Synthesis of $\Delta^3$-2-Hydroxybakuchiol Analogues and Their Growth Inhibitory Activity against Rat UMR106 Cells

Qun Zhao $^1$, Qianqian Xu $^1$, Guangsheng Shan $^1$, Chao Dong $^1$, Hong Zhang $^{2,*}$ and Xinsheng Lei $^{1,3,*}$

$^1$ School of Pharmacy, Fudan University, Shanghai 201203, China
$^2$ Department of Pharmaceutical Botany, School of Pharmacy, Second Military Medical University, Shanghai 200433, China
$^3$ Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

* Author to whom correspondence should be addressed; E-Mails: zhanghong@smmu.edu.cn (H.Z.); leixs@fudan.edu.cn (X.L.); Tel./Fax: +86-021-5198-0128 (X.L.).

Received: 17 January 2014; in revised form: 9 February 2014 / Accepted: 11 February 2014 / Published: 20 February 2014

Abstract: A series of $\Delta^3$-2-hydroxybakuchiol analogues have been synthesized and tested for their growth inhibitory activity against rat UMR106 cells by using the MTT method. Some of them exhibit enhanced activities compared with the natural product, and the preliminary SAR profile shows that the chain tail on the natural product could be subtly modified to enhance the activity and the aromatic moiety or the terminal olefin on the main chain can also be modified without any evident loss of activity. The stereo-configuration of the quaternary chiral center has an important influence on the activity.

Keywords: bakuchiol; natural product analogues; cytotoxic activity

1. Introduction

Natural products from plants are an important source of potential therapeutic agents for human health. The medicinal plant *Psoralea corylifolia* L., a member of the Leguminosae family, has been used for a long time as a Traditional Chinese Medicine for the treatment of premature ejaculation, knee pain, pollakiuria, callus, psoriasis, vitiligo and psoriasis [1]. The seed extract has been suggested as a useful remedy for bone fractures, osteomalacia and osteoporosis [2]. A number of monoterpene
phenols occurring in the plant have been isolated and demonstrated to possess interesting biological activities [3–7], and among them, bakuchiol (15b, Figure 1), one of the major components in the plant seed, has attracted great attention due to its diverse activities, such as antibacterial, antihelminthic, antioxidant, and especially antitumor properties [8–23]. In contrast to that, \( \Delta^3 \)-2-hydroxybakuchiol (15a), a congener of bakuchiol, has not attracted much interest among medicinal chemists, probably due to its scarcity and lability [24,25]. To the best of our knowledge, only Guo and co-workers have recently investigated its inhibitory effects against monoamine transporters, suggesting that it might be a potential psychopharmacologic agent for the treatment of psychogenic disorders [26].

Given the fact that the analog bakuchiol shows various biological activities, we have put \( \Delta^3 \)-2-hydroxybakuchiol into our natural product-based drug discovery program [27–30]. Recently, a facile asymmetric synthesis of \( \Delta^3 \)-2-hydroxybakuchiol was established and the compound was tested for antiosteoporosis effects [31,32]. Unexpectedly, this natural product did not show the desired activity, but it exhibited growth inhibitory activity against osteosarcoma cells (rat UMR106 cell) with an \( \text{IC}_{50} \) value of 69 µM, suggesting that it was worthy of further investigation [33].

**Figure 1.** The structures of bakuchiol (15b) and \( \Delta^3 \)-2-hydroxybakuchiol (15a) and the proposed modifications.

Herein the synthesis of \( \Delta^3 \)-2-hydroxybakuchiol analogues was described and their growth inhibitory activity against rat UMR106 cells was demonstrated. The preliminary structure-activity relationship knowledge of this natural product has been obtained by modifying the substituent (G) on the aromatic ring and the \( R^1 \) group on the chain, while keeping the main chain unchanged. In addition, we would also replace the terminal olefin with an ethyl moiety (\( R^2 \)) in order to probe the effect of this moiety on the activity (Figure 1).

### 2. Results and Discussion

#### 2.1. Chemistry

Our synthetic approach to the analogues of \( \Delta^3 \)-2-hydroxybakuchiol is depicted in Scheme 1. Starting from (\( E \))-2-methylbut-2-enoyl chloride and (\( R \))-4-isopropylazolidin-2-one, the \( \alpha,\beta \)-unsaturated imide 3
bearing an Evans’ auxiliary was prepared in excellent yield. Then, the α-alkylation of 3 with tert-butyl iodoacetate afforded the fragment 4 in a moderate yield with an excellent diastereoselectivity (dr > 20: 1). After selective reduction of the imide group, the key chiral intermediate 5 was obtained in an acceptable yield. To avoid the formation of the volatile lactone from 5, the free hydroxyl group in 5 was protected with a TBS group to afford compound 6. Upon reduction of the ester group and subsequent oxidation, compound 8a was prepared in 94% yield (over two steps).

Scheme 1. Synthetic approach to the analogues of Δ<sup>3</sup>-2-hydroxybakuchiol.

Reagents and conditions: (a) n-BuLi, THF, 96%; (b) NaHMDS, −78 °C, 1.5 h; ICH<sub>2</sub>CO$_2$Bu$^+$, −50 °C, 6 h, 68%; (c) LiBH$_4$, THF, 0 °C, 3 h, 70%; (d) TBSCl, imidazole, CH$_2$Cl$_2$, rt, 3 h, 84%; (e) DIBALH, CH$_2$Cl$_2$, −78 °C, 2 h; (f) IBX, DMSO, rt, 5 h, for 8a: 94%; for 8b: 100%; two steps; (g) Ph$_3$P=CHCO$_2$Et, toluene, reflux, 2 h, for 9a: 92%; for 9b: 81%; (h) HCl, EtOH, 0 °C, 7 h, for 10a: 97%; for 10b: 86%; (i) IBX, DMSO, rt, 5 h, for 11a: 95%; for 11b: 97%; (j) CHI$_3$, CrCl$_2$, THF, 0 °C, 3 h, for 12a: 86%; for 12b: 80%; (k) ArBr, n-BuLi/ZnCl$_2$; Pd(OAc)$_2$/PPh$_3$, THF, 60%–98%; (l) RLi, THF, rt, 5 h, up to 34%–100%; for 14b, 14h–j, additional step required for deprotection of TBDPS group: Bu$_4$NF, THF, quantitative yield; (m) H$_2$, Pd/C (10%), rt, overnight, 100%.

Compound 8a successfully underwent a Wittig reaction to afford the α,β-unsaturated ester 9a. Next, the TBS group was removed and oxidized to afford the corresponding aldehyde 11a in 92% yield (over two steps). Through a Takai-Utimoto reaction with CrCl$_2$ and CH$_3$I, the trans-iodo-olefin 12a was obtained in up to 86% yield. The iodo-olefin was coupled with different substituted aryl zinc species via the Negishi reaction to give the desired cross-coupling product 13a,c–f, respectively. After selective 1,2-addition reactions of the esters 13a, c–g with alkyllithiums, the corresponding products 14a, c–j were obtained in acceptable (up to 73%) yields.
In order to assess the effect of the terminal olefin moiety in Δ³-2-hydroxybakuchiol on the biological activity, compound 14b was prepared. Hydrogenation of 7a provided saturated alcohol 7b in a quantitative yield which was successfully transformed into 14b by a method similar to that shown in Scheme 1. As positive control, bakuchiol (15b) and its methyl ether (15e), together with their corresponding enantiomers 15d and 15e, were also prepared according to our recently reported method [31].

