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A SHORT TOTAL SYNTHESIS OF (+)-CRYPTOCARYA DIACETATE

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Abstract – A short synthesis of (+)-cryptocarya diacetate was achieved by employing three component linchpin coupling, diastereoselective reduction of β-hydroxyketone, and *Z*-selective HWE reaction as key transformations.

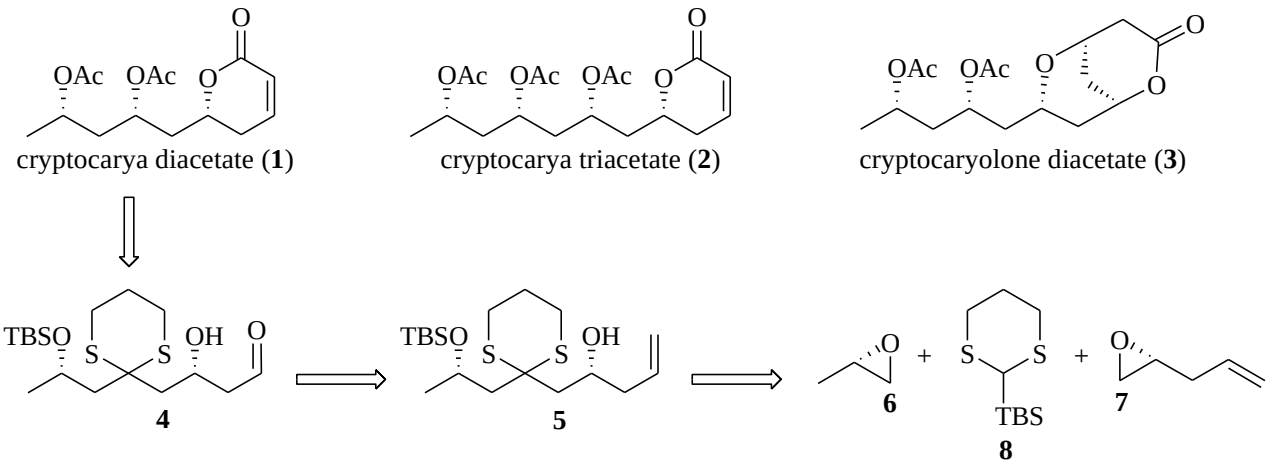
INTRODUCTION

Cryptocarya diacetate (**1**) is one of several 6-substituted 5,6-dihydropyran-2-one natural products that were isolated by Horn et al from the leaves and bark of the South African plant *Cryptocarya latifolia*.[1] These compounds have long been known for their promising biological activities ranging from the treatment of headaches and morning sickness to cancer, pulmonary diseases, and various bacterial and fungal infections.[2] Simplicity of structure and broad-spectrum biological activities of **1** have stimulated substantial synthetic work, culminating in several total syntheses.[2,3]

RESULTS AND DISCUSSION

In this article, we wish to report a short synthesis of **1** that exploits a one-flask three-component linchpin coupling reaction (Figure 1) for building the central carbon chain with requisite stereochemical features. As depicted in Fig. 1, a *Z*-selective Horner-Wadsworth-Emmons reaction (HWE reaction)[4] of aldehyde **4** was opted for 5,6-dihydropyran-2-one construction. Considering an olefin group as surrogate for the requisite aldehyde, the advanced dithiane derivative **5** was identified as the key intermediate, which in turn was planned by linchpin coupling[5] of dithiane **8** with known epoxides **6** and **7**.[6]

