Enantioselective Synthesis of (+)-Juvabione

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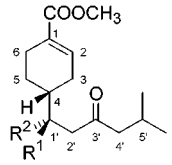
Introduction

In 1965 (+)-juvabione (**1a**, Figure 1) was discovered[1] due to its high insect juvenile hormone activity.[2] Out of four stereoisomers, the (+)-(4*R*,1′*R*)-isomer displays the highest biological activity.[3] For a synthesis of pure juvabione a high degree of diastereoselectivity is important as separation of *epi*-juvabione, the C-1′ epimer, from juvabione is difficult. While numerous syntheses of racemic juvabione are recorded,[4] the number of reports on enantiomerically pure compound (EPC) syntheses of (+)-juvabione is small: Ex-chiral-pool syntheses were carried out using (+)-perillaldehyde or (+)-limonene as starting materials.[5] Asymmetric syntheses based on enzyme controlled reductions (with yeast) were reported by Mori et al.[6] In a formal synthesis, Miles and Brinkman used an auxiliary controlled alkylation of an organomanganese compound as key step.[7]

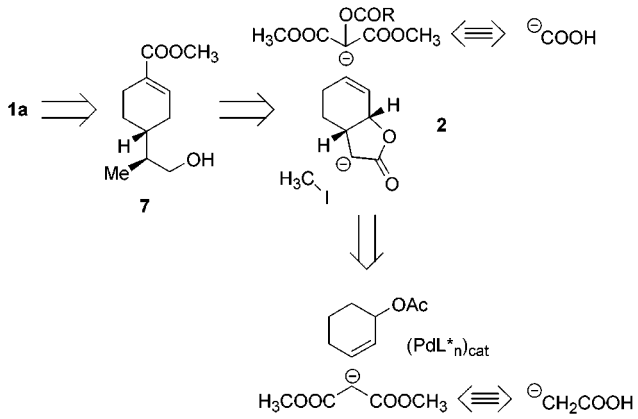


1a: $R^1 = CH_3$, $R^2 = H$, (+)-(4*R*,1′*R*)-juvabione
1b: $R^1 = H$, $R^2 = CH_3$, (+)-(4*R*,1′*S*)-*epi*-juvabione

Figure 1. Compounds with juvenile hormone activity isolated from fir trees.

We now report an efficient synthesis of enantiomerically pure (+)-juvabione (**1a**). Starting material is the lactone **2** (Scheme 1) which was previously used in syntheses of natural products by us and, for another synthesis of juvabione, by Mori.[8] Both enantiomers of the lactone are accessible in high yield and enantiomeric purity via Pd-catalyzed asymmetric allylic alkylation of cyclohexenyl acetate with malonates and a few subsequent steps.[9] The relative configuration of the stereogenic centers C-4 and C-1′ can be established by diastereoselective methylation of the enolate of lactone **2**.[8] As we have shown by a synthesis of wine lactone,[10] it is possible to epimerize the center C-1′ via deprotonation-reprotonation with complete diastereoselectivity;[11] i.e., *epi*-juvabione is accessible via an analogous route.[12] The methoxycarbonyl group was introduced by Pd-catalyzed allylic substitution with acyloxycarbonyl-malonate, a synthetic equivalent of formiate introduced by Trost,[13] and subsequent oxidative degradation and isomerization of the double bond. In previous syntheses of juvabione, elongation of the side chain of intermediate **7** required numerous steps. We have now found an efficient solution to this problem by Wittig olefination with a C_5-ylide to give a thioenolether and subsequent hydrolysis.

Scheme 1



Realization of the plan outlined above is described in Scheme 2. Methylation of **2** using Mori's procedure[8] gave **3** in 95% yield with diastereomeric purity of >99.9%. The crucial palladium-catalyzed reaction of lactone **3** with dimethyl sodio(pivaloyloxy)malonate as nucleophile, obtained by treatment of ester **4b**[14] with NaH, was carried out in 88% yield using 1 mol-% of palladium precomplex and 1.5 mol-% of $Ph_2PCH_2CH_2PPh_2$ (dppe) as ligand (THF, reflux). Diastereo- and regioselectivity of the allylic substitution were very high; an isomer of **5** was not found.[15]

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(12) Epimerization of **3** was carried out by deprotonation with LDA at −78 °C and reprotonation with $CH_2(COOtBu)_2$ with diastereoselectivity of 96: 4. After flash chromatography *epi*-**3** was obtained in 70% yield with diastereomeric purity >99.9%.
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(15) Under otherwise equal reaction conditions, the reaction with dimethyl acetoxymalonate (**4a**) resulted in 50% cleavage of the acetoxy group; at room temperature after a reaction time of 24 h, the substitution product (66%) was still accompanied by the deacetylation product (10%). This side reaction does not occur with ester **4b**.