2.2. Activity against Rat UMR106 Cell

With the various analogues of Δ³-2-hydroxybakuchiol in hand, their cytotoxic activity against rat UMR106 osteosarcoma cells was tested by the MTT assay after two days of treatment [34] and the results are shown in Table 1.

Among those compounds, Δ³-2-hydroxybakuchiol (15a) displayed the expected [33] cytotoxic activity with an IC₅₀ value of 69 µM (Entry 21, Table 1). When the chain tail was modified with an α,β-unsaturated ester (compound 13a), the activity increased (IC₅₀: 27 µM, Entry 1) compared with 14a (IC₅₀: 66 µM, Entry 7). When the methoxy group was replaced with other substituent (compounds 13c–g), the corresponding activity was significantly reduced (IC₅₀: > 263 µM, Entries 2–6), suggesting that the substituent on the aromatic ring had an important influence on the activity in the case of α,β-unsaturated ester analogues.

When the modifications were performed only on the aromatic moiety of Δ³-2-hydroxybakuchiol, the substituent effect seemed to have somewhat of an effect on the activity (compounds 14a, c, d, f). For example, the activity was still retained in the case of a para-methoxy (14a; Entry 7), but other groups such as H and para-methyl led to slightly reduced activities (14c, 14d; Entries 8 and 9). Notably, a strong electron-withdrawing group gave a slightly increased activity (14f, Entry 11). When a larger bulky group was used (compounds 14e,g; Entries 10 and 12), the activity was just slightly decreased. Surprisingly, if the phenolic hydroxyl was moved to the meta-position (14h), its IC₅₀ value was still up to 123 µM, with about one-fold reduced activity in contrast to Δ³-2-hydroxybakuchiol (Entry 13). Modification on the R¹ group (14i,j) in the tertiary alcohol moiety suggested that this domain could accommodate a bulky hydrophobic space, and 14j gave the best result (IC₅₀: 17 µM; Entries 14 and 15). In addition, the terminal double bond could be saturated without influence on the activity, implied by the almost identical activities of 14b (IC₅₀: 71 µM; Entry 16) and Δ³-2-hydroxybakuchiol.

On the other hand, bakuchiol (15b), with a slight structural difference on the chain tail of Δ³-2-hydroxybakuchiol, showed almost the same potency (IC₅₀: 62 µM, Entry 18). Interestingly, ent-bakuchiol (15d) had a one-fold enhanced activity (IC₅₀: 33 µM, Entry 20). However, in comparison with (S- or R)bakuchiol methyl ether showed different influences on the activity, namely, (S)-bakuchiol methyl ether (15e) maintained the activity (IC₅₀: 60 µM, Entry 17) but (R)-bakuchiol methyl ether (15e) gave less activity (IC₅₀: 161 µM, Entry 19), indicating that the stereochemistry played an important role to the activity.
Table 1. Cytotoxic activities of Δ3-2-hydroxybakuchiol and its analogues against rat UMR106 osteosarcoma cell.

| Entry | Comp. | Ar       | R¹     | R²     | IC₅₀ (µM) |
|-------|-------|----------|--------|--------|----------|
| 1     | 13a   | 4-MeO-C₆H₄ | CO₂Et  | CH=CH₂ | 27       |
| 2     | 13c   | C₆H₅     | CO₂Et  | CH=CH₂ | 330      |
| 3     | 13d   | 4-Me-C₆H₄ | CO₂Et  | CH=CH₂ | 263      |
| 4     | 13e   | 2-C₁₀H₇   | CO₂Et  | CH=CH₂ | >500     |
| 5     | 13f   | 4-CF₃-C₆H₄ | CO₂Et  | CH=CH₂ | 242      |
| 6     | 13g   | 3,4-OCH₂O-C₆H₄ | CO₂Et  | CH=CH₂ | 511      |
| 7     | 14a   | 4-MeO-C₆H₄ | Me₂CH(OH) | CH=CH₂ | 66       |
| 8     | 14c   | C₆H₅     | Me₂CH(OH) | CH=CH₂ | 107      |
| 9     | 14d   | 4-Me-C₆H₄ | Me₂CH(OH) | CH=CH₂ | 87       |
| 10    | 14e   | 2-C₁₀H₇   | Me₂CH(OH) | CH=CH₂ | 128      |
| 11    | 14f   | 4-CF₃-C₆H₄ | Me₂CH(OH) | CH=CH₂ | 46       |
| 12    | 14g   | 3,4-OCH₂O-C₆H₄ | Me₂CH(OH) | CH=CH₂ | 115      |
| 13    | 14h   | 3-HO-C₆H₄ | Me₂CH(OH) | CH=CH₂ | 123      |
| 14    | 14i   | 4-HO-C₆H₄ | Et₂CH(OH) | CH=CH₂ | 57       |
| 15    | 14j   | 4-HO-C₆H₄ | n-Bu₂CH(OH) | CH=CH₂ | 17       |
| 16    | 14b   | 4-HO-C₆H₄ | Me₂CH(OH) | CH₃CH₃ | 71       |
| 17    |       | bakuchiol methyl ether (15c) |        |        | 60       |
| 18    |       | bakuchiol (15b) |        |        | 62       |
| 19    |       | ent-bakuchiol methyl ether (15e) |        |        | 161      |
| 20    |       | ent-bakuchiol (15d) |        |        | 33       |
| 21    |       | Δ₃-2-hydroxybakuchiol (15a) |        |        | 69       |

3. Experimental

3.1. General Information

Solvents were distilled from the appropriate drying agents before use. All the reagents were purchased from Acros (Shanghai, China), Alfa Aesar (Shanghai, China), and National Chemical Reagents Group Co. Ltd (Shanghai, China). Unless otherwise stated, all the reactions were performed under argon. Column chromatography: commercial silica gel (Qingdao Haiyang Chemical Group Co.; 300–400 mesh, Qingdao, China). Spots on the TLC plates (GF 254, Yantai Jiangyou Silica R&D Co. Ltd., Yantai, China) were detected under UV light or with iodine, KMnO₄, and H₃PO₄·12MoO₃·xH₂O.
1H and 13C-NMR spectra (400 MHz for 1H, and 100 MHz for 13C): Varian Mercury-Plus (Palo Alto, CA, USA) spectrometer; chemical shifts δ in parts per million, with residual CHCl3 [d (H) 7.26; d (C) 77.0] as internal standard; J in Hertz. ESI-MS and HR-APCI/ESI-MS: Finnigan Mat-95 mass spectrometer (Waltham, MA, USA); in m/z. Compounds 3–7a, 8–14a, Δ3-2-hydroxybakuchiol, (S)-bakuchiol and (R)-bakuchiol as well as their corresponding methyl ethers (15a–e) were prepared by our previously reported method [32].