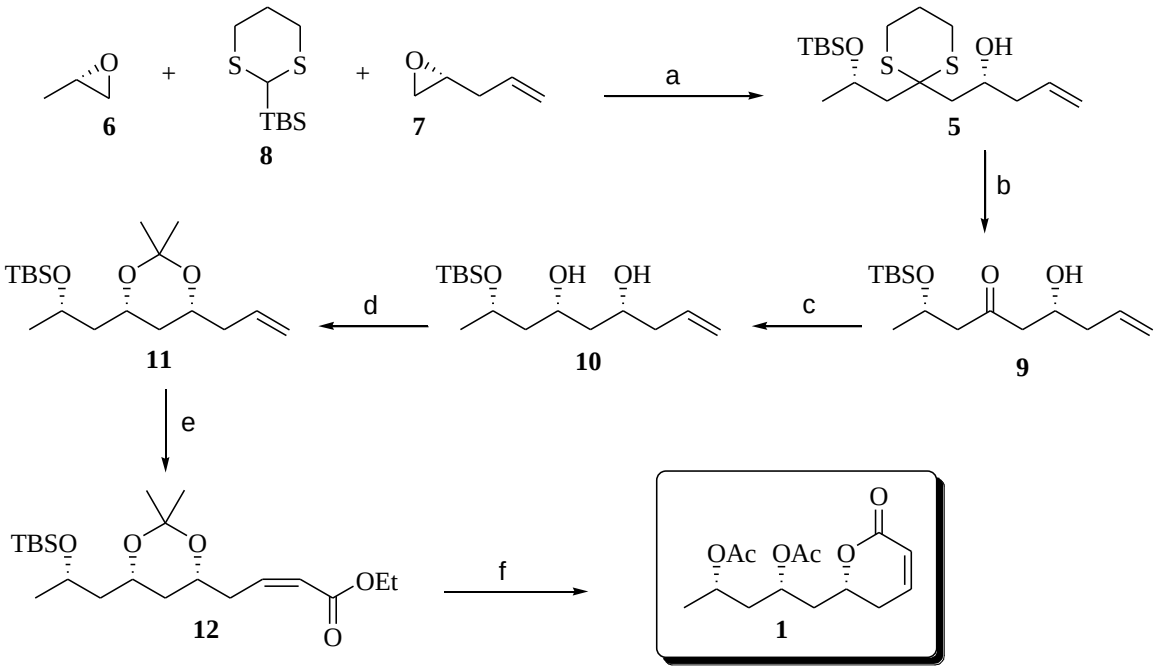
This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



The synthesis of cryptocarya diacetate (**1**) was initiated by conducting the projected dialkylation of lithiated dithiane **8** using commercially available (*S*)-propyleneoxide **6** as first alkylating agent, HMPA for triggering the Brook rearrangement and the known epoxide **7** (prepared in one step from commercially available (*R*)-epichlorohydrin)[6] as the second alkylating agent. This protocol resulted in the generation of the advanced intermediate **5**.

Amongst a few reagents examined, $PhI(CF_3COO)_2$ in CH_3CN-phosphate buffer (4:1) effectively deprotected the dithioketal to give the corresponding hydroxyketone **9** in good yield. The diastereoselective reduction of **9** with $LiAlH_4$ in the presence of LiI as a chelating agent in ether at –100 ^oC[7] afforded diol **10** as the major product (*syn*/*anti* in 9:1 ratio). The diol **10** was subsequently transformed into the isopropylidene derivative **11** by treatment with 2,2-dimethoxypropane-catalytic CSA. In the ^{13}C NMR of **11**, the acetonide methyl groups resonated at 19.7 and 30.2 ppm indicating a 1,3-*syn*-relationship that was further substantiated by the appearance of the quaternary carbon in the downfield region (98.4 ppm).[8]

Having established all the required stereo centers in compound **11**, our next target was to install the dihydropyran ring. The oxidative cleavage of the terminal double bond of **11** using $OsO_4/NaIO_4$/2,6-lutidine[9] in dioxane-H_2O afforded the corresponding aldehyde **4** which was directly used for HWE reaction with ethyl (di-*o*-tolylphosphono)acetate[4] and NaH in THF to obtain the *Z*-unsaturated ester **12** exclusively. After some experimentation, TFA in CH_2Cl_2 at 0 ^oC was found to be apt for the deprotection of TBS and acetonide groups of **12** with concomitant lactonization to afford the dihydroxy lactone which was acylated further by treatment with acetic anhydride, triethylamine-DMAP in CH_2Cl_2 thereby completing the synthesis of cryptocarya diacetate (**1**). The spectral and analytical data of the synthetic sample **1** were in good agreement with the reported data of natural cryptocarya diacetate.[1]



