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Graphical Abstract

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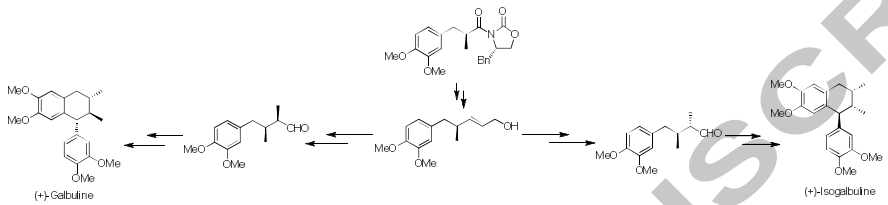

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A practical total synthesis of (+)-isogalbulin and (+)-galbulin

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ABSTRACT

A practical total synthesis of the natural products (+)-isogalbulin and (+)-galbulin has been achieved in ten steps from readily available 3-(3,4-dimethoxyphenyl)propanoic acid. The total yields were 12.3% and 12.9% respectively. The key steps involved Evans asymmetric alkylation, Sharpless asymmetric epoxidation, and a highly regioselective opening of 1-benzyloxy-2,3-epoxides with an organoaluminum ate-complex formed by Me_3Al and n-BuLi.

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(+)-Isogalbulin (**1**) and (+)-galbulin (**2**) (**Figure 1**), which were isolated from *Himantandra baccata* and *Himantandra belgraveana*[1] belong to the category of tetrahydronaphthalene lignans. Lignans, especially those with 1-arylnaphthalen skeleton, possess a series of biological activities such as anti-HIV, anti-tumor[2], anti-Parkinson's disease and anti-Alzheimer's disease[3]. In addition, a recent study revealed that isogalbulin could significantly increase osteoblast differentiation, and might possess therapeutic potentials for osteoporosis[4]. In spite of the particularly important pharmacological properties, efforts for their synthetic study are scarce. Only a few synthesis of the racemic isogalbulin and galbulin were reported[5-9]. Perry[6] described the synthesis of isogalbulin using an acid-catalyzed cyclization of 1,4-bis(3,4-dimethoxyphenyl)-2,3-dimethylbutan-1-ol. Most recently, Whitby[7] and co-workers had completed the total synthesis of (±)-isogalbulin and (±)-galbulin via zirconium-promoted cyclization of 1,7-dienes[7]. Charlton[8] and co-workers detailed another synthetic route of (±)-galbulin in 2001[8]. The key step in their total synthesis is acid-catalyzed cyclization of 2,3-dibenzylidenesuccinates. The only asymmetric total synthesis of (+)-galbulin (**2**) was presented by Bor-Cherng Hong[9]. Their synthetic work utilized organocatalytic domino Michael–Michael–aldol condensation and organocatalytic kinetic resolution as the key steps[9]. Herein, we would like to report a practical total synthesis of (+)-isogalbulin (**1**) and (+)-galbulin (**2**).

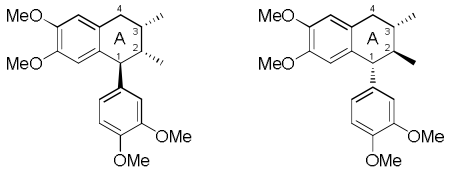

Figure 1. (+)-isogalbulin (**1**) and (+)-galbulin (**2**)

According to the retrosynthetic analysis (**Figure 2**), (+)-isogalbulin (**1**) could be prepared by the intramolecular Friedel–Crafts cyclization of diarylbutane alcohol **12**[6]. In turn, the compound **12** could be accessed from the nucleophilic addition reaction of (3,4-dimethoxyphenyl)lithium and aldehyde **11**. The key intermediate **11** might be formed via attack of epoxide **7** with Me_3Al and subsequently treatment with $NaIO_4$, while the intermediate **7** could be obtained via the Sharpless asymmetric epoxidation. Obviously, we could obtain the compound **6** by the Wittig reaction of compound **4** and reduction. The aldehyde **4** could be prepared from compound **3**, which should be available through Evans asymmetric alkylation reaction from the commercially available materials following a protocol previously reported[10]. Likewise, the analysis of (+)-galbulin (**2**) can employ a similar synthetic strategy.