3.2. Synthetic Procedures for the New Compounds

(R)-3-(((tert-Butyldimethylsilyl)oxy)methyl)-3-methylpentan-1-ol (7b). A mixture of (S)-3-(((tert-butylidemethylsilyl)oxy)methyl)-3-methylpent-4-en-1-ol (1.0 g, 4.09 mmol) and Pd/C (100 mg, 10% w/w) in methanol (20 mL) was purged with H2 gas and was stirred overnight at room temperature under H2. The reaction mixture was directly passed through a pad of silica gel with ethyl acetate and the solvent was removed under vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate 10:1) to afford 7b (1.01 g, 100%) as a colorless oil. Rf = 0.26 (petroleum ether/ethyl acetate 10:1), [α]20D +4.8 (c 0.65, CHCl3). 1H-NMR (CDCl3) δ 3.64 (t, J = 5.6 Hz, 2H), 3.41 (brs, 1H), 3.39 (d, J = 10.0 Hz, 1H), 3.34 (d, J = 10.0 Hz, 1H), 1.64–1.48 (m, 2H), 1.39–1.20 (m, 2H), 0.91 (s, 9H), 0.85–0.78 (m, 6H), 0.08 (s, 6H). 13C-NMR (CDCl3) δ 70.6, 58.8, 41.2, 37.4, 29.6, 25.8, 21.7, 18.2, 7.7, −5.6. ESI-MS: 247.1 [M+H], HRMS (ESI): Calcd. for C13H30O2Si [M+H]: 247.2088, found: 247.2091.

(R)-3-(((tert-Butyldimethylsilyl)oxy)methyl)-3-methylpentanal (8b). IBX (1.71 g, 4.9 mmol) was added to a solution of 7b (1.01 g, 4.09 mmol) in DMSO (20 mL). The mixture was stirred overnight at room temperature. Then the mixture was diluted with ethyl acetate (200 mL) and was washed successively with saturated NaHCO3 aq. solution (30 mL × 2), water (30 mL), brine (30 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 20:1) to afford 8b (1.00 g, 99%) as a colorless oil. Rf = 0.74 (petroleum ether/ethyl acetate = 10:1), [α]20D −2.6 (c 0.50, CHCl3). 1H-NMR (CDCl3) δ 9.84 (t, J = 3.1 Hz, 1H), 3.42 (d, J = 9.7 Hz, 1H), 3.35 (d, J = 9.7 Hz, 1H), 2.32–2.21 (m, 2H), 1.46–1.37 (m, 2H), 0.96 (s, 3H), 0.92–0.83 (m, 12H), 0.03 (s, 6H). 13C-NMR (CDCl3) δ 203.8, 69.6, 41.2, 37.4, 29.6, 25.8, 21.7, 18.2, 7.9, −5.6. ESI-MS: 283.7 [M+K].

(R,E)-Ethyl 5-(((tert-butyldimethylsilyl)oxy)methyl)-5-methylhept-2-enoate (9b). To a solution of 8b (0.978 g, 4.0 mmol) in toluene (10 mL) was added a solution of ethyl-2-(triphenylphosphoranylidene)acetate (1.71 g, 4.9 mmol) in toluene (10 mL). The mixture was stirred for 2 h under argon at reflux and then cooled to rt. The reaction mixture was concentrated under reduced pressure, diluted with ether (50 mL) and filtered. The filter cake was washed successively with ether (10 mL) and petroleum ether (10 mL). The combined filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 80:1) to afford 9b (0.953 g, 81%) as a colorless oil. Rf = 0.60 (petroleum ether/ethyl acetate = 20:1), [α]20D −11.5 (c 0.60, CHCl3). 1H-NMR (CDCl3) δ 6.97 (dt, J = 15.7, 7.9 Hz, 1H), 5.81 (d, J = 15.7 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.28 (d, J = 9.7 Hz, 1H), 3.23 (d, J = 9.7 Hz, 1H), 2.14 (d, J = 7.9 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.85–0.76 (m, 6H), 0.02 (s, 6H). 13C-NMR (CDCl3) δ 166.6, 146.8,
123.2, 68.6, 60.1, 39.4, 38.8, 29.0, 3.82, 21.1, 18.2, 14.3, 7.8, −5.6. ESI-MS: 315.2 [M+H], HRMS(ESI): Calcd. for C_{17}H_{35}O_{3}Si [M+H]: 315.2350, found: 315.2356.

(R,E)-Ethyl-5-(hydroxymethyl)-5-methylhept-2-enoate (10b). To a solution of 9b (950 mg, 3.02 mmol) in methanol (10 mL) at 0 °C was added concentrated hydrochloric acid (0.75 mL). The mixture was stirred for 7 h at rt. The reaction was quenched with saturated NaHCO₃ (10 mL). The mixture was concentrated under reduced pressure. The residue was extracted with ethyl acetate (15 mL × 3). The organic phase was combined, washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 20:1) to afford 10b (517 mg, 86%) as a colorless oil. Rₛ = 0.81 (petroleum ether/ethyl acetate = 5:1), [α]₂⁰D ≈ −14.7 (c 0.60, CHCl₃). ¹H-NMR (CDCl₃) δ 7.10–6.88 (m, 1H), 5.86 (ddd, J = 15.5, 3.0, 1.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.40 (d, J = 10.8 Hz, 1H), 3.36 (d, J = 10.8 Hz, 1H), 2.18 (dd, J = 7.9, 1.3 Hz, 2H), 1.37–1.25 (m, 5H), 0.91–0.81 (m, 6H). ¹³C-NMR (CDCl₃) δ 166.4, 146.0, 123.6, 68.9, 60.2, 39.1, 38.6, 28.8, 21.1, 14.33, 7.8. ESI-MS: 201.1 [M+H], HRMS(ESI): Calcd. for C_{11}H_{21}O₃ [M+H]: 201.1485, found: 201.1489.

(R,E)-Ethyl 5-formyl-5-methylhept-2-enoate (11b). Compound 10b (447 mg, 2.23 mmol) and IBX (938 mg, 3.4 mmol) in a 100 mL flask was dissolved with DMSO (20 mL). The mixture was stirred overnight at rt. Then the mixture was diluted with ethyl acetate (300 mL), washed successively with saturated NaHCO₃ aq. solution (40 mL × 2), water (40 mL), brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 20:1) to afford 11b (430 mg, 97%) as a colorless oil. Rₛ = 0.74 (petroleum ether/ethyl acetate = 5:1), [α]₂⁰D ≈ −21.6 (c 0.45, CHCl₃). ¹H-NMR (CDCl₃) δ 7.04–6.89 (m, 1H), 5.86 (ddd, J = 15.5, 3.0, 1.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.40 (d, J = 10.8 Hz, 1H), 3.36 (d, J = 10.8 Hz, 1H), 2.18 (dd, J = 7.9, 1.3 Hz, 2H), 1.44–1.22 (m, 5H), 0.92–0.79 (m, 6H). ¹³C-NMR (CDCl₃) δ 205.3, 166.0, 143.6, 124.6, 60.4, 49.3, 36.7, 27.9, 18.6, 14.2, 8.3. ESI-MS: 237.1, [M+K] HRMS(ESI): Calcd. for C_{11}H_{19}O₃ [M+H]: 199.1329, found: 199.1331.