Scheme 1. *Reagents and Conditions*: a) *n*-BuLi, THF–HMPA, –78 and –40 °C; b) $PhI(CF_3COO)_2$, MeCN–phosphate buffer pH 7.0 (4:1), rt, 1h; c) $LiAlH_4$, LiI, Et_2O, –100 °C, 1 h; d) cat. CSA, 2,2-DMP, acetone, rt, 0.5 h; e) *i.* OsO_4, $NaIO_4$, 2,6-lutidine, dioxane–H_2O (3:1), rt, 3 h; *ii.* ethyl (di-*o*-tolylphosphono)acetate, NaH, THF, –78 °C, 1 h; f) *i.* TFA, CH_2Cl_2, 0 °C → rt, 1 h; *ii.* Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 3 h.

In summary, a concise total synthesis of cryptocarya diacetate was accomplished in 6 linear steps starting from known epoxide **7** in 23% overall yield.

EXPERIMENTAL

General: Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven-dried glassware. All anhydrous solvents were distilled prior to use: THF and diethyl ether, dioxane from Na and benzophenone; CH_2Cl_2, CH_3CN from CaH_2; acetone from $KMnO_4$. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel (60–120, 200-400 mesh). Optical rotations were determined on a Jasco DIP-370 digital polarimeter. Specific optical rotations $[\alpha]_D$ are given in 10^{-1} $degcm^2g^{-1}$. ^1H and ^{13}C NMR spectrometry measurements were carried out on Bruker AC 200 MHz or Bruker DRX 400 MHz spectrometers, and TMS was used as internal standard. ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectrometry (EI, 70 eV, direct inlet system) was carried out on a Finnigan MAT-1020 spectrometer. Elemental analysis data were obtained on a Thermo Finnigan Flash EA 1112 Series CHNS Analyzer.

(*R*)-2-Allyloxirane (7).

A suspension of CuI (2.056 g, 10.8 mmol) in THF (100 mL) was cooled to –78 °C, and 1M THF solution of vinylmagnesium bromide (52 mL, 52.0 mmol), followed by addition of (*R*)-(-)-epichlorohydrin (5 g, 54.0 mmol) and stirred for 2 days at –40 °C . The reaction mixture was poured into water, extracted with ether and combined organic fractions were dried over $MgSO_4$ and concentrated to afford crude chlorohydrin (5.4 g, 44.8 mmol). The crude chlorohydrin was treated with KOH (2.9 g) in a reaction flask fitted with a distillation head. Wet epoxide **33** was distilled at atmospheric pressure (bp 80-85 °C), then dried with $MgSO_4$ and decanted to furnish clean **7** (3.1 g, 84% yield). ^{1}H and ^{13}C NMR were identical to the reported data for **7**, $[\alpha]_D$ 0 (*c* 1.5, $CHCl_3$).[6a]

(*R*)-1-(2-((*S*)-2-(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)pent-4-en-2-ol (5).

