Synthesis of Racemic Δ^3-2-Hydroxybakuchiol and Its Analogues

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The first synthetic approach to (±)-Δ^3-2-hydroxybakuchiol (=4-[(1*E*,5*E*)-3-ethenyl-7-hydroxy-3,7-dimethylocta-1,5-dien-1-yl]phenol; **14**) and its analogues **13a**–**13f** was developed by 12 steps (*Schemes 2* and *3*). The key features of the approach are the construction of the quaternary C-center bearing the ethenyl group by a *Johnson–Claisen* rearrangement (→**6**); and of an (*E*)-alkenyl iodide *via* a *Takai–Utimoto* reaction (→**11**); and an arylation *via* a *Negishi* cross-coupling reaction (→**12e**–**12f**).

Introduction. – The medicinal plant *Psoralea corylifolia* L. has been used over a long time as Chinese traditional medicine to treat a wide variety of disorders such as deobstruent, anthelmintic, and diuretic diseases as well as certain skin diseases such as vitiligo [1][2]. A number of monoterpene phenols occurring in the plant have been isolated and demonstrated to possess versatile biological activities [3–8] (see *Fig.*). For example, bakuchiol[1]), a major constituent obtained from the seed of the plant [9][10], exhibits β-secretase (BACE-1) [11] and protein tyrosine phosphatase B (PTP1B) inhibition [12], hepatoprotective and antifibrotic effects [13], and other activities [14–19], which have attracted much interest of medicinal chemists [20–26]. In contrast to bakuchiol, few attention has been paid to Δ^3-2-hydroxybakuchiol (= 3,4-didehydro-2,3-dihydro-2-hydroxybakuchiol)[1]) [27], a congener metabolized oxidatively from bakuchiol, probably due to its scarcity and lability [28]. Most recently, *Guo* and co-workers have disclosed that Δ^3-2-hydroxybakuchiol could inhibit monoamine transporters and regulate monoaminargic transmission, which are associated with psychogenic disorders such as *Parkinson*'s disease, depression, and cocaine addiction [29]. Therefore, the natural product might be a lead compound for the development of potential psychopharmacologic agents.

To the best of our knowledge, racemic or enantiomerically pure Δ^3-2-hydroxybakuchiol has not been synthesized so far since its first isolation and identification. Though there are several available accesses to racemic or optically active bakuchiol [20–26], there remain, however, some limitations. For instance, the general feature for the construction of the styrene moiety of bakuchiol is to use the *Grignard* reaction of the appropriate aliphatic aldehydes with (4-methoxyphenyl)magnesium bromide or (4-

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

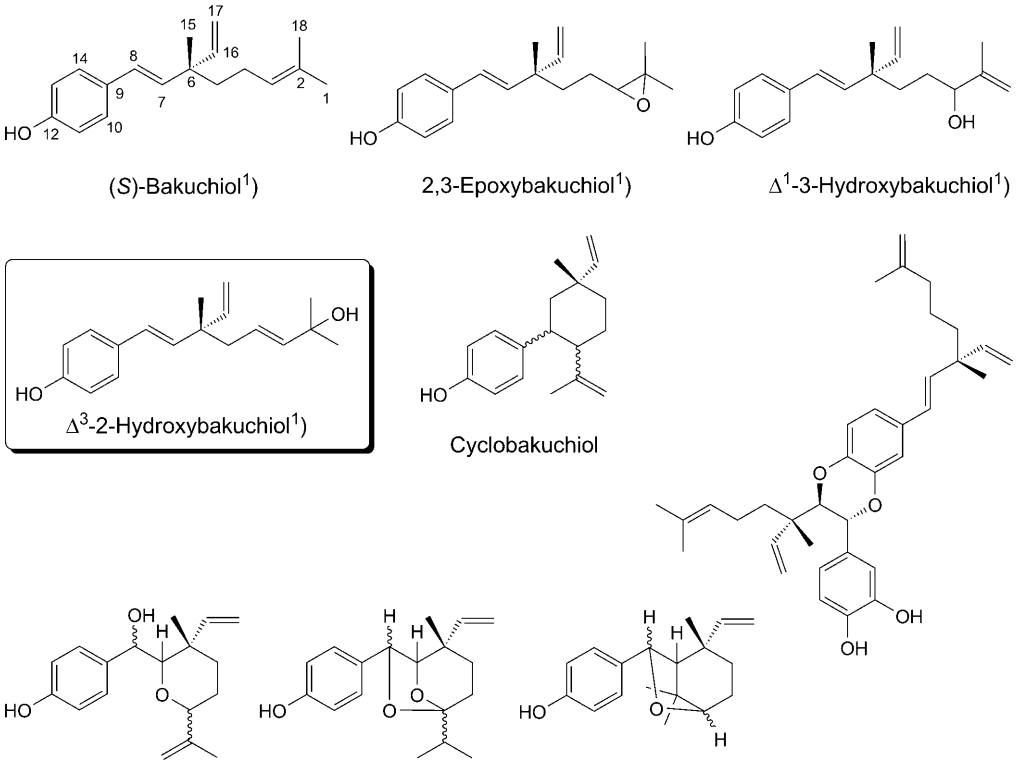


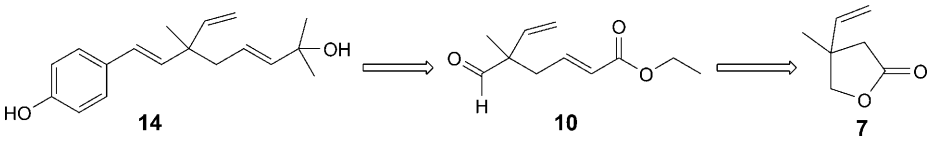
Figure. *(+)-(*S*)-Bakuchiol and some of its congeners*

methoxybenzyl)magnesium chloride and subsequent dehydration of the resulting alcohols. Moreover, demethylation of 12-*O*-methylbakuchiol to form bakuchiol has to be performed at a surprisingly high temperature (180°) with MeMgI. Previous research has shown that 2,3-epoxybakuchiol derived from bakuchiol could not be chemically converted to Δ^3-2-hydroxybakuchiol but rather to Δ^1-3-hydroxybakuchiol [30], despite the evident biogenetic relationship between them. Therefore, the reported methods for the synthesis of bakuchiol seem to be unsuitable for the preparation of the labile Δ^3-2-hydroxybakuchiol. Herein, we report the first synthesis of racemic Δ^3-2-hydroxybakuchiol.