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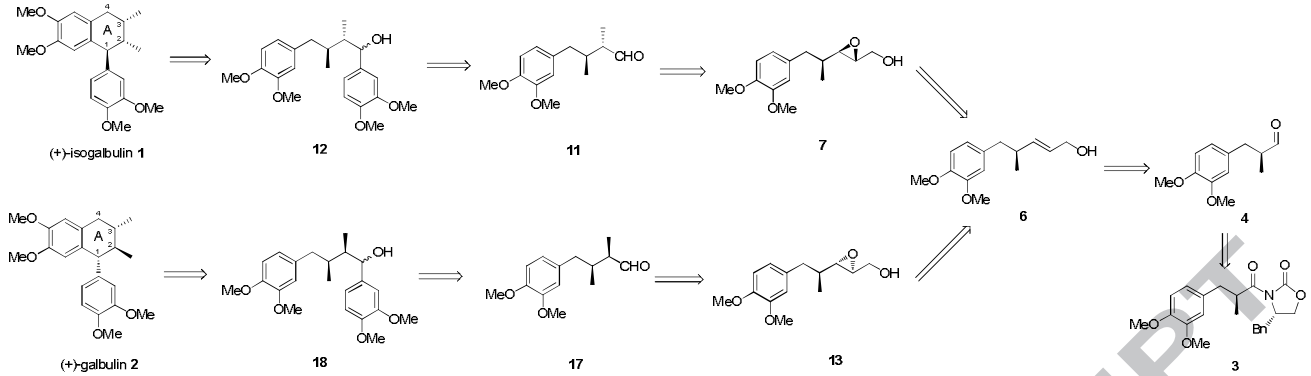
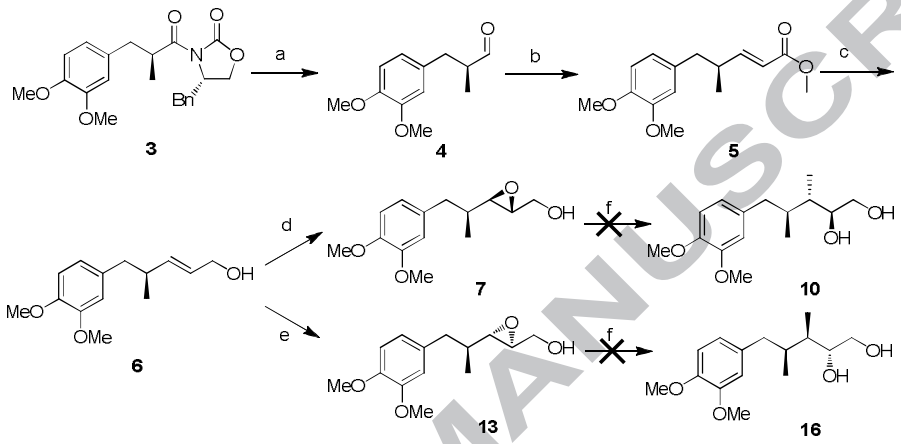
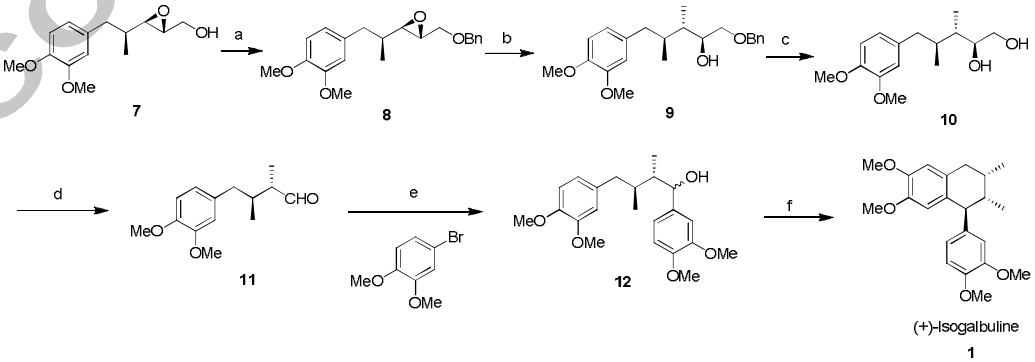


Figure 2, Retrosynthetic analysis of (+)-isogalbulin (**1**) and (+)-galbulin (**2**)



Scheme 1. Preparation of **10** and **16**. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78°C, 80%; (b) $Ph_3P{=}CHCO_2Me$, toluene, CH_2Cl_2, 50 °C , 89%; (c) DIBAL-H, CH_2Cl_2, 0°C, 87%; (d) $Ti(O\text{-}iPr)_4$, D-(-)-DIPT, TBHP, 4Å MS, CH_2Cl_2, −78°C to -23°C, 81%; (e) $Ti(O\text{-}iPr)_4$, L-(+)-DIPT, TBHP, 4Å MS, CH_2Cl_2, −78°C to -23°C, 85%; (f) Me_3Al, CH_2Cl_2, 0°C.