At –10 °C, a solution of TBS-dithiane **8** (500 mg, 2.13 mmol) in THF (10 mL) was treated with *n*-BuLi (0.92 mL, 2.34 M in hexanes, 2.15 mmol) under argon and allowed to stir for 2 h. The mixture was cooled to –78 °C and (*S*)-propyleneoxide **6** (124 mg, 2.13 mmol) in THF (1 mL) was added. The first alkylation was complete in 1 h while warming the reaction mixture slowly to –40 °C. The mixture was cooled to –78 °C and HMPA (1.15 g, 6.4 mmol) was added. Warming the mixture to –40 °C and stirring for 30 min at the same temperature resulted in complete Brook's rearrangement. The mixture was re-cooled to –78 °C and the second epoxide **7** (250 mg, 2.5 mmol) in THF (1 mL) was added. After 1 h stirring at –10 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in petroleum ether) to furnish **5** (549 mg, 68%) as a colorless oil. $[\alpha]_D$ –2.5 (*c* 1 $CHCl_3$). IR ($CHCl_3$): υ max 3438, 2954, 1640, 1439, 1374, 1254, 1130, 1001, 836, 775 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.86 (m, 1H), 5.16–5.06 (m, 2H), 4.22–4.06 (m, 2H), 3.42 (br s, 1H), 2.95–2.76 (m, 4H), 2.39–1.88 (m, 8H), 1.22 (d, *J* = 6.19 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ –4.2 (q), –3.9 (q), 17.9 (s), 24.7 (t), 25.9 (q), 26.0 (d), 26.1 (t), 26.5 (t), 42.2 (t), 45.0 (t), 49.2 (t), 51.3 (s), 65.9 (d), 67.9 (d), 117.4 (t), 134.7 (d) ppm. ESI-MS *m/z*: 399.2 $(M+Na)^+$. *Anal*. Calcd for $C_{18}H_{36}O_2S_2Si$: C, 57.39; H, 9.63; S, 17.02. Found: C, 57.72; H, 9.75; S, 17.22.

(2*S*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-hydroxynon-8-en-4-one (9).

To an ice cooled solution of dithiane **5** (500 mg, 1.32 mmol) in MeCN–phosphate buffer (pH 7, 4:1, 10 mL) was added $PhI(CF_3COO)_2$ (645 mg, 1.5 mmol). Reaction mixture was stirred at rt for 1 h after which the TLC indicated the disappearance of starting material. The mixture was diluted with ethyl acetate and two layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (20% EtOAc in petroleum ether) to give the hydroxy ketone **9** (295 mg, 78% yield) as a colorless oil. $[\alpha]_D$ –7.1 (*c* 0.5 $CHCl_3$). IR

($CHCl_3$): υ max 3419, 2928, 2855, 1707, 1376, 1256, 1128, 1088, 836, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.84–5.76 (m, 1H), 5.14–5.12 (m, 1H), 5.10 (br t, *J* = 1.3 Hz, 1H) 4.34–4.26 (m, 1H), 4.11 (ddd, *J* = 2.4, 8.3,14.8 Hz, 1H), 3.06 (bs, 1H), 2.69–2.62 (m, 2H), 2.54 (dd, *J* = 9.0,17.8 Hz, 1H), 2.45 (dd, *J* = 5.0, 15.0 Hz, 1H), 2.31–2.20 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.9 (q), –4.5 (q), 17.9 (s), 23.9 (q), 25.8 (q), 40.8 (t), 50.0 (t), 53.0 (t), 65.4 (d), 66.9 (d), 117.9 (t), 134.2 (d), 210.9 (s) ppm. ESI-MS *m/z*: 309.2 $(M+Na)^+$. *Anal*. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.93; H, 10.61.

(4*R*,6*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)non-1-ene-4,6-diol (10).