Results and Discussion. – Our retrosynthetic route for the synthesis of (±)-Δ^3-2-hydroxybakuchiol (**14**) is outlined in *Scheme 1*. According to the designed route from **7** *via* **10**, it was our idea not only to construct (±)-Δ^3-2-hydroxybakuchiol but also to modify afterwards the structure of the target compound conveniently for the structure – activity-relationship study.

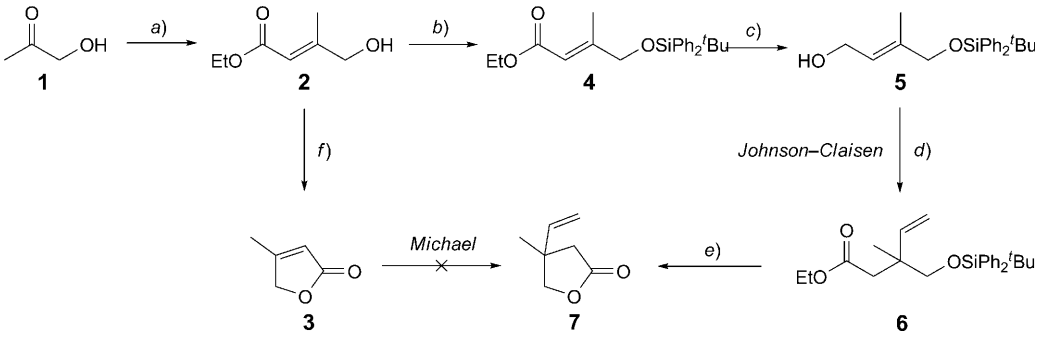
Thus, starting from commercial 2-hydroxyacetone (=1-hydroxypropan-2-one; **1**) and ethyl (triphenylphosphoranylidene)acetate, ethyl (2*E*)-4-hydroxy-3-methylbut-2-enoate (**2**) was prepared in 77.7% yield according to the described method [31–33], and then, the corresponding α,β-unsaturated lactone **3** was obtained in 68.3% yield by

Scheme 1. *Restrosynthetic Route for Racemic Δ^3-2-Hydroxybakuchiol* (**14**)



subsequent saponification and intramolecular cyclization (*Scheme 2*). Our attempt to construct the key intermediate **7** by using the *Michael*-addition reaction [34] of lactone **3** with vinylcuprate species, prepared *in situ* from vinylmagnesium bromide and CuI (or $CuBr \cdot Me_2S$), failed, although the same strategy was successfully applied to an α,β-unsaturated aldehyde by *Li*'s group [22] or to a cyclic α,β-unsaturated amide by *Esumi*'s group [20] in the course of our project. Thus, we turned our attention to an alternative approach aiming to obtain intermediate **7**: Butenoate **2** was protected as $^t BuPh_2Si$ ether **4** and reduced to the allyl alcohol **5** with DIBALH (=diisobutylaluminium hydride) in CH_2Cl_2 at $-20°$ (yields 91.8% and 82.6%, resp.). Then, compound **6** with the quaternary C-center bearing the ethenyl group was constructed via a *Johnson–Claisen* rearrangement [35][36]. The reaction resulted in 73.4% of **6** (based on **5**), when the allyl alcohol **5** was treated with an excess of triethyl orthoacetate in the presence of catalytic amounts of propanoic acid. After removal of the protective group and spontaneous cyclization, the key intermediate **7** was provided in 83.7% yield from **6**.

Scheme 2. *Synthesis of the Key Intermediate* **7**

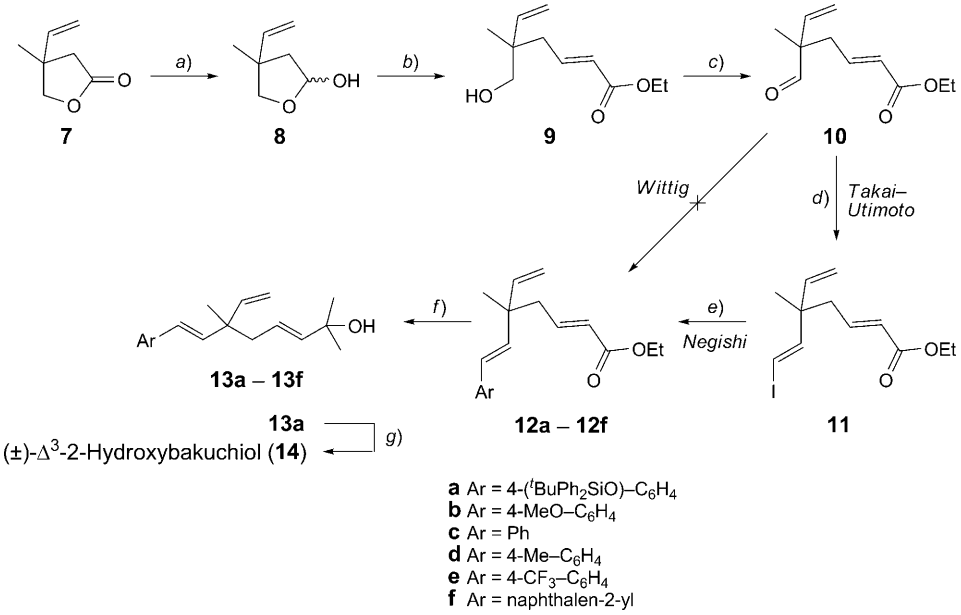


a) $Ph_3P{=}CHCOOEt$, toluene, reflux; 77.7%. *b*) $^t BuPh_2SiCl$, DMAP (= *N*,*N*-dimethylpyridin-4-amine), 1*H*-imidazole,CH_2Cl_2; 91.8%. *c*) DIBALH, CH_2Cl_2, $-20°$, 82.6%. *d*) $Me(OEt)_3$, EtCOOH, reflux; 73.4%. *e*) Bu_4NF, THF; 83.7%. *f*) NaOH (aq.); HCl (aq.).

