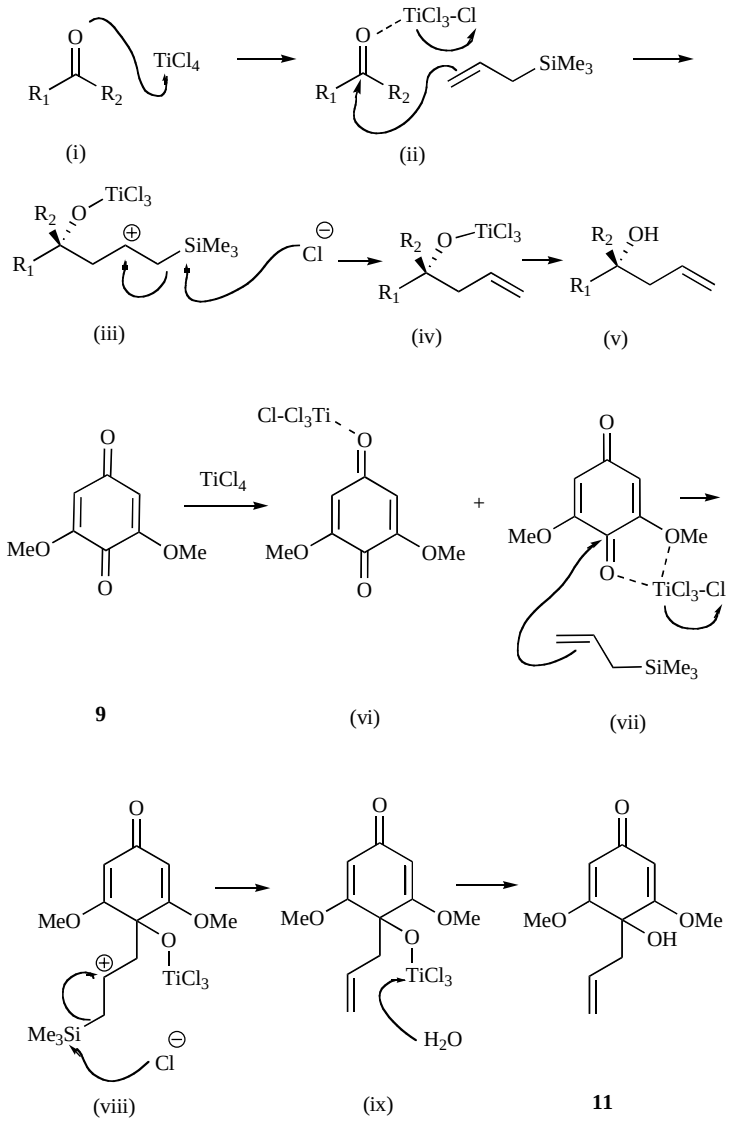
NaOH/H_2O (2g/20mL) was added to a solution of **11** (2.887g, 13.75mmol), tetrabutylammonium bromide (8.85g, 27.50mmol), and toluene (20mL) at room temperature. ten minutes later, Me_2SO_4 (2.6mL) was added, and then the solution became black. Six hours later, the solution was evaporated under reduced pressure.The black solid was washed with water (50mL) and ethyl acetate (3×50mL). After dried over anhydrous Na_2SO_4, the organic layer was concentrated; a brown semisolid was obtained. The residue was purified by silica gel column chromatography (petroleum/acetone 10:1) to afford **12** (1.85g, 60%) as white solid. TLC: R_f = 0.32 (petroleum/acetone 3:1) mp. 102-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 5.61 (s, 2H), 5.37 (m, 1H), 5.00 (t, 2H), 3.77 (s, 6H), 3.11 (s, 3H), 2.74 (d, *J*=7.6 Hz, 2H); NOE: correlations among peaks at 3.77 ppm, 5.60 ppm and 3.10 ppm were observed; ^{13}C NMR (100 MHz, $CDCl_3$, δ) 187.0, 168.9, 130.3, 119.3, 104.4, 79.0, 56.1, 52.5, 41.0; MS (EI) *m/z* 223(M+); HRMS (EI+) *m/z* calculated for [MNa^+] $C_{12}H_{16}O_4Na^+$ 247.0946, found 247.0948.