To a solution of β-hydroxy ketone **9** (250 mg, 0.87 mmol) in Et_2O (10 mL) at rt under argon was added LiI (584 mg, 4.36 mmol) and the mixture was stirred at –40 °C for 5 min. The resulting mixture was then cooled to –100 °C and $LiAlH_4$ (166 mg, 4.36 mmol) was added. The reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched with ice, diluted with EtOAc and subsequently filtered through a celite pad. The filtrate was concentrated and the residue was purified by column chromatography (25% EtOAc in petroleum ether) to afford the title compound **10** (225 mg, 89% yield) as a colorless oil. $[\alpha]_D$ +29.5 (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): υ max 3460, 3019, 2932, 2400, 1597, 1428, 1215, 838, 758, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.89–5.79 (m, 1H), 5.14–5.08 (m, 2H), 4.11–4.00 (m, 3H), 3.95–3.89 (m, 1H), 2.31–2.19 (m, 2H), 1.67–1.47(m, 4H), 1.18 (d, *J* = 6.0, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.8 (q), –3.9 (q), 17.9 (s), 24.5 (d), 25.8 (d), 42.2 (t), 42.7 (t), 46.2 (t), 69.8 (d), 71.4 (d), 72.4 (d), 117.4 (t), 134.9 (d) ppm. ESI-MS *m/z*: 311.3 $(M+Na)^+$. *Anal*. Calcd for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18. Found: C, 62.46; H, 11.16.

((*S*)-1-((4*R*,6*R*)-6-Allyl-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-yloxy)(*tert*-butyl)dimethylsilane (11).

A solution of diol **10** (200 mg, 0.69 mmol), 2,2-dimethoxypropane (0.17 mL, 1.4 mm) in dry acetone (5 mL) was exposed to CSA (16 mg, 0.07 mmol) at 0 °C and the reaction mixture was allowed to stir for 30 min at rt. The mixture was neutralized by adding few drops of triethylamine and concentrated under vacuum. The crude was purified by column chromatography (10% EtOAc in petroleum ether) to afford the mixture of diastereomers of **11**, *syn* : *anti* (9:1) (227 mg, 91% yield) as a colorless liquid. $[\alpha]_D$ +13.3 (*c* 0.9, $CHCl_3$). IR ($CHCl_3$): υ max 3369, 3019, 2930, 2857, 1597, 1381, 1216, 1117, 836, 758, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.83–5.73 (m, 1H), 5.10–5.03 (m, 2H), 3.98–3.90 (m, 2H), 3.88–4.81 (m, 1H), 2.33–2.27 (m, 1H), 2.13 (dt, *J* = 7.1, 14.2 Hz, 1H), 1.73 (dt, *J* = 6.5, 13.5 Hz, 1H), 1.54 (dt, *J* = 2.5, 12.9 Hz, 1H), 1.44–1.33 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H) 1.13 (d, *J* = 5.9 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H) 0.03 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ –4.8 (q), –4.2 (q), 18.1 (s), 19.7 (q), 23.7 (q), 25.8 (q), 30.2 (q), 36.5 (t), 40.9 (t), 46.1 (t), 65.0 (d), 66.2 (d), 68.6 (d), 98.4 (s), 117.1 (t), 134.2 (d) ppm. ESI-MS *m/z*: 351.3 $(M+Na)^+$. *Anal*. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found: C, 65.86; H, 11.07.

***(Z)*-Ethyl-4-((4*R*,6*R*)-6-((*S*)-2-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)but-2-enoate (12).**

To a solution of olefin **11** (100 mg, 0.3 mmol) in dioxane–water (3:1, 40 mL) were added 2,6-lutidine (70 μL, 0.6 mmol), OsO_4 (0.1 mL, 0.1 M in toluene, 165 mg, 0.01 mmol), and $NaIO_4$ (257 mg, 1.2 mmol). The reaction was stirred at rt and the progress of the reaction was monitored by TLC. After the reaction was complete (3 h), water (5 mL) and CH_2Cl_2 (10 mL) were added. The layers ware separated, and the water layer was extracted by CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed, and the crude aldehyde **4** was directly used for next reaction without any further purification.