The intermediate **7** was carefully reduced to the hemiacetal **8** in 82.4% yield, which consisted of two stereoisomers in a *ca.* 1:1 ratio (*Scheme 3*). *Wittig* reaction of **8** with $Ph_3P{=}CHCO_2Et$ in toluene under reflux for 2 h led to the desired **9** in 79% yield (65% over both steps). Oxidation of **9** with IBX (=2-iodylbenzoic acid = 1-hydroxy-1λ^3,2-benziodoxol-3(1*H*)-one 1-oxide) afforded aldehyde **10** in 94.5% yield. With the aldehyde in hand, we tested the *Wittig* or *Horner–Wadsworth–Emmons* reaction by treating **10** with the appropriate phosphorus ylides, prepared *in situ* from (4-

methoxybenzyl)triphenylphosphonium bromide or diethyl (4-methoxybenzyl)phosphonate in the presence of various bases such as ^{t}BuOK, NaH, LHMDS (= lithium hexamethyldisilazide), *etc.*, to get compound **12b**. However, several efforts proved to be unsuccessful, possibly due to the steric hindrance exerted by the quaternary C-atom in α position.

Scheme 3. *Synthesis of (±)-Δ^3-2-Hydroxybakuchiol* (**14**) *and Its Analogues* **13a**–**13f**



a) DIBALH, CH_2Cl_2, $-20°$; 82.4%. *b*) $Ph_3P{=}CHCOOEt$, toluene, reflux; 79%. *c*) IBX, DMSO; 94.5%. *d*) CHI_3,$CrCl_2$,THF; 78.6%. *e*) ArBr, BuLi/$ZnCl_2$; [$Pd(OAc)_2$]/PPh_3, THF; 47.3–90.1%. *f*) MeMgI, Et_2O/THF; 48.3–88.0%. *g*) Bu_4NF, THF; 77.8%.

Fortunately, we found that the aldehyde **10** could be converted into the corresponding (*E*)-alkenyl iodide **11** via the *Takai–Utimoto* reaction [37][38] in a satisfying yield. Especially, the reaction resulted in up to 78.6% yield of **11** by using commercial greyish $CrCl_2$, in comparison with 42% or lower yields when greenish $CrCl_2$ or freshly prepared $CrCl_2$ from $CrCl_3 \cdot 6\,H_2O$ and Zn powder were used [39]. After the successful synthesis of iodoalkene derivative **11**, *Suzuki* reaction of **11** with various arylboronic acids were performed. To our disappointment, the reaction led to very low conversion (< 10%) over a period of 24 h under either the standard condition ([$Pd(PPh_3)_4$]/Na_2CO_3, toluene, 110°) [40] or *Fu*'s condition ([$Pd(dba)_2$]/P(^{t}Bu)$_3$/KF, THF, r.t.; dba = dibenzylideneacetone = 1,5-diphenylpenta-1,4-dien-3-one) [41]. Finally, *Negishi* reaction [42][43] was selected for the transformation of **11**. To our delight, the desired cross-coupling compounds **12a**–**12f** were produced in good yields (47.3–90.1%), by using [$Pd(OAc)_2$] (0.05 equiv.)/PPh_3 (0.10 equiv.) as the catalyst. After selective 1,2-addition reaction with MeMgI, compounds **13a**–**13f** were obtained in rewarding yields (48.3–88.0%). Finally, **13a** (Ar = 4-(^{t}BuPh$_2$SiO)–C_6H_4) was converted into (±)-Δ^3-2-

hydroxybakuchiol (**14**) in 77.8% yield after deprotection of the ^{t}BuPh$_2$Si group with $Bu_4NF \cdot 3\,H_2O$ in THF. As mentioned in the literature [28], the prepared compound (±)Δ^3-2-hydroxybakuchiol (**14**) indeed underwent decomposition at room temperature, especially in $CDCl_3$, but it was enough stable in AcOEt or (D_6)-DMSO. Since decomposition of the precursors **13a**–**13f** was not observed, it seems that the free phenolic OH group might cause the lability of Δ^3-2-hydroxybakuchiol.

Conclusions. – In summary, we have developed the first synthetic approach to (±)-Δ^3-2-hydroxybakuchiol (**14**) and its analogues. The key features of the approach include the construction of the quaternary C-center bearing the ethenyl group by a *Johnson–Claisen* rearrangement, and of an (*E*)-alkenyl iodide via a *Takai–Utimoto* reaction, and an arylation *via* a *Negishi* cross-coupling reaction. The (±)-Δ^3-2-hydroxybakuchiol (**14**) was obtained by this approach in 12 steps and in 9.4% overall yield. The optimized approach and asymmetric synthesis of Δ^3-2-hydroxybakuchiol is under way.

We thank the Fudan University and the *National Natural Science Foundation of China* (20872019) for financial research support, and we are grateful to the Shanghai Institute of Organic Chemistry for recording the EI-MS or ESI-MS, HR-MS, ^{1}H-NMR, and ^{13}C-NMR spectra.

Experimental Part

General. Solvents were distilled from the appropriate drying agents before use. All the reagents were purchased from *Acros*, *Alfa Aesar*, and *National Chemical Reagents Group Co. Ltd.,* P. R.China. Column chromatography (CC): Commercial silica gel (*Qingdao Hai Yang Chemical Group Co.*; 300–400 mesh). TLC: silica gel *GF 254* plates (*Yantai Jiangyou Silica R&D Co. Ltd.*, P. R. China); detection under UV light or with I_2. ^{1}H- and ^{13}C-NMR Spectra: *Varian-Mercury-Plus* (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) spectrometer; in $CDCl_3$ if not stated otherwise; chemical shifts δ in ppm, with residual $CHCl_3$ (δ(H) 7.26 and δ(C) 77.0) as internal standard; *J* in Hz. EI-MS, ESI-MS and HR-MS: *Finnigan-Mat-95* mass spectrometer; in *m*/*z*.