(R,2E,6E)-Ethyl 5-ethyl-7-ido-5-methylhepta-2,6-dienoate (12b). To a suspension of anhydrous CrCl₂ (1.85 g, 8.82 mmol) in THF (20 mL) at 0 °C was added dropwise a solution of 11b (388 mg, 2.0 mmol) and CHI₃ (1.16 g, 2.9 mmol) in THF (10 mL). After 3 h, the mixture was quenched with 10% Na₂S₂O₃ aq. solution (20 mL). The combined organic phase was washed with ethyl acetate (20 mL × 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 50:1) to afford 12b (504 mg, 80%) as a colorless oil. Rₛ = 0.61 (petroleum ether/ethyl acetate = 10:1), [α]₂⁰D ≈ −39.2 (c 0.65, CHCl₃). ¹H-NMR (CDCl₃) δ 6.96–6.75 (m, 1H), 6.44 (d, J = 14.7 Hz, 1H), 5.97 (d, J = 14.7 Hz, 1H), 5.82 (d, J = 15.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.26–2.13 (m, 2H), 1.43–1.24 (m, 5H), 0.98 (s, 3H), 0.82 (t, J = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃) δ 166.2, 153.2, 144.8, 124.0, 74.3, 60.2, 44.3, 42.6, 32.6, 22.1, 14.2, 8.4. ESI-MS: 323.0 [M+H], HRMS(ESI): Calcd. for C_{12}H_{20}IO₂ [M+H]: 323.0502, found: 323.0511.

General procedure for the synthesis of compounds 13b–g, exemplified by (R,2E,6E)-ethyl 7-(4-((tert-butyldiphenylsilyl)oxy)phenyl)-5-ethyl-5-methylhepta-2,6-dienoate (13b). A dried flask was charged
with ZnCl₂ (300 mg, 2.2 mmol), and heated by a hot gun under vacuum until the ZnCl₂ was melted. Then the flask was filled with Ar gas and cooled to rt. Anhydrous THF (5 mL) was added into the flask to dissolve the ZnCl₂. Another dried flask was charged with 1-bromo-4-((R)-BuPh₂SiO)-C₆H₄Br (823 mg, 2.0 mmol) and THF (5 mL) under argon, and then cooled to -78 °C. n-BuLi (0.8 mL, 2.0 mmol) was added dropwise to the bromoarene solution over 30 min, and stirring was continued for 30 min. Then the organolithium solution was added dropwise to the ZnCl₂ solution at -78 °C over 15 min, and the resulting solution was stirred at rt for 1 h. Meanwhile, a mixture of [Pd(OAc)₂] (22 mg, 0.1 mmol), PPh₃ (26 mg, 0.1 mmol) and THF (2 mL) was stirred at rt for about 30 min until the brown solution was formed, and this solution was added to the organozinc solution, followed by a solution of the 12b (322 mg, 1.0 mmol) in THF (2 mL). The mixed solution was stirred overnight at rt. The reaction solution was quenched with saturated NH₄Cl aq. solution (15 mL), and extracted with ethyl acetate (15 mL × 3). The extract was washed with brine (15 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 80:1) to afford 13b (463 mg, 88%) as a colorless oil. Rf = 0.43 (petroleum ether/ethyl acetate = 20:1), [α]²⁰ -40.4 (c 0.50, CHCl₃). ¹H-NMR (CDCl₃) δ 7.77–7.66 (m, 4H), 7.46–7.31 (m, 6H), 7.10 (d, J = 8.4 Hz, 2H), 6.91 (dt, J = 15.4, 7.6 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 6.16 (d, J = 16.3 Hz, 1H), 5.90 (d, J = 16.3 Hz, 1H), 5.81 (d, J = 15.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.31–2.18 (m, 2H), 1.49–1.33 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.09 (s, 9H), 1.03 (s, 3H), 0.80 (t, J = 7.4 Hz, 3H). ¹³C-NMR (CDCl₃) δ 166.4, 154.8, 146.2, 135.7, 135.5, 132.9, 130.6, 129.9, 127.8, 127.2, 126.9, 123.4, 119.6, 60.1, 43.7, 39.6, 33.5, 26.5, 19.4, 14.3, 8.5. ESI-MS: 527.2 [M+H].

(S,2E,6E)-Ethyl 5-methyl-7-phenyl-5-vinylhepta-2,6-dienoate (13c). Yield: 98%, Rf = 0.43 (petroleum ether/ethyl acetate = 20:1), [α]²⁰ -3.1 (c 0.55, CHCl₃). ¹H-NMR (CDCl₃) δ 7.39–7.17 (m, 5H), 6.93 (dt, J = 15.4, 7.6 Hz, 1H), 6.36 (d, J = 16.2 Hz, 1H), 6.20 (d, J = 16.2 Hz, 1H), 5.93–5.82 (m, 2H), 5.11 (d, J = 10.7 Hz, 1H), 5.06 (d, J = 17.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.41 (d, J = 7.6 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.23 (s, 3H). ¹³C-NMR (CDCl₃) δ 166.3, 145.3, 144.4, 137.3, 136.4, 128.5, 128.1, 127.2, 126.2, 123.9, 113.1, 60.2, 43.8, 42.62, 23.7, 14.2. ESI-MS: 271.2 [M+H], 293.1 [M+Na], HRMS(ESI): Calcd. for C₁₈H₂₂O₂Na [M+H]: 293.1512, found: 293.1518.

(S,2E,6E)-ethyl 5-methyl-7-(p-tolyl)-5-vinylhepta-2,6-dienoate (13d). Yield: 82%, Rf = 0.41 (petroleum ether/ethyl acetate = 20:1), [α]²⁰ +3.3 (c 0.55, CHCl₃). ¹H-NMR (CDCl₃) δ 7.25 (d, J = 7.7 Hz, 2H), 7.11 (d, J = 7.7 Hz, 2H), 6.92 (dt, J = 15.4, 7.6 Hz, 1H), 6.32 (d, J = 16.2 Hz, 1H), 6.14 (d, J = 16.2 Hz, 1H), 5.94–5.77 (m, 2H), 5.12–5.01 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 2.40 (d, J = 7.4 Hz, 2H), 2.33 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.23 (s, 3H). ¹³C-NMR (CDCl₃) δ 166.3, 145.5, 144.6, 137.0, 135.4, 134.5, 129.2, 127.9, 126.1, 123.8, 113.0, 60.2, 43.8, 42.62, 23.7, 14.2. ESI-MS: 307.1 [M+Na], HRMS(ESI): Calcd. for C₁₉H₂₅O₂ [M+Na]: 285.1512, found: 285.1512.