The synthesis of (+)-isogalbulin (**1**) began with compound **3** (**Scheme 1**) which was readily prepared from commercially available 3-(3,4-dimethoxyphenyl)propanoic acid via Evans asymmetric alkylation reaction according to a literature procedure[10,11]. Direct reduction of compound **3** with DIBAL-H provided the corresponding aldehyde **4**[12]. The Wittig reaction was employed to convert aldehyde **4** into α,β-unsaturated ester **5**[13] followed by reduction with DIBAL-H to afford alcohol **6**[14]. The Sharpless asymmetric epoxidation[15,16] of allylic alcohol **6** using D-(-)-DIPT, $Ti(O\text{-}iPr)_4$ and TBHP in CH_2Cl_2 furnished the epoxide **7** in good yield and diastereoselectivity (80%, de 92/8) as shown in **Scheme 1**. The de% could be further improved to 99.7% by converting to their corresponding 3,5-dinitrobenzoate[17] ester after epoxidation, followed by chromatography purification (for **7**) or recrystallization (for **13**) and subsequent hydrolysis. With the intermediate **7** in hand, we initially planned to prepare **10** (**Scheme 1**) by attacking the epoxide **7** with Me_3Al directly[18]. Unfortunately, complex mixtures were generated under the conditions.



Scheme 2. The synthesis of (+)-isogalbulin (**1**). Reagents and conditions: (a) NaH, Bu_4NI, THF, BnBr, 90%; (b) Me_3Al-n-BuLi(2:1), toluene, −78°C to rt, 77%; (c) H_2, $Pd(OH)_2$, MeOH/CH_3COOH(2:1), rt, 2 h, 90%; (d) $NaIO_4$, THF/H_2O(2:1), rt, 71%; (e) n-BuLi, THF, −78°C, 75%; (f) HF-pyridine, CH_3CN, rt, 75%.

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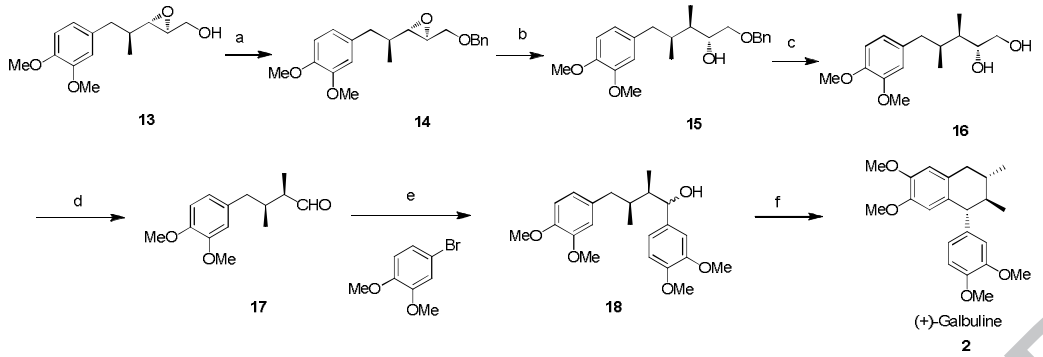

Scheme 3. The synthesis of (+)-galbulin (**2**). Reagents and conditions: (a) NaH, Bu_4NI, THF, BnBr, 92%; (b) Me_3Al-n-BuLi(2:1), toluene, −78°C to rt, 76%; (c) H_2, $Pd(OH)_2$, MeOH/CH_3COOH(2:1), rt, 2 h, 93%; (d) $NaIO_4$, THF/H_2O(2:1), rt, 72%; (e) n-BuLi, THF, −78°C, 73%; (f) HF-pyridine, CH_3CN, rt, 72%.

After many failed attempts, we decided to use Pfalts's method, thus the hydroxyl group of epoxy alcohol **7** was protected as benzyl ether **8** (**Scheme 2**). But, under Pfalts's condition[19a], using Me_3Al in the presence of catalytic amounts of butyllithium proved to be unsatisfactory with our substrate as the substrate was not completely consumed. It was then observed that the ratio of Me_3Al and n-BuLi is critical, and a condition (Me_3Al/n-BuLi=2:1) which Flippin used in related study on the 1-(benzyloxy)-3,4-epoxyhexane[19b] system could highly regioselectively open the epoxide core of intermediate **8**[20] to provide alcohol **9** as a single epimer in 5 hours. The latter was deprotected over $Pd(OH)_2$ to afford the diol **10**[21], which was followed by oxidative cleavage with $NaIO_4$ to give aldehyde **11**[18,22]. Then, treatment of compound **11** with aryllithium, formed in situ from 4-Bromoveratrole and n-BuLi, gave the diarylbutane alcohol **12**. Finally, we smoothly obtained (+)-isogalbulin (**1**)[23] exclusively by stirring alcohol **12** at room temperature with HF-pyridine, through the cyclisation of carbocation [5d, 5e, 6, 24].