*Ethyl (2*E*)-4-Hydroxy-3-methylbut-2-enoate* (**2**). To a soln. of 1-hydroxypropan-2-one (15 ml, 0.219 mol) in toluene (100 ml) was added a soln. of $Ph_3P{=}CHCO_2Et$ in toluene (200 ml), and the soln. was then refluxed for 4 h. After accomplishment of the reaction monitored by TLC, the soln. was allowed to reach r.t. and concentrated. The resulting residue was treated with Et_2O (100 ml), and then the white precipitate was removed by filtration. The resulting filtrate was washed with H_2O and brine, dried (Na_2SO_4), and concentrated, and the crude product purified by CC (silica gel, petroleum ether/AcOEt 5 : 1, R_f 0.25): 24.5 g (77.7%) of **2**. Colorless oil. ^{1}H-NMR: 5.93 (*d*, *J* = 1.2, H–C(2)); 4.08–4.15 (*m*, CH_2(4), MeC*H*$_2$O); 2.72 (br. *s*, OH); 2.03 (*s*, Me–C(3)); 1.23 (*t*, *J* = 7.5, *Me*CH$_2$O).

*Ethyl (2*E*)-4-{[(tert-Butyl)diphenylsilyl]oxy}-3-methylbut-2-enoate* (**4**). To a soln. of **2** (4.85 g, 33.7 mmol), 1*H*-imidazole (4.58 g, 67.3 mmol), and DMAP (0.205 g, 1.68 mmol) in CH_2Cl_2 (60 ml) was added dropwise ^{t}BuPh$_2$SiCl (12.1 ml, 47.1 mmol) within 30 min at 0°, and the mixture was stirred for another 2 h at r.t. The mixture was diluted with CH_2Cl_2 (40 ml) the soln. washed with H_2O and brine, dried (Na_2SO_4), and concentrated, and the crude product purified by CC (petroleum ether/CH_2Cl_2 5 : 1: R_f 0.20): 11.4 g (91.8%) of **4**. Colorless oil. ^{1}H-NMR: 7.39–7.68 (*m*, 10 arom. H); 6.02 (*s*, H–C(2)); 4.18 (*q*, 2 H, J = 7.5, MeC*H*$_2$O); 4.08 (*d*, *J* = 1.2, CH_2(4)); 2.00 (*s*, Me–C(3)); 1.32 (*t*, *J* = 7.5, *Me*CH$_2$O); 1.08 (*s*, ^{t}Bu). EI-MS: 337 ([*M* – OEt]$^+$), 325 ([M – ^{t}Bu]$^+$).

*(2*E*)-4-{[(tert-Butyl)diphenylsily]loxy}-3-methylbut-2-en-1-ol* (**5**). To a soln. of **4** (5.04 g, 12.3 mmol) in CH_2Cl_2 (150 ml) was added dropwise a soln. of DIBALH in hexane (12.3 ml, 25% (*w*/*w*), 15 mmol) within 30 min at –20°. After stirring for 2 h, the reaction was quenched with MeOH (80 ml) and the mixture warmed to r.t. and stirred for 0.5 h. The resulting mixture was filtered through *Celite*, the filtrate

washed with brine (30 ml), dried (Na_2SO_4) and concentrated, and the residue purified by CC (petroleum ether/AcOEt 10:1, R_f 0.12): 3.73 g (82.6%) of **5**. Colorless oil. ^{1}H-NMR: 7.26–7.69 (*m*, 10 arom. H), 5.73–5.78 (*m*, H–C(2)); 4.21 (*d*, *J* = 5.7, CH_2(1)); 4.07 (*s*, CH_2(4)); 1.62 (*s*, Me–C(3)); 1.40–1.50 (br. *s*, OH); 1.07 (*s*, ^{t}Bu). ESI-MS: 363.0 ($[M+Na]^+$).

*Ethyl 3-{[[(*tert*-Butyl)diphenylsilyl]oxy}methyl]-3-methylpent-4-enoate* (**6**). A soln. of **5** (6.12 g, 18.0 mmol) and $MeCH_2CO_2H$ (0.7 ml) in triethyl orthoacetate (98 ml) was refluxed overnight, and then the excess triethyl orthoacetate was removed by evaporation. The resulting residue was purified by CC (petroleum ether/Et_2O 200:1, R_f 0.20): 5.4 g (73.4%) of **6**. Colorless oil. ^{1}H-NMR: 7.23–7.57 (*m*, 10 arom. H); 5.78–6.03 (*dd*, *J*(4,5) = 10.8 and 17.4, H–C(4)); 4.98 (*d*, *J*(4,5) = 10.8, H_{cis}–C(5)); 4.94 (*d*, *J*(4,5) = 17.4, H_{trans}–C(5)); 3.96 (*q*, *J* = 6.9, Me*C*H_2O); 3.46 (*d*, J_{gem} = 9.9, 1 H, $SiOCH_2$–C(3)); 3.39 (*d*, J_{gem} = 9.9, 1 H, $SiOCH_2$–C(3)); 2.46 (*d*, J_{gem} = 12.9, 1 H–C(2)); 2.40 (*d*, J_{gem} = 12.9, 1 H–C(2)); 1.07 (*s*, *Me*–C(3)); 1.08 (*t*, *J* = 6.9, *Me*CH_2O); 0.97 (*s*, ^{t}Bu). ^{13}C-NMR: 171.9 (C=O); 143.0; 135.7; 133.5; 129.7; 127.7; 113.4 (C(5)); 70.7 ($SiOCH_2$–C(3)); 60.0 (Me*C*H_2O); 41.7 (C(2)); 41.6 (C(3)); 26.9 (*Me*–C(3)); 20.9 (Me_2C), 19.5 (Me_3C), 14.3 (*Me*CH_2O). ESI-MS: 411.0 ($[M+H]^+$), 433.1 ($[M+Na]^+$). HR-ESI-MS: 433.2169 ($C_{25}H_{34}NaO_3Si^+$, $[M+Na]^+$; calc. 433.2167).