(S,2E,6E)-ethyl 5-methyl-7-(naphthalen-2-yl)-5-vinylhepta-2,6-dienoate (13e). Yield: 60%, Rf = 0.34 (petroleum ether/ethyl acetate = 20:1), [α]²⁰ +4.4 (c 0.50, CHCl₃). ¹H-NMR (CDCl₃) δ 7.84–7.74 (m, 3H), 7.71 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.50–7.37 (m, 2H), 6.96 (dt, J = 15.4, 7.5 Hz, 1H), 6.52 (d, J = 16.2 Hz, 1H), 6.33 (d, J = 16.2 Hz, 1H), 6.00–5.82 (m, 2H), 5.17–5.05 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 2.31–2.18 (m, 2H), 1.49–1.33 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.09 (s, 9H), 1.03 (s, 3H), 0.80 (t, J = 7.4 Hz, 3H). ¹³C-NMR (CDCl₃) δ 166.4, 145.3, 144.4, 137.3, 136.4, 128.5, 128.1, 127.2, 126.2, 123.9, 113.1, 60.2, 43.8, 42.62, 23.7, 14.2. ESI-MS: 307.1 [M+Na], HRMS(ESI): Calcd. for C₁₉H₂₅O₂ [M+Na]: 285.1512, found: 285.1515.
2.46 (d, $J = 7.5$ Hz, 2H), 1.30–1.23 (m, 6H). ESI-MS: 343.3 [M+Na], HRMS (ESI): Calcd. for C$_{22}$H$_{25}$O$_2$ [M+H]: 321.1849, found: 321.1857.

(S,2E,6E)-Ethyl-5-methyl-7-(4-(trifluoromethyl)phenyl)-5-vinylhepta-2,6-dienoate (13f). Yield: 90%, $R_f = 0.41$ (petroleum ether/ethyl acetate = 20:1), $[\alpha]_D^{20} +9.8$ (c 0.50, CHCl$_3$). $^1$H-NMR (CDCl$_3$) $\delta$ 7.55 (d, $J = 8.2$ Hz, 2H), 6.98–6.84 (m, 1H), 6.39 (d, $J = 16.2$ Hz, 1H), 6.29 (d, $J = 16.2$ Hz, 1H), 5.96–5.82 (m, 2H), 5.20–5.11 (m, 1H), 5.08 (dd, $J = 17.4$, 0.8 Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.43 (dd, $J = 7.6$, 1.3 Hz, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.24 (s, 3H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 166.2 (C$_4$), 144.9 (C$_7$), 143.9 (C$_{11}$), 140.8 (C$_{15}$), 139.1 (C$_{14}$), 128.9 (C$_{18}$), 127.0 (C$_{10}$), 126.3 (C$_{16}$), 125.5 (C$_{17}$), 124.1 (C$_5$), 113.6 (13), 60.3 (C$_2$), 43.6 (C$_8$), 42.8 (C$_9$), 23.5 (C$_{12}$), 14.2 (C$_1$). ESI-MS: 361.2 [M+Na], HRMS (ESI): Calcd. for C$_{19}$H$_{22}$F$_3$O$_2$ [M+H]: 339.1566, found: 339.1575.

(S,2E,6E)-Ethyl-7-(benzo[d][1,3]dioxol-5-yl)-5-methyl-5-vinylhepta-2,6-dienoate (13g). Yield: 96%, $R_f = 0.30$ (petroleum ether/ethyl acetate = 20:1), $[\alpha]_D^{20} -15.0$ (c 0.50, CHCl$_3$). $^1$H-NMR (CDCl$_3$) $\delta$ 6.97–6.86 (m, 2H, C($7$)H, C($20$)H), 6.81–6.71 (m, 2H, C($16$)H, C($17$)H), 6.26 (d, $J = 16.2$ Hz, 1H, C($14$)H), 6.02 (d, $J = 16.2$ Hz, 1H, C($10$)H), 5.94 (s, 2H, C($22$)H), 5.92–5.81 (m, 2H, C($5$)H, C($11$)H), 5.10 (dd, $J = 10.7$, 0.7 Hz, 1H, C($13$)H), 5.05 (d, $J = 17.5$ Hz, 1H, C($13$)H), 4.18 (q, $J = 7.1$ Hz, 2H, C($2$)H$_2$), 2.42–2.36 (m, 2H, C($8$)H), 1.28 (t, $J = 7.1$ Hz, 3H, C($1$)H), 1.20 (s, 3H, C($12$)H$_3$). $^{13}$C-NMR (CDCl$_3$) $\delta$ 166.3 (C($4$)), 147.9 (C($19$)), 145.4 (C($7$)), 144.5 (C($11$)), 134.7 (C($14$)), 131.8 (C($15$)), 127.6 (C($10$)), 123.8 (C($5$)), 120.7, 113.0 (C($13$)), 108.2, 105.5, 101.0 (C($16$), C($17$), C($20$)), 60.2 (C$_2$), 43.8 (C$_8$), 42.5 (C$_9$), 23.7 (C$_{12}$), 14.2 (C$_1$). ESI-MS: 315.2[M+H], 337.2 [M+Na], HRMS(ESI): Calcd. for C$_{19}$H$_{23}$O$_4$ [M+H]: 315.1591, found: 315.1602.

**General procedure for the synthesis for 14b–g**, exemplified by 4-((R,1E,5E)-3-ethyl-7-hydroxy-3,7-dimethylocta-1,5-dien-1-yl)phenol (14b). To a stirred solution of 13b (267 mg, 0.51 mmol,) in THF (5 mL) at 0°C was added MeLi (1.0 mL, 1.5 mmol). The mixture was stirred overnight at rt. The reaction was quenched with saturated NH$_4$Cl (10 mL). The mixture was extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 5:1) to afford the silyl protected 14b (124 mg, 48%) together with 14b (47 mg, 34%) as a colorless oil. The protected compound could be deprotected quantitatively into 14b by n-Bu$_4$NF in THF at rt for 3–4 h.

Silyl protected 14b: $R_f = 0.45$ (petroleum ether/ethyl acetate = 5:1), $[\alpha]_D^{20} -65.5$ (c 0.20, CHCl$_3$). $^1$H-NMR (CDCl$_3$) $\delta$ 7.76–7.67 (m, 4H), 7.46–7.31 (m, 6H), 7.09 (d, $J = 8.6$ Hz, 2H), 6.69 (d, $J = 8.6$ Hz, 2H), 6.12 (d, $J = 16.3$ Hz, 1H), 5.90 (d, $J = 16.2$ Hz, 1H), 5.64–5.50 (m, 2H), 2.12–1.98 (m, 2H), 1.40–1.32 (m, 2H), 1.27 (s, 6H), 1.09 (s, 9H), 0.98 (s, 3H), 0.79 (t, $J = 7.4$ Hz, 3H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 154.6, 140.6, 136.9, 135.5, 132.9, 130.9, 129.8, 127.7, 126.8, 126.5, 123.4, 119.6, 70.7, 43.6, 39.4, 33.3, 29.9, 26.5, 22.9, 19.4, 8.6. ESI-MS: 530.2 [M+NH$_4$].