Similarly, the total synthesis of (+)-galbulin (**2**)[25] could be achieved via the Sharpless asymmetric epoxidation of compound **6** induced by L-(+)-DIPT and followed above synthetic strategy (**Scheme 3**). The ^{1}H-NMR, ^{13}C-NMR, optical rotations, MS data and physical properties of synthetic (+)-isogalbulin (**1**) and (+)-galbulin (**2**) were consistent with reported data[5c, 5g, 9].

In summary, an efficient strategy for the synthesis of (+)-isogalbulin (**1**) and (+)-galbulin (**2**) has been successfully achieved in 10 steps from a common intermediate. The total yields were 12.3% and 12.9% respectively. The principal features of our synthetic strategy include using Evans asymmetric alkylation, Sharpless asymmetric epoxidation reaction, and a highly regioselective bimolecular nucleophilic substitution as the key steps. This method might be of great value in terms of simplicity and efficiency in elaboration of natural products which possess 1-arylnaphthalen carbon skeleton.

Acknowledgment

We are grateful to Professor Jiangong Shi and Ying Guo for helpful discussions.

Supplementary data

Supplementary data (experimental procedures and analytical data for all the new compounds) associated with this article can be found, in the online version, at

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12. *Compound* **4**: $[\alpha]_D^{20}$ -0.492° (C 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 6.81-6.79 (d, J = 8.0 Hz, 1H), 6.72-6.70 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.05-3.00 (dd, J = 13.5, 5.9 Hz, 1H), 2.68-2.63 (m, 1H), 2.60-2.54 (dd, J = 13.5, 8.2 Hz, 1H), 1.11-1.09 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.5, 148.9, 147.6, 131.3, 121.0, 112.1, 111.2, 55.9, 55.8, 48.1, 36.3, 13.2; HR-MS (ESI) calcd for $C_{12}H_{16}O_3Na$ $(M+Na)^+$: 231.09971, Found 231.09869.
13. *Compound* **5**: $[\alpha]_D^{20}$ +54.0° (C 0.50,$CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98-6.93 (dd, J=15.6, 6.4 Hz, 1H), 6.79-6.77 (d, J = 8.0 Hz, 1H), 6.68-6.66 (d, J = 8.0 Hz, 1H), 6.64 (s, 1H), 5.76-5.72 (d, J = 15.6 Hz, 1H), 3.86 (s, 6H), 3.71 (s, 3H), 2.70-2.67 (m, 1H), 2.60-2.52 (m, 1H), 1.06-1.05 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 153.8, 148.6, 147.3, 132.0, 121.0, 119.5, 112.3, 111.0, 55.8, 55.7, 51.4, 42.0, 38.3, 18.7; HR-MS (ESI) calcd for $C_{15}H_{20}O_4Na$ $(M+Na)^+$: 287.12538, Found 287.12454.
14. *Compound* **6**: $[\alpha]_D^{20}$ +34.71° (C 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.79-6.77 (d, J = 8.1 Hz, 1H), 6.68-6.66 (m, 2H), 5.69-5.64 (dd, J = 15.5, 6.3 Hz, 1H), 5.60-5.54 (m, 1H), 4.08-4.06 (d, J = 5.5 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 2.65-2.60 (m, 1H), 2.50-2.41 (m, 2H), 1.00-0.99 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.5, 147.1, 138.0, 133.1, 127.4, 121.0, 111.0, 63.6, 55.8, 55.7, 42.8, 38.0, 19.5; HR-MS (ESI) calcd for $C_{28}H_{41}O_6$ $(2M+H)^+$: 473.28977, Found 473.28979.
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20. *Compound* **8**: $[\alpha]_D^{20}$ +51.48° (C 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.28 (m, 5H), 6.75-6.73 (d, *J* = 8.4 Hz, 1H), 6.67-6.65 (m, 2H), 4.55-4.48 (m, 2H), 3.84 (s, 6H), 3.60-3.57 (dd, *J* = 11.5, 2.6 Hz, 1H), 3.31-3.27 (dd, *J* = 11.5, 5.6 Hz, 1H), 2.74-2.73 (m, 1H), 2.68-2.67 (m, 1H), 2.59-2.57 (m, 2H), 1.69-1.62 (m, 1H), 1.06-1.05 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.7, 147.3, 138.0, 132.5, 128.3, 127.7, 127.6, 120.9, 112.1, 111.0, 73.1, 70.0, 59.7, 57.0, 55.8, 55.7, 39.9, 38.0, 17.0; HR-MS (ESI) calcd for $C_{21}H_{26}O_4Na$ $(M+Na)^+$: 365.17233, Found 365.17175.