*4-Ethenyldihydro-4-methylfuran-2(3*H*)-one* (**7**). To a soln. of **6** (9.09 g, 20.8 mmol) in THF (50 ml) was added a soln. of $Bu_4NF \cdot 3\ H_2O$ (25.4 g, 83.2 mmol) in THF (100 ml) at r.t., and then stirring was continued overnight. The reaction was quenched by addition of H_2O (150 ml), the org. phase washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (petroleum ether/AcOEt 20:1, R_f 0.14): 2.34 g (83.7%) of **7**. Colorless oil. ^{1}H-NMR: 5.85–5.95 (*dd*, *J*(1′,2′) = 10.5, 17.7, H–C(2′)); 5.16 (*d*, *J*(1′,2′) = 17.7, H_{trans}–C(1′)); 5.16 (*d*, *J*(1′,2′) = 10.5, H_{cis}–C(2′)); 4.14 (*d*, J_{gem} = 9.0, 1 H–C(5)); 4.01 (*d*, J_{gem} = 9.0, 1 H–C(5)); 2.59 (*d*, J_{gem} = 16.8, 1 H–C(3)); 2.35 (*d*, J_{gem} = 16.8, 1 H–C(3)); 1.03 (*s*, Me–C(4)). ^{13}C-NMR: 176.1 (C(2)); 140.7 (C(1′)); 114.1 (C(2′)); 77.3 (C(5)); 42.1 (C(4)); 40.9 (C(3)); 22.7 (*Me*–C(4)). EI-MS: 126 (M^+). HR-EI-MS: 126.0682 ($C_7H_{10}O_2^+$, M^+; calc. 126.0681).

4-Ethenyltetrahydro-4-methylfuran-2-ol (**8**). To a soln. of **7** (1.11 g, 8.81 mmol) in CH_2Cl_2 (30 ml) was added dropwise a soln. of DIBALH in hexane (7.97 ml, 25% (*w*/*w*)) within 30 min at −20°. Two hours later, NH_4Cl (0.642 g) was added to the soln., followed by a drop of MeOH. The resulting mixture was stirred for 0.5 h at r.t., and then filtered through *Celite*. The filtrate was concentrated and the residue purified by CC (petroleum ether/AcOEt 7:1, R_f 0.23): 0.930 g (82.4%) of **8** as a *ca.* 1:1 mixture of stereoisomers. Colorless oil. ^{1}H-NMR: 6.02–5.84 (*m*, H–C(1′)); 5.64–5.59 (*m*, H–C(2)); 5.14–4.98 (*m*, CH_2(2′)); 4.55 (br., 0.5 H, OH of one isomer); 4.44 (br., 0.5 H, OH of the other isomer); 3.92–3.51 (*m*, CH_2(5)); 2.25–1.70 (*m*, CH_2(3)); 1.28–1.18 (*m*, *Me*–C(4)). ^{13}C-NMR: 144.5; 143.3 (C(6)); 112.8, 111.5 (C(2′)); 99.2 (C(2)); 77.4 (C(5)); 47.0, 46.2 (C(3)); 45.4, 44 (C(4)); 23.5, 22.9 (*Me*–C(4)). ESI-MS: 127.1 ($[M-1]^-$). HR-EI-MS: 128.0837 ($C_7H_{12}O_2^+$, M^+; calc. 128.0838).

*Ethyl (2*E*)-5-(Hydroxymethyl)-5-methylhepta-2,6-dienoate* (**9**). To a soln. of **8** (1.37 g, 10.7 mmol) in dry toluene (30 ml) was added a soln. of $Ph_3P{=}CHCO_2Et$ (7.45 g, 21.4 mmol) in dry toluene (60 ml), and the resulting soln. was refluxed for 2 h. The soln. was allowed to warm to r.t. and concentrated. The resulting residue was treated with Et_2O (50 ml), and then the white precipitate was removed by filtration. The filtrate was washed with H_2O and brine, dried (Na_2SO_4), and evaporated and the crude product purified by CC (silica gel, petroleum ether/AcOEt 7:1, R_f 0.22): 1.67 g (79.0%) of **9**. Colorless oil. ^{1}H-NMR: 6.86 (*dt*, *J*(2,3) = 15.6, *J*(3,4) = 7.8, H–C(3)); 5.85 (*d*, *J*(2,3) = 15.6, H–C(2)); 5.77 (*dd*, *J*(6,7) = 17.7 and 10.8, H–C(6)); 5.18 (*d*, *J*(6,7) = 10.8, H_{cis}–C(7)); 5.08 (*d*, *J*(6,7) = 17.7, 1 H, H_{trans}–C(7)); 4.14 (*q*, *J* = 7.2, Me*C*H_2O); 3.34 (*s*, CH_2–C(5)); 2.30–2.12 (*m*, CH_2(4)); 2.2–2.1 (br., OH); 1.16 (*t*, *J* = 7.2, *Me*CH_2O); 0.97 (*s*, Me–C(5)). ^{13}C-NMR: 166.4 (C(1)); 145.4 (C(6)); 142.7 (C(3)); 123.7 (C(2)); 114.9 (C(7)); 69.5 (CH_2–C(5)); 60.2 (Me*C*H_2O); 42.3 (C(4)); 39.5 (C(5)); 20.2 (*Me*–C(5)); 14.1 (*Me*CH_2O). EI-MS: 198(M^+). HR-EI-MS: 198.1256 ($C_{11}H_{18}O_3^+$, M^+; calc. 198.1254).

*Ethyl (2*E*)-5-Formyl-5-methylhepta-2,6-dienoate* (**10**). To a soln. of IBX (7.10 g, 25.4 mmol) in DMSO (120 ml) was added dropwise a soln. of **9** (1.68, 8.45 mmol) in DMSO (120 ml) at r.t. The reaction was monitored by TLC until the alcohol disappeared. The mixture was diluted with CH_2Cl_2 (200 ml), the soln. washed with H_2O (3 × 150 ml) and brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (petroleum ether/AcOEt 4:1, R_f 0.18): 1.57 g (94.5%) of **10**. Colorless oil. ^{1}H-NMR: 9.39 (*s*, CHO); 6.83 (*dt*, *J*(2,3) = 15.6, *J*(3,4) = 7.8, H–C(3)); 5.81 (*d*, *J*(2,3) = 15.6, H–C(2)); 5.73 (*dd*, *J*(6,7) = 17.7 and 10.5, H–C(6)); 5.32 (*d*, *J*(6,7) = 10.5, H_{cis}–C(7)); 5.15 (*d*, *J*(6,7) = 17.7, H_{trans}–C(7));

4.18 (*q*, *J* = 7.5, MeC*H*$_2$O); 2.57–2.43 (*m*, CH$_2$(4)); 1.28 (*t*, *J* = 7.5, *Me*CH$_2$O); 1.21 (*s*, *Me*–C(5)). ^{13}C-NMR: 201.0 (CHO); 165.8 (C(1)); 143.1 (C(6)); 137.2 (C(3)); 124.7 (C(2)); 118.0 (C(7)); 60.2 (Me*C*H$_2$O); 52.3 (C(5)); 37.7 (C(4)); 18.0 (*Me*–C(5)); 14.1 (*Me*CH$_2$O). EI-MS: 181 ([*M*–CH$_3$]$^+$). HR-EI-MS: 196.1099 ($C_{11}H_{16}O_3^+$, M^+; calc.196.1101).