14b: $R_f = 0.09$ (petroleum ether/ethyl acetate = 5:1), $[\alpha]_D^{20} -36.3$ (c 0.07, CHCl$_3$). $^1$H-NMR (CDCl$_3$) $\delta$ 7.23 (d, $J = 8.6$ Hz, 2H), 6.77 (d, $J = 8.6$ Hz, 2H), 6.18 (d, $J = 16.3$ Hz, 1H), 5.96 (d, $J = 16.3$ Hz, 1H), 5.68–5.49 (m, 2H), 2.17–2.03 (m, 2H), 1.46–1.34 (m, 2H), 1.30 (s, 6H), 1.02 (s, 3H), 0.82 (t, $J = 7.5$ Hz,
3H). $^{13}$C-NMR (CDCl$_3$) δ 154.7, 140.5, 136.8, 130.8, 127.2, 126.4, 123.5, 115.3, 70.9, 43.6, 39.5, 33.3, 29.8, 22.8, 8.6. ESI-MS: 530.2 [M+NH$_4$].

(S,3E,7E)-2,6-Dimethyl-8-phenyl-6-vinylocta-3,7-dien-2-ol (14c) Yield: 73%, $R_f = 0.42$ (petroleum ether/ethyl acetate = 5:1), $[\alpha]_{D}^{20}$ = −9.5 ($c$ 0.55, CHCl$_3$). $^1$H-NMR (CDCl$_3$) δ 7.36 (d, $J = 8.0$ Hz, 2H), 7.33–7.25 (m, 2H), 7.20 (t, $J = 6.6$ Hz, 1H), 6.32 (d, $J = 16.2$ Hz, 1H), 6.20 (d, $J = 16.2$ Hz, 1H), 5.89 (dd, $J = 17.4$, 10.7 Hz, 1H), 5.70–5.55 (m, 2H), 5.09–4.98 (m, 2H), 2.23 (d, $J = 6.3$ Hz, 2H), 1.38 (s, 1H), 1.30 (s, 6H), 1.18 (s, 3H). $^{13}$C-NMR (CDCl$_3$) δ 145.3, 141.2, 137.6, 137.4, 128.5, 127.4, 127.0, 126.1, 122.9, 112.3, 70.7, 43.8, 42.7, 29.9, 23.4. ESI-MS: 274.2 [M+NH$_4$], HRMS (ESI): Calcd. for C$_{19}$H$_{24}$O$_3$Na [M+Na]: 257.1900, found: 257.1899.

(S,3E,7E)-2,6-Dimethyl-8-(p-toly)-6-vinylocta-3,7-dien-2-ol (14d) Yield: 98%, $R_f = 0.46$ (petroleum ether/ethyl acetate = 5:1), $[\alpha]_{D}^{20}$ = −9.1 ($c$ 0.55, CHCl$_3$). $^1$H-NMR (CDCl$_3$) δ 7.25 (d, $J = 7.3$ Hz, 2H), 7.10 (d, $J = 7.3$ Hz, 2H), 6.28 (d, $J = 16.2$ Hz, 1H), 6.14 (d, $J = 16.2$ Hz, 1H), 5.88 (dd, $J = 17.4$, 10.7 Hz, 1H), 5.70–5.53 (m, 2H), 5.11–4.94 (m, 2H), 2.32 (s, 3H), 2.22 (d, $J = 5.9$ Hz, 2H), 1.42 (brs, 1H), 1.29 (s, 6H), 1.17 (s, 3H). $^{13}$C-NMR (CDCl$_3$) δ 145.4, 141.1, 136.7, 136.4, 134.9, 129.2, 127.3, 126.0, 123.0, 112.2, 70.7, 43.8, 42.6, 29.8, 23.4, 21.1. ESI-MS: 293.2 [M+Na].

(S,3E,7E)-2,6-Dimethyl-8-(naphthalen-2-yl)-6-vinylocta-3,7-dien-2-ol (14e) Yield: 100%, $R_f = 0.41$ (petroleum ether/ethyl acetate = 5:1), $[\alpha]_{D}^{20}$ = −13.7 ($c$ 0.35, CHCl$_3$). $^1$H-NMR (CDCl$_3$) δ 7.83–7.74 (m, 3H), 7.70 (s, 1H), 7.59 (d, $J = 8.6$ Hz, 1H), 7.48–7.38 (m, 2H), 6.49 (d, $J = 16.2$ Hz, 1H), 6.34 (dd, $J = 16.2$, 2.0 Hz, 1H), 5.93 (ddd, $J = 17.4$, 10.7, 2.0 Hz, 1H), 5.72–5.57 (m, 2H), 5.14–5.01 (m, 2H), 2.26 (dd, $J = 5.9$, 1.7 Hz, 2H), 1.41 (s, 1H), 1.30 (s, 6H), 1.23 (s, 3H). $^{13}$C-NMR (CDCl$_3$) δ 145.3, 141.2, 137.9, 135.1, 133.6, 132.7, 128.0, 127.8, 127.6, 126.1, 125.68, 125.5, 123.5, 122.9, 112.4, 70.8, 43.8, 42.8, 29.9, 23.4. ESI-MS: 293.2 [M+Na], HRMS (ESI): Calcd. for C$_{22}$H$_{26}$ONa [M+Na]: 329.1876, found: 329.1885.

(S,3E,7E)-2,6-Dimethyl-8-(4-(trifluoromethyl)phenyl)-6-vinylocta-3,7-dien-2-ol (14f) Yield: 96%, $R_f = 0.42$ (petroleum ether/ethyl acetate = 5:1), $[\alpha]_{D}^{20}$ = +2.0 ($c$ 0.75, CHCl$_3$). $^1$H-NMR (CDCl$_3$) δ 7.54 (d, $J = 8.2$ Hz, 2H), 7.44 (d, $J = 8.2$ Hz, 2H), 6.35 (d, $J = 16.3$ Hz, 1H), 6.30 (d, $J = 16.3$ Hz, 1H), 5.89 (dd, $J = 17.5$, 10.7 Hz, 1H), 5.70–5.53 (m, 2H), 5.09 (dd, $J = 10.7$, 1.0 Hz, 1H), 5.03 (dd, $J = 17.5$, 1.0 Hz, 1H), 2.24 (d, $J = 6.6$ Hz, 2H), 1.37 (brs, 1H), 1.30 (s, 6H), 1.20 (s, 3H). $^{13}$C-NMR (CDCl$_3$) δ 144.7, 141.4, 141.1, 140.2, 126.3, 126.2, 125.4, 125.4, 122.5, 112.8, 70.7, 43.7, 42.9, 29.9, 23.2. ESI-MS: 347.2 [M+Na], HRMS(ESI): Calcd. for C$_{19}$H$_{24}$F$_3$O$_3$Na [M+Na]: 325.1774, found: 325.1774.