To a solution of ethyl (di-*o*-tolylphosphono)acetate (210 mg, 0.6 mmol) in THF (12 mL) at 0 ^oC was added NaH (24 mg, 60% w/w in paraffin oil, 0.6 mmol). 30 min later the reaction mixture was cooled to –78 ^oC and a solution of aldehyde **4** in THF (3 mL) was added drop wise. The resulting reaction mixture was stirred for 45 min at the same temperature. Reaction was quenched with ice water and slowly warmed to ambient temperature. The mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (10% EtOAc in petroleum ether) to produce the *Z*-unsaturated ester **12** exclusively (95 mg, 76% over two steps) as a pale yellow oil. $[\alpha]_D$ +24.0 (*c* 1, $CHCl_3$). IR ($CHCl_3$): υ max 3401, 3020, 2930, 2857, 1712, 1596, 1381, 1216, 1119, 1036, 938, 836, 757, 668, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.32 (dt, *J* =11.5, 7.0 Hz, 1H), 5.84 (dt, *J* = 11.5, 1.8 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.99–3.90 (m, 3H), 2.94–2.86 (m, 1H), 2.77–2.69 (m, 1H), 1.73 (dt, *J* = 6.8, 13.5 Hz, 1H), 1.52 (dt, *J* = 2.5, 13.0 Hz, 1H), 1.44–1.32 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H) 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.8 (q), –4.3 (q), 14.3 (q), 18.0 (s), 19.7 (q), 23.6 (q), 25.8 (q), 30.1 (q), 35.6 (t), 36.7 (t), 46.1 (t), 59.8 (t), 65.0 (d), 66.2 (d), 68.4 (d), 98.5 (s), 121.1 (d), 145.7 (d), 166.4 (s) ppm. ESI-MS *m/z*: 423.4 $(M+Na)^+$. *Anal*. Calcd for $C_{21}H_{40}O_5Si$: C, 62.96; H, 10.06. Found: C, 63.12; H, 10.11.

Cryptocarya diacetate (1).

A solution of ester **12** (30 mg, 0.075 mmol) in CH_2Cl_2 was treated with TFA at 0 ^oC and allowed to stir for 1 h at the same temperature. Reaction mixture was concentrated and co-distilled twice with toluene under reduced pressure. The crude dihydroxylactone was then dissolved in CH_2Cl_2, and was treated with triethylamine (0.1 mL, 0.75 mmol), Ac_2O (0.05 mL, 0.375 mmol) and catalytic amount of DMAP. The reaction mixture was stirred for 3 h at rt. The mixture was concentrated under reduced pressure and the residue was consequently purified by flash chromatography (40% EtOAc in petroleum ether) to afford Cryptocarya diacetate (**1**) (15 mg, 70% yield, over two steps) as a colorless oil. $[\alpha]_D$ +51.5 (*c* 0.5, $CHCl_3$) {Lit.[1a], $[\alpha]_D^{22}$ +55.8 (*c* 1.06, $CHCl_3$)}. IR ($CHCl_3$): υ max 3449, 3018, 1734, 1490, 1376, 1216, 875, 755, 667 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 6.85 (ddd, *J* = 9.5, 6.0, 2.5 Hz, 1H), 6.00 (ddd, *J* = 9.5, 2.5,

0.9 Hz, 1H), 5.12–5.06 (m, 1H), 5.01–4.93 (m, 1H), 4.48 (br.dddd, *J* = 11.5, 6.5, 4.1 Hz, 1H), 2.44 (dddd, *J* = 18.4, 5.8, 3.9, 0.9 Hz, 1H), 2.30 (ddt, *J* = 18.4, 11.5, 2.6 Hz, 1H), 2.15 (ddd, *J* = 14.6, 8.5, 6.5 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.98 (dd, *J* = 14.4, 7.2 Hz, 1H),1.93 (ddd, *J* = 14.6, 6.6, 3.9 Hz, 1H), 1.78 (dt, *J* = 14.3, 5.8 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (q), 21.2 (q), 21.3 (q), 29.2 (t), 39.2 (t), 40.5 (t), 67.7 (d), 67.8 (d), 74.9 (d), 121.4 (d), 144.7 (d), 163.8 (s), 170.6 (s), 170.7 (s) ppm. ESI-MS *m/z*: 297.2 $(M+Na)^+$. *Anal*. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.19; H, 7.11.

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