21. *Compound* **10**: $[\alpha]_D^{20}$ -13.26° (C 0.86, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.80-6.77 (d, *J* = 8.0 Hz, 1H), 6.73-6.72 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82-3.79 (m, 1H), 3.67-3.62 (m, 1H), 3.52-3.48 (m, 1H), 2.79-2.77 (d, *J* = 10.0 Hz, 1H), 2.21-2.11 (m, 4H), 0.87-0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 147.0, 134.4, 120.9, 112.4, 111.0, 73.7, 65.2, 55.8, 55.7, 40.8, 37.2, 35.2, 17.5, 10.9; HR-MS (ESI) calcd for $C_{30}H_{49}O_8$ $(2M+H)^+$: 537.34219, Found 537.34235.

22. *Compound* **11**: $[\alpha]_D^{20}$ +39.16° (C 0.41, $CHCl_3$); 1H NMR ($CDCl_3$, 400 MHz) δ 9.70 (s, 1H), 6.80-6.78 (d, *J* = 7.9 Hz, 1H), 6.70-6.68 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.70-2.65 (dd, *J* = 13.5, 5.6 Hz, 1H), 2.38-2.32 (m, 2H), 2.20-2.18 (m, 1H), 1.15-1.13 (d, *J* = 7.0 Hz, 3H), 0.97-0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.1, 148.7, 147.3, 132.8, 121.0, 112.2, 111.0, 55.8, 55.7, 50.5, 39.2, 36.5, 17.0, 10.1; HR-MS (ESI) calcd for $C_{14}H_{21}O_3$ $(M+H)^+$: 237.14852, Found 237.14812.

23. *(+)-isogalbulin* (**1**): $[\alpha]_D^{20}$ +44.25° (C 0.52, $CHCl_3$) [lit.[5c, 5g] $[\alpha]_D^{20}$ +46°(c 0.10, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.75-6.74 (d, *J* = 8.2 Hz, 1H), 6.60 (s, 1H), 6.57 (d, *J* = 1.8 Hz, 1H), 6.52-6.50 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.34 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.69-3.68 (d, *J* = 5.4 Hz, 1H), 3.67 (s, 3H), 2.88-2.84 (dd, *J* = 16.5, 5.4 Hz, 1H), 2.48-2.44 (dd, *J* = 16.5, 8.0 Hz, 1H), 2.04-2.02 (m, 1H), 1.95-1.93 (m, 1H), 0.92-0.91 (d, *J* = 2.8 Hz, 3H), 0.91-0.90 (d, *J* = 2.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.5, 147.2, 147.0, 139.8, 129.4, 128.4, 121.3, 113.2, 112.1, 111.1, 110.5, 55.81, 55.76, 55.72, 55.67, 50.8, 40.7, 34.7, 28.5, 16.5, 15.3; HR-MS (ESI) calcd for $C_{22}H_{28}O_4Na$ $(M+Na)^+$: 379.18798, Found 379.18784.

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25. *(+)-galbulin* (**2**): $[\alpha]_D^{20}$ +7.95° (C 0.64,$CHCl_3$) [lit.[9] $[\alpha]_D^{20}$ +8.0°(c 0.3, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.81-6.79 (d, *J* = 8.1 Hz, 1H), 6.72-6.69 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.58-6.57 (d, *J* = 1.9 Hz, 1H), 6.56 (s, 1H), 6.16 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.56 (s, 3H), 3.44-3.42 (d, *J* = 10.3 Hz, 1H), 2.79-2.74 (dd, *J* = 16.2, 4.6 Hz 1H), 2.65-2.58 (dd, *J* = 16.2, 11.6 Hz, 1H), 1.67-1.63 (m, 1H), 1.55-1.50 (m, 1H), 1.09-1.08 (d, *J* = 6.4 Hz, 3H), 0.88-0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.8, 147.3, 147.0, 146.9, 139.0, 132.5, 129.1, 121.9, 112.8, 112.1, 110.7, 110.6, 55.9, 55.82, 55.78, 54.3, 43.8, 39.0, 35.6, 20.0, 17.2; HR-MS (ESI) calcd for $C_{22}H_{29}O_4$ $(M+H)^+$: 357.20658, Found 357.20657.

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