Synthesis of 4-iodo-2-methoxyphenol (14)

As Sushma Manda *et al.* [11] reported, guaiacol **13** (5mL, 45.97mmol), NaI (10.34g, 68.95mmol) and NaOH (2.76g, 68.95mmol) were dissolved in methanol (ca. 120mL) and cooled below 0 °C. Then aq NaOCl (46mL, 68.95mmol) solution was added dropwise over 30 min. Twenty min later, the reaction was warmed up to room temperature and acidified to pH=1. Then 10% $Na_2S_2O_3$ (17g) was added. The precipitate was filtered out and the filtrate was evaporated to remove methanol. Then the aqueous solution was extracted with ethyl acetate. The organic layer was then washed with water, aqueous $NaHCO_3$ and brine, dried with anhydrous Na_2SO_4 and then concentrated and purified by silica gel column chromatography (petroleum/acetone 100:1, 50:1) to afford the target product **14** (8.04g, 70%) mp. 38-40°C. ^{1}H NMR (400MHz, $CDCl_3$,δ) 7.18 (dd, J_1=8.4Hz, J_2=2Hz, 1H), 7.11 (d, *J*=2Hz, 1H), 6.68 (d, *J*=8Hz, 1H), 5.58 (s,1H); ^{13}C NMR (100MHz, $CDCl_3$, δ) 130.5, 119.8, 118.9, 116.9, 116.5, 80.9, 56.2; MS (EI) *m/z* 250 (M+); HRMS (EI+) *m/z* calculated for $C_7H_7IO_2$ 249.9491, found 249.9494.

Synthesis of Tarennane/ Magnolianone (1)

Compound **12** (200mg, 0.8929mmol), 4-iodo-2-methoxyphenol **14** (268mg, 1.0715mmol), $PdCl_2(PPh_3)_2$ (63mg, 0.0893mmol), lithium chloride anhydrous (113mg, 2.6787mmol) and Et_3N (0.4mL, 2.6787mmol) were stirred in



Scheme 3. Possible region-selective mechanism in preparation compound **11**.

DMF (ca 30mL) at 90°C under argon for 50h, during which **14** (123mg, 43mg) and Et_3N (0.4mL plus 0.4 mL) were added at 24h and 36h after the beginning of the reaction respectively. The black solution was evaporated under reduced pressure, and the residue was wash with water (50mL). The aqueous solution was then extracted with ethyl acetate (3×50mL). After dried with Na_2SO_4, the brown organic layer was concentrated and purified by silica gel column chromatography (petroleum/acetone 10:1, 5:1, 3:1) to afford the target product **1** (510mg, 54%) as a yellow powder. TLC: R_f=0.07 (petroleum/acetone 3:1) R_f=0.57 (petroleum/acetone 1:1) mp. 84-86°C; ^1H and ^{13}C NMR spectroscopic data, see Table **2**; IR (KBr) 3419.61, 1656.14, 1593.73, 1512.76, 1375.79, 1279.14, 1243.72, 1204.77; MS (EI) *m/z* 346 (M+); HRMS (EI+) *m/z* calculated for $C_{19}H_{22}O_6$ $+H^+$ 347.1489, found 347.1499.

RESULTS AND DISCUSSION

The Sakurai allylation reaction started with the activation of the carbonyl group by the Lewis acid. Subsequent carbon-carbon bond formation leaded to a silyl-stabilized carbocation, which after loss of the trimethylsilyl group, gave the double bond [13] (Scheme **3 i-v**).

The possible mechanism of the region-selectivity in the preparation of compound **11** might be as follows: With $TiCl_4$ in DCM, it would probably produce two parallel intermediates **vi** and **vii**. However, in **vii**, there was a structure of metal complex, which would display more stability than the single link with **9** and $TiCl_4$ in **vi** at the low temperature (Scheme **3**). This could also explain the reason why the lower the temperature was, the higher the yield was. The following product compound **12** was analyzed by NOEDS spectrum for its structure, and the result matched the assumption well.

CONCLUSIONS

In summary, we designed and first synthesized the naturally occuring potent antioxidant tarennane, a Chalcone constituent from *Tarenna attenuata* or *Magnolia officinalis*.

The key step of the synthesis relies on a highly regioselective Heck reaction applying a free phenol iodide and a homogeneous palladium catalyst. The outstanding features of the last Heck coupling reaction include: (i) the phenolic hydroxyl group is not protected, different from the literature method [14]; (ii) the position of the isolated carbon-carbon double bond on the molecule of intermediate **10,** unlike other common Heck reactions, is not connected to ethers, carbonyl groups or benzene rings. The overall yield was 14%. Anti-angiogenisis biological evaluations of the final target are currently being investigated in model organism. The SAR studies of the derivatives and synthetic intermediates are underway. This is a highly convergent and flexible synthetic strategy which not only provides access to the target molecule **1**, but also provides a new insight on the synthesis of chalcone analogues containing a propylene linker between an aromatic ring and a non-aromatic one.

ACKNOWLEDGEMENT

This work was supported by the National Major Program of China during the 11th Five-Year Plan Period (2009ZX09501-015).

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