(S,3E,7E)-8-(Benzo[1,3]dioxol-5-yl)-2,6-dimethyl-6-vinylocta-3,7-dien-2-ol (14g) Yield: 38%, $R_f = 0.26$ (petroleum ether/ethyl acetate = 5:1), $[\alpha]_{D}^{20}$ = −10.2 ($c$ 0.50, CHCl$_3$). $^1$H-NMR (CDCl$_3$) δ 6.91 (s, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 6.22 (d, $J = 16.2$ Hz, 1H), 6.03 (d, $J = 16.2$ Hz, 1H), 5.93 (d, $J = 1.0$ Hz, 2H), 5.87 (dd, $J = 17.5$, 10.7 Hz, 1H), 5.68–5.52 (m, 2H), 5.05 (d, $J = 10.7$ Hz, 1H), 5.00 (d, $J = 17.5$ Hz, 1H), 2.21 (d, $J = 6.5$ Hz, 2H), 1.42 (brs, 1H), 1.29 (s, 6H), 1.16 (s, 3H). $^{13}$C-NMR (CDCl$_3$) δ 147.9, 146.7, 145.3, 141.1, 135.7, 132.2, 127.0, 122.9, 120.5, 112.3, 108.2, 105.4, 100.9, 70.7, 43.8, 42.6, 29.9, 29.7, 23.4. ESI-MS: 318.4 [M+NH$_4$], HRMS (ESI): Calcd. for C$_{19}$H$_{24}$O$_3$Na [M+Na]: 323.1618, found: 323.1639.
3.3. Activity Tests

The MTT assay was used to measure cell viability. All the tested compounds were dissolved in 0.5% DMSO. Before analysis, UMR 106 cells (rat osteosarcoma cell line) were cultured with or without different concentrations of compounds for 48 h, respectively. At the end of incubation 0.5% MTT (20 μL) was added to each well, followed by incubation at 37 °C in 5% CO₂ atmosphere for 4 h. The medium was then removed carefully, and DMSO (150 μL) was added to each well. The plates were shaken gently for 10 min to dissolve the blue formazan crystals. Absorbance was measured at 570 nm using an ELx-800 universal microplate reader (Bio-Tek, Winooski, VT, USA).

4. Conclusions

In summary, a series of the analogues of Δ³-2-hydroxybakuchiol have been synthesized, and some of them have been found to possess evident cytotoxic activity against rat UMR106 cells. Furthermore, the SAR study gives a preliminary profile, including: (1) the chain tail on the natural product could be somewhat modified to enhance the activity; (2) the aromatic moiety or the terminal olefin attached on the main chain are allowed to be modified without evident loss of activity; (3) the stereoconfiguration at the quaternary chiral center has an important influence on the activity.

Acknowledgments

We thank National Natural Foundation of China (21242008) and National High-tech R&D Program of China (2013AA092903) for the financial support. We are grateful to Luyan Zhang for his helpful discussion.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Sun, N.J.; Woo, S.H.; Cassady, J.M.; Snapka, R.M. DNA polymerase and topoisomerase II inhibitors from Psoralea corylifolia. J. Nat. Prod. 1998, 61, 362–366.
2. Miura, H.; Nishida, H.; Linuma, M. Effect of Crude Fractions of Psoralea corylifolia Seed Extract on Bone Calcification. Planta Med. 1996, 62, 150–153.
3. Yin, S.; Fan, C.-Q.; Yue, J.-M. Cyclobakuchiol C, a new bakuchiol derivative from Psoralea corylifolia. J. Asian Nat. Prod. Res. 2007, 9, 29–33.
4. Matsuda, H.; Sugimoto, S.; Morikawa, T.; Matsuhira, K.; Mizuguchi, E.; Nakamura, S.; Yoshikawa, M. Bioactive constituents from chinese natural medicines. XX. Inhibitors of antigen-induced degranulation in RBL-2H3 cells from the seeds of Psoralea corylifolia. Chem. Pharm. Bull. 2007, 55, 106–110.
5. Wu, C.-Z.; Cai, X.F.; Dat, N.T.; Hong, S.S.; Han, A.-R.; Seo, E.-K.; Hwang, B.Y.; Nan, J.-X.; Lee, D.; Lee, J.J. Bisbakuchiols A and B, novel dimeric meroterpenoids from Psoralea corylifolia. Tetrahedron Lett. 2007, 48, 8861–8864.
6. Yin, S.; Fan, C.-Q.; Dong, L.; Yue, J.-M. Psoracorylifols A–E, five novel compounds with activity against Helicobacter pylori from seeds of Psoralea corylifolia. Tetrahedron 2006, 62, 2569–2575.

7. Backhouse, C.N.; Delporte, C.L.; Negrete, R.E.; Erazo, S.; Zuniga, A.; Pinto, A.; Cassels, B.K. Active constituents isolated from Psoralea glandulosa L. with antiinflammatory and antipyretic activities. J. Ethnopharmacol. 2001, 78, 27–31.

8. Majeed, R.; Reddy, M.V.; Chinthakindi, P.K.; Sangwan, P.L.; Hamid, A.; Chashoo, G.; Saxena, A.K.; Koul, S. Bakuchiol derivatives as novel and potent cytotoxic agents: A report. Eur. J. Med. Chem. 2012, 49, 55–67.

9. Reddy, M.V.; Thota, N.; Sangwan, P.L.; Malhotra, P.; Ali, F.; Khan, I.A.; Chimni, S.S.; Koul, S. Novel bisstyryl derivatives of bakuchiol: Targeting oral cavity pathogens. Eur. J. Med. Chem. 2010, 45, 3125–3134.

10. Chen H.; Du, X.; Tang, W.; Zhou, Y.; Zuo, J.; Feng, H.; Li, Y. Synthesis and structure–immunosuppressive activity relationships of bakuchiol and its derivatives. Bioorg. Med. Chem. 2008, 16, 2403–2411.

11. Chen, Z.; Jin, K.; Gao, L.; Lou, G.; Jin, Y.; Yu, Y.; Lou, Y. Anti-tumor effects of bakuchiol, an analogue of resveratrol, on human lung adenocarcinoma A549 cell line. Eur. J. Pharmcol. 2010, 643, 170–179.

12. Yan, D.-M.; Chang, Y.-X.; Wang, Y.-F.; Liu, E.-W.; Li, J.; Kang, L.-Y.; Gao, X.-M. In vivo pharmacokinetics of bakuchiol after oral administration of bakuchiol extraction in rat plasma. J. Ethnopharmacol. 2010, 128, 697–702.