*Ethyl (2*E*,6*E*)-5-Ethenyl-7-iodo-5-methylhepta-2,6-dienoate* (**11**). To a suspension of anh. $CrCl_2$ (1.00 g, 8.14 mmol) in THF (20 ml) were added dropwise a soln. of CHI_3 (0.791 g, 2.01 mmol) and **10** (0.263 g, 1.34 mmol) in THF (15 ml) at 0°. After 2 h, the mixture was quenched with 10% aq. $Na_2S_2O_3$ soln. (20 ml) (brown → green mixture). The mixture was extracted with AcOEt, the combined org. phase was washed with H_2O and brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (petroleum ether/CH_2Cl_2 4:1, R_f 0.20): 0.337 g (78.6%) of **11**. Colorless oil. ^{1}H-NMR: 6.84 (*dt*, *J*(2,3) = 15.6, *J*(3,4) = 7.8, H–C(3)); 6.53 (*d*, *J*(6,7) = 15.0, H–C(6)); 6.08 (*d*, *J* = 15.0, H–C(7)); 5.83 (*d*, *J*(2,3) = 15.6, H–C(2)); 5.75 (*dd*, *J*(1′,2′) = 17.4, 10.5, H–C(1′)); 5.13 (*d*, *J*(1′,2′) = 10.5, H$_{cis}$–C(2′)); 5.04 (*d*, *J*(1′,2′) = 17.4, H$_{trans}$–C(2′)); 4.18 (*q*, *J* = 7.5, MeC*H*$_2$O); 2.31 (*d*, *J*(3,4) = 7.8, CH$_2$(4)); 1.30 (*t*, *J* = 7.5, *Me*CH$_2$O); 1.12 (*s*, Me–C(5)). ^{13}C-NMR: 166.3 (C(1)); 151.1 (C(6)); 144.4, 142.7 (C(3), C(1′)); 124.5 (C(2)); 114.3 (C(2′); 75.5 (C(7)); 60.5 (Me*C*H$_2$O); 47.0 (C(5)); 43.1 (C(4)); 23.1 (*Me*–C(5)); 14.4 (*Me*CH$_2$O). ESI-MS: 321.0 ([*M* + H]$^+$). HR-ESI-MS: 343.0165 ($C_{12}H_{17}INaO_2^+$, [*M* + Na]$^+$; calc. 343.1063).

Negishi *Reaction: General Procedure.* A dried flask was charged with $ZnCl_2$ (1.3 equiv.), and heated by a hot gun under vacuum until the $ZnCl_2$ was melted. Then the flask was filled with Ar gas and cooled to r.t. Anh. THF (10 ml) was added into the flask to dissolve the anh. $ZnCl_2$. Another dried flask was charged with the appropriate bromoarene (1.1 mmol, 1.1 equiv.) and THF (10 ml) under Ar, and then cooled to −78° for 0.5 h. A soln. of (1.6M BuLi 1.2 equiv.) in THF was added dropwise to the bromoarene soln. at −78° over 15 min, and stirring was continued for 30 min. Then the $ZnCl_2$ soln. was added dropwise to the organolithium soln. at −78° over 15 min, and the resulting soln. was stirred at r.t for 1 h. Meanwhile, a mixture of [Pd(OAc)$_2$] (0.05 equiv.), PPh_3 (0.10 equiv.), and THF (5 ml) was stirred at r.t. for *ca.* 30 min until the brown soln. was formed, and this soln. was added to the organozinc soln., followed by a soln. of the iodoalkadienoate **11** (1.0 mmol, 1.0 equiv.). The mixed soln. was stirred for one 1 h at r.t., then quenched with H_2O (20 ml), and extracted with AcOEt (20 ml × 4). The extract was dried (Na_2SO_4) and concentrated and the crude product purified by CC (petroleum ether/AcOEt 6:1 to 100:1): **12a** (90.1%), **12b** (52.3%), **12c** (58.7%), **12d** (53.7%), **12e** (48.3%), or **12f** (71.3%). Colorless oils.

*Data of Ethyl (2*E*,6*E*)-7-{4-{[(*tert*-Butyl)diphenyl-silyl]oxy}phenyl}-5-ethenyl-5-methylhepta-2,6-dienoate* (**12a**) *as an Example.* ^{1}H-NMR: 7.72–7.34 (*m*, 10 H, Ph$_2$Si); 7.10 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$); 6.89 (*dt*, *J*(2,3) = 15.6, *J*(3,4) = 7.5, H–C(3)); 6.70 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$); 6.21 (*d*, *J*(6,7) = 16.5, H–C(7)); 5.98 (*d*, *J*(6,7) = 16.5, H–C(6)); 5.88–5.79 (*m*, H–C(2), H–C(1′)); 5.07–4.98 (*m*, CH$_2$(2′)); 4.16 (*q*, *J* = 7.5, MeC*H*$_2$O); 2.36 (*d*, *J*(3,4) = 7.5, CH$_2$(4)); 1.26 (*t*, *J* = 7.5, *Me*CH$_2$O); 1.16 (*s*, Me–C(5)); 1.09 (*s*, ^{t}Bu). ^{13}C-NMR: 166.2 (C=O); 144.9; 143.9; 140.8; 139.1; 129.2; 128.9; 127.0; 126.3; 125.5; 125.5; 125.4; 125.4; 125.3; 124.1; 122.8; 113.5 (C(2′)), 60.2 (Me*C*H$_2$O), 43.6 (C(4)); 42.8 (C(5)); 29.6 (Me$_3$*C*); 25.6 (*Me*$_3$C); 23.5 (*Me*–C(5)); 14.2 (*Me*CH$_2$O). ESI-MS: 525.6 ([*M* + H]$^+$). HR-ESI-MS: 547.2639 ($C_{34}H_{40}NaO_3Si^+$, [*M* + Na]$^+$; calc. 547.2647).

Selective 1,2-Addition Reaction of **12** *with MeMgI: General Procedure.* To a soln. of (3.0M MeMgI 1.2 ml, 3.0 equiv.) was added dropwise a soln. of ester **12** (0.12 mmol, 1.0 equiv.) in THF (5 ml) at r.t., and the mixture was stirred for 1 h. The reaction was quenched with H_2O (5 ml), the mixture extracted with AcOEt (3 × 10 ml), dried (Na_2SO_4), and concentrated, and the crude product purified by CC (petroleum ether/AcOE): **13a** (88.0%), **13b** (48.3%), **13c** (68.4%), **13d** (72.0%), or **13f** (80%). Colorless oils.

*(3*E*,7*E*)-8-{4-{[(*tert*-Butyl)diphenylsilyl]oxy}phenyl}-6-ethenyl-2,6-dimethylocta-3,7-dien-2-ol* (**13a**): ^{1}H-NMR: 7.72–7.33 (*m*, 10 H, Ph$_2$Si); 7.09 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$); 6.69 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$); 6.18 (*d*, *J*(7,8) = 16.5, H–C(8)); 6.00 (*d*, *J*(7,8) = 16.5, H–C(7)); 5.83 (*dd*, *J*(1′,2′) = 17.4, 10.5, H–C(1′)); 5.60–5.56 (*m*, H–C(3), H–C(4)); 5.08–4.98 (*m*, CH$_2$(2′)); 2.17 (*d*, *J*(4,5) = 5.7, CH$_2$(5)); 1.5–1.4 (br., OH); 1.27 (*s*, 2 Me–C(2)); 1.12 (*s*, Me–C(6)); 1.09 (*s*, ^{t}Bu). ^{13}C-NMR: 154.8; 145.5; 141.1; 135.5; 135.3; 132.9; 130.7; 129.9; 127.8; 127.0; 126.9; 123.0; 119.7; 112.2 (C(2′)); 70.8 (C(2)); 43.9 (C(5)); 42.5 (C(6));

29.9; 29.8; 26.5; 23.4; 19.5. ESI-MS: 533.3 ($[M+Na]^+$). HR-ESI-MS: 533.2846 ($C_{34}H_{42}NaO_2Si^+$, $[M+Na]^+$; calc. 533.2859).

*(3*E*,7*E*)-6-Ethenyl-8-(4-methoxyphenyl)-2,6-dimethylocta-3,7-dien-2-ol* (**13b**): ^{1}H-NMR: 7.30 (*d*, *J* = 8.4, 2 H, C_6H_4); 6.84 (*d*, *J* = 8.4, 2 H, C_6H_4), 6.27 (*d*, *J*(7,8) = 15.9, H–C(8)); 6.07 (*d*, *J*(7,8) = 15.9, H–C(7)); 5.88 (*dd*, *J*(1′,2′) = 10.2, 17.4, H–C(1′)); 5.63–5.59 (*m*, H–C(3), H–C(4)); 5.07–4.98 (*m*, CH_2(2′)); 3.81 (*s*, MeO); 2.22 (*d*, *J*(4,5) = 5.7, CH_2(5)); 1.5–1.4 (br., OH); 1.30 (*s*, 2 Me–C(2)); 1.17 (*s*, Me–C(6)). ^{13}C-NMR: 158.8; 145.6; 141.1; 135.4; 130.5; 127.2; 126.8; 123.0; 113.9; 112.1 (C(2′)), 70.7 (C(2)); 55.3 (MeO); 43.9 (C(5)); 42.6 (C(6)); 29.9 (2 *Me*–C(2)); 23.4 (*Me*–C(6)). EI-MS: 286 (M^+). HR-EI-MS: 286.1933 ($C_{19}H_{26}O_2^+$, M^+; calc. 286.1930).

*(3*E*,7*E*)-6-Ethenyl-2,6-dimethyl-8-phenylocta-3,7-dien-2-ol* (**13c**): ^{1}H-NMR ($CDCl_3$) 7.31–7.28 (*m*, 5 arom. H), 6.32 (*d*, *J*(7,8) = 16.2, H–C(8)); 6.20 (*d*, *J*(7,8) = 16.2, H–C(7)); 5.88 (*dd*, *J*(1′,2′) = 10.8, 17.4, H–C(1′)); 5.63–5.59 (*m*, H–C(3), H–C(4)); 5.07–4.98 (*m*, CH_2(2′)); 2.22 (*d*, *J*(4,5) = 5.7, CH_2(5)); 1.5–1.4 (br., OH); 1.30 (*s*, 2 Me–C(2)); 1.17 (*s*, Me–C(6)). ^{13}C-NMR: 145.4; 141.2; 137.7; 137.5; 128.5; 127.5; 127.0; 126.1; 122.9; 112.4 (C(2′)); 70.8 (C(2)); 43.8 (C(5)); 42.7 (C(6)); 29.9 (2 *Me*–C(2)); 23.4 (*Me*–C(6)). EI-MS: 256 (M^+). HR-EI-MS: 256.1827 ($C_{18}H_{24}O_2^+$, M^+; calc. 256.1821).

*(3*E*,7*E*)-6-Ethenyl-2,6-dimethyl-8-(4-methylphenyl)octa-3,7-dien-2-ol* (**13d**): ^{1}H-NMR ($CDCl_3$) 7.25 (*d*, *J* = 8.1, 2 arom. H); 7.10 (*d*, *J* = 8.1, 2 arom. H); 6.28 (*d*, *J*(7,8) = 16.5, H–C(8)); 6.14 (*d*, *J*(7,8) = 16.5, H–C(7)); 5.88 (*dd*, *J*(1′,2′) = 10.8, 17.7, H–C(1′)); 5.68–5.54 (*m*, H–C(3), H–C(4)); 5.06–4.98 (*m*, CH_2(2′)); 2.32 (*s*, *Me*C_6H_4); 2.22 (*d*, *J*(4,5) = 6.0, CH_2(5)); 1.5–1.4 (br., OH); 1.29 (*s*, 2 Me–C(2)); 1.17 (*s*, Me–C(6)). ^{13}C-NMR: 145.5; 141.1; 136.7; 136.4; 134.9; 129.2; 127.3; 126.0; 123.0; 112.2 (C(10)); 70.8 (C(2)); 43.9 (C(5)); 42.6 (C(6)); 29.9 (2 *Me*–C(2)); 23.5 (*Me*–C(6)); 21.1 (*Me*C_6H_4). EI-MS: 270 (M^+). HR-EI-MS: 270.1983 ($C_{19}H_{26}O^+$, M^+; calc. 270.1984).