13. Choi, S.Y.; Lee, S.; Choi, W.-H.; Lee, Y.; Jo, Y.O.; Ha, T.-Y. Isolation and anti-inflammatory activity of bakuchiol from Ulmus davidiana var. japonica. J. Med. Food 2010, 13, 1019–1023.

14. Lim, S.-H.; Ha, T.-Y.; Kim, S.-R.; Ahn, J.; Park, H.J.; Kim, S. Ethanol extract of Psoralea corylifolia L. and its main constituent, bakuchiol, reduce bone loss in ovariectomised Sprague–Dawley rats. Br. J. Nutr. 2009, 101, 1031–1039.

15. Choi, Y.H.; Yon, G.H.; Hong, K.S.; Yoo, D.S.; Choi, C.W.; Park, W.-K.; Kong, J.Y.; Kim, Y.S.; Ryu, S.Y. In vitro BACE-1 inhibitory phenolic components from the seeds of Psoralea corylifolia. Planta Med. 2008, 74, 1405–1408.

16. Wu, C.-Z.; Hong, S.S.; Cai, X.F.; Dat, N.T.; Nan, J.-X.; Hwang, B.Y.; Lee, J.J. Lee, D. Hypoxia-inducible factor-1 and nuclear factor-κB inhibitory meroterpenoids analogues of bakuchiol, a constituent of the seeds of Psoralea corylifolia. Bioorg. Med. Chem. Lett. 2008, 18, 2619–2623.

17. Kim, Y.-C.; Oh, H.; Kim, B.S.; Kang, T.-H.; Ko, E.-K.; Han, Y.M.; Kim, B.Y.; Ahn, J.S. In vitro Protein Tyrosine Phosphatase 1B inhibitory phenols from the seeds of Psoralea corylifolia. Planta Med. 2005, 71, 87–89.

18. Park, E.-J.; Zhao, Y.-Z.; Kim, Y.-C.; Sohn, D.H. Bakuchiol-induced caspase-3-dependent apoptosis occurs through c-Jun NH2-terminal kinase-mediated mitochondrial translocation of Bax in rat liver myofibroblasts. Eur. J. Pharmacol. 2007, 559, 115–123.

19. Adhikari, S.; Joshi, R.; Patro, B.S.; Ghanty, T.K.; Chintalwar, G.J.; Sharma, A.; Chattopadhyay, S.; Mukherjee, T. Antioxidant activity of bakuchiol: Experimental evidences and theoretical treatments on the possible involvement of the terpenoid chain. Chem. Res. Toxicol. 2003, 16, 1062–1069.
20. Haraguchi, H.; Inoue, J.; Tamura, Y.; Mizutani, K. Antioxidative components of *Psoralea corylifolia* (Leguminosae). *Phytother. Res.* **2002**, *16*, 539–544.

21. Cho, H.; Jun, J.-Y.; Song, E.-K.; Kang, K.-H.; Baek, H.-Y.; Ko, Y.-S.; Kim, Y.-C. Bakuchiol: A hepatoprotective compound of *Psoralea corylifolia* on tacrine-induced cytotoxicity in Hep G2 Cells. *Planta Med.* **2001**, *67*, 750–751.

22. Haraguchi, H.; Inoue, J.; Tamura, Y.; Mizutani, K. Inhibition of mitochondrial lipid peroxidation by bakuchiol, a meroterpene from *Psoralea corylifolia*. *Planta Med.* **2000**, *66*, 569–571.

23. Krenisky, J.M.; Luo, J.; Reed, M.J.; Carney, J.R. Isolation and antihyperglycemic activity of bakuchiol from *Otholobium pubescens* (Fabaceae), a peruvian medicinal plant used for the treatment of diabetes. *Biol. Pharm. Bull.* **1999**, *22*, 1137–1140.

24. Labbè, C.; Faini, F.; Coll, J.; Connolly, J.D. Bakuchiol derivatives from the leaves of *Psoralea glandulosa*. *Phytochemistry* **1996**, *42*, 1299–1304.

25. Shah, C.C.; Bhalla, V.K.; Dev, S. Meroterpenoids-V: *Psoralea Corylifolia* Linn. - 4. 2,3-Epoxybakuchiol, Delta 1,3-Hydroxybakuchiol, and Delta 3,2-Hydroxybakuchiol. *J. Indian Chem. Soc.* **1997**, *74*, 970–973.

26. Zhao, G.; Zang, S.-Y.; Zheng, X.-W.; Zhang, X.-H.; Guo, L.-H. Bakuchiol analogs inhibit monoamine transporters and regulate monoaminergic functions. *Biochem. Pharmacol.* **2008**, *75*, 1835–1847.

27. Zhang, Q.; Deng, C.; Fang, L.; Xu, W.; Zhao, Q.; Zhang, J.; Wang, Y.; Lei X. Synthesis and Evaluation of the Analogues of Penicillide against Cholesterol Ester Transfer Protein. *Chin. J. Chem.* **2013**, *31*, 355–370.

28. Deng, C.-L.; Zhang, Q.; Fang, L.-S.; Lei, X.; Lin, G.-Q. A Convergent Approach to Dibenzo(dioxocinones: Synthesis of Racemic Penicillide. *Helv. Chim. Acta* **2012**, *95*, 626–635.

29. Fang, L.-S.; Zhang, Q.; Deng, C.-L.; Lei, X.; Lin, G.-Q. Regio-selective chlorination of vinca alkaloids catalyzed by Lewis acid. *Sci. China Chem.* **2011**, *54*, 1039–1043.

30. Lei, X.; Yu, X.; Yin, L.; Liu, Z.; Tang, P.C. Synthesis and biological evaluation of C-12' substituted vinflunine derivatives. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4602–4605.

31. Shi, L.; Zhang, J.; Lei, X.; Lin, G. Synthesis of racemic Δ3-2-Hydroxybakuchiol and its analogues. *Helv. Chim. Acta* **2010**, *93*, 555–564.

32. Xu, Q.-Q.; Zhao, Q.; Shang, G.-S.; Yang, X.-C.; Lei, X. A facile asymmetric synthesis of Δ3-2-Hydroxybakuchiol, Bakuchiol and ent-Bakuchiol. *Tetrahedron* **2013**, *69*, 10739–10746.

33. Cha, M.-R.; Choi, C.W.; Lee, J.Y.; Kim, Y.S.; Yon, G.H.; Choi, S.-U.; Ryn, S.Y. Anti-proliferative effect of synthesized bakuchiol analogues on cultured human tumor cell lines. *Bull. Korean Chem. Soc.* **2012**, *33*, 2378–2380.

34. Zheng, C.; Hua, C.; Ma, X.; Peng, C.; Zhang, H.; Qin, L. Cytotoxic phenylpropanoid glycosides from *Fagopyrum tataricum* (L.) Gaertn. *Food Chem.* **2012**, *132*, 433–438.

**Sample Availability**: Samples of the compounds are available from the authors.