*(3*E*,7*E*)-6-Ethenyl-2,6-dimethyl-8-[4-(trifluoromethyl)phenyl]octa-3,7-dien-2-ol* (**13e**): ^{1}H-NMR: 7.55 (*d*, *J* = 8.0, 2 arom. H); 7.44 (*d*, *J* = 8.0, 2 arom. H); 6.36 (*d*, *J*(7,8) = 16.5, H–C(8)); 6.30 (*d*, *J*(7,8) = 16.5, H–C(7)); 5.88 (*dd*, *J*(1′,2′) = 10.5, 17.7, H–C(1′)); 5.69–5.59 (*m*, H–C(3), H–C(4)); 5.09 (*d*, *J*(1′,2′) = 10.5, H_{cis}–C(2′)); 5.03 (*d*, *J*(1′,2′) = 17.7, H_{trans}–C(2′)); 2.22 (*d*, *J*(4,5) = 6.0, CH_2(5)); 1.45 (br. *s*, OH); 1.30 (*s*, 2 Me–C(2)); 1.20 (*s*, Me–C(6)). ^{13}C-NMR: 144.8; 141.5; 141.2; 140.2; 126.4; 126.2; 125.5; 125.4; 125.4; 122.6; 112.8 (C(2′)); 70.8 (C(2)); 43.7 (C(5)); 42.9 (C(6)); 29.9 (2 *Me*–C(2)); 23.3 (*Me*–C(6)). EI-MS: 324 (M^+). HR-EI-MS: 324.1705 ($C_{19}H_{23}F_3O^+$, M^+; calc. 324.1701).

*(3*E*,7*E*)-6-Ethenyl-2,6-dimethyl-8-(naphthalen-2-yl)octa-3,7-dien-2-ol* (**13f**): ^{1}H-NMR: 7.80–7.30 (*m*, 7 arom. H); 6.48 (*d*, *J*(7,8) = 16.2, H–C(8)); 6.33 (*d*, *J*(7,8) = 16.2, H–C(7)); 5.88 (*dd*, *J*(1′,2′) = 10.5, 17.7, H–C(1′)); 5.69–5.59 (*m*, H–C(3), H–C(4)); 5.09 (*d*, *J*(1′,2′) = 10.5, H_{cis}–C(2′)); 5.05 (*d*, *J*(1′,2′) = 17.7, H_{trans}–C(2′)); 2.24 (*d*, *J*(4,5) = 5.7, CH_2(5)); 1.40–1.50 (br. *s*, OH); 1.30 (*s*, 2 *Me*–C(2)); 1.20 (*s*, Me–C(6)). ^{13}C-NMR: 145.3; 141.3; 137.9; 135.1; 133.7; 132.8; 128.1; 127.8; 127.6; 126.2; 125.7; 125.6; 123.6; 122.9; 112.5 (C(2′)); 70.8 (C(2)); 43.9 (C(5)); 42.8 (C(6)); 29.9 (2 *Me*–C(2)); 23.3 (*Me*–C(6)). EI-MS: 306 (M^+). HR-EI-MS: 306.1984 ($C_{22}H_{26}O^+$, M^+; calc. 306.1984).

(±)-Δ³-2-Hydroxybakuchiol (*=4-[(1*E*,5*E*)-3-Ethenyl-7-hydroxy-3,7-dimethylocta-1,5-dien-1-yl]phenol*; **14**). To a soln. of **13a** (0.117 g, 0.23 mmol) in THF (5 ml) was added dropwise a soln. of $Bu_4NF \cdot 3\,H_2O$ (0.218 g, 0.69 mmol) in THF (5 ml) at r.t., and then the resulting soln. was stirred for 1 h. The soln. was quenched with H_2O (10 ml) and extracted with AcOEt (20 ml × 3), the extract dried (Na_2SO_4) and concentrated, and the crude product purified by CC (petroleum ether/AcOEt 6:1, R_f 0.18): 0.049 g (77.8%) of **14**. Colorless oil. Spectral data: consistent with [28]. ^{1}H-NMR: 7.23 (*d*, *J* = 8.4, 2 arom. H); 6.76 (*d*, *J* = 8.4, 2 arom. H); 6.24 (*d*, *J*(7,8) = 16.5, H–C(8)); 6.04 (*d*, *J*(7,8) = 16.5, H–C(7)); 5.87 (*dd*, *J*(1′,2′) = 10.5, 17.7, H–C(1′)); 5.63–5.59 (*m*, H–C(3), H–C(4)); 5.50–5.40 (br. *s*, O*H*C_6H_4); 5.04 (*d*, *J*(1′,2′) = 10.5, H_{cis}–C(2′)); 5.00 (*d*, *J*(1′,2′) = 17.7, H_{trans}–C(2′)); 2.21 (*d*, *J*(4,5) = 5.7, CH_2(5)); 1.60–1.55 (br. *s*, 1 OH); 1.30 (*s*, 2 *Me*–C(2)); 1.16 (s, Me–C(6)). ^{13}C-NMR ((D_6)DMSO): 157.1; 146.2; 142.7; 134.4; 128.6; 127.6; 127.0; 121.6; 115.8; 112.3 (C(2′)); 69.3 (C(2)); 44.0 (C(5)); 42.7 (C(6)); 30.6 (2 *Me*–C(2)); 23.6 (*Me*–C(6)). ESI-MS : 295.0 ($[M+Na]^+$). HR-ESI-MS: 295.1668 ($C_{18}H_{24}NaO_2^+$, $[M+Na]^+$; calc. 295.1672).

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