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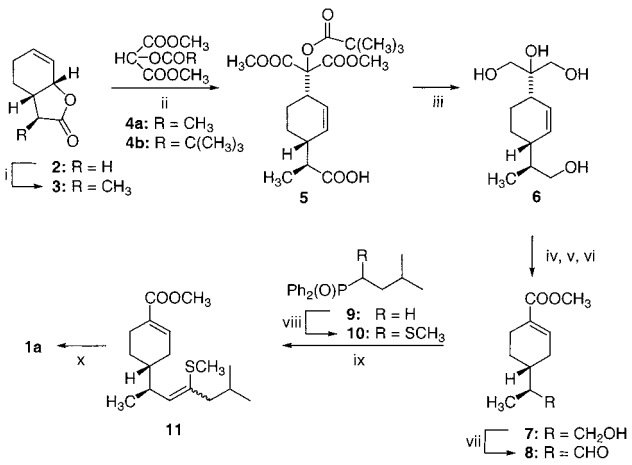
Scheme 2[a]



[a]Key: i) LDA, CH_3I, THF, -78 °C, 95 %; ii) $Pd(OAc)_2$, dppe, THF, reflux, 88 %; iii) $LiAlH_4$, THF, reflux, 72 %; iv) $NaIO_4$, H_2O, rt; v) CH_2N_2, Et_2O, rt; vi) $NaOCH_3$, MeOH, rt, 54 % (via 3 steps); vii) Dess-Martin periodinane, CH_2Cl_2, rt, 87 %; viii) *n*-BuLi, TMEDA, $(CH_3S)_2$, THF, -78 °C, 68 % ; ix) *n*-BuLi, THF, -78 °C; x) $HClO_4$, Et_2O, rt, 50 % (via 2 steps).

The carboxylic acid **5** was reduced with lithium aluminum hydride to give the water soluble, crystalline tetraol **6** in 72% yield. Workup using the procedure of Mihailovic[16] required thorough extraction of aluminum salts with THF as otherwise the alcohol **6** was obtained in low yield. Treatment of tetraol **6** with periodate, esterification of the resultant carboxylic acid with diazomethane and subsequent base-catalyzed isomerization of the double bond gave ester **7** in 54% yield over three steps.

Build-up of the side chain via a Wittig−Horner olefination required access to aldehyde **8**. Oxidation of alcohol **7** using the Dess−Martin method gave an excellent result (yield of 87%).[17] Application of the Swern method[18] led to up to 50% epimerization at C_α of the aldehyde. For the chain elongation of **8** a method developed by Warren et al.[19] was employed; this method is a Wittig−Horner reaction of a lithium derivative of a (methylthio)alkylphosphine oxide with an aldehyde to give an alkenyl sulfide which is hydrolyzed to a ketone. For the present application, the new reagent **10** was required, which was prepared in 68% yield by reaction of the known phosphine oxide **9** with $(CH_3S)_2$ using a procedure of Warren et al.[20] Phosphine oxide **10** was treated with *n*-BuLi at −78 °C to give the lithium derivative which was reacted with aldehyde **8**. The resultant crude alkenyl sulfide **11** was hydrolyzed with aqueous perchloric acid. Flash chromatography gave pure (+)-juvabione (**1a**) in 50% yield (from aldehyde **8**) and pure *epi*-juvabione (**1b**) in 3% yield.[21] (+)-Juvabione (**1a**) displayed an optical rotation of $[\alpha]^{25}_D$ = +66.9 (*c* 2.57, C_6H_6, > 99.9 % ee) which is in good agreement with values previously reported, $[\alpha]^{25}_D$ = +62.7 (*c* 0.45, C_6H_6)[8] and $[\alpha]^{25}_D$ = +64.5 (*c* 0.57, C_6H_6).[5c]

In conclusion, our synthesis starting from **2** requires nine steps and provides a total yield of 14%. It compares favorably with previous syntheses of (+)-juvabione (**1a**) (nine steps, total yield 0.9%,[8] 10 steps, total yield 2.5%).[6] The superior result is mainly due to the more efficient buildup of the side chain. The bicyclic lactone **2** was prepared from racemic (±)-2-cyclohexen-1-yl acetate in a five-step synthesis with an overall yield of 47% as previously reported.[10]

Experimental Section

General Methods. Melting points and boiling points are uncorrected. TLC: Machery-Nagel Polygram Sil G/UV precoated sheets, treatment with I_2 and/or aqueous $KMnO_4$ solution for visualization. For flash chromatography ICN Kieselgel S (0.032−0.063 mm) was used. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer [300.13 MHz (^1H), 75.46 MHz (^{13}C), $CDCl_3$]. Optical rotations were determined with a Perkin-Elmer 241 Polarimeter. Reactions in dry solvents were carried out under an argon atmosphere. $Pd(OAc)_2$ was purchased from Aldrich; $(CH_3S)_2$ and dppe were purchased from Fluka.

2-(2,2-Dimethyl-propionyloxy)malonic Acid Dimethyl Ester (4b). A solution of 2,2-dimethylpropanoic acid (11.2 g, 110 mmol) in dry DMF (50 mL) was added to a suspension of NaH (2.640 g, 110 mmol) in dry DMF (250 mL) under vigorous stirring at room temperature. After 30 min stirring brommalonic acid dimethylester (21.0 g, 100 mmol) was added slowly. The reaction mixture was further stirred at room temperature for 12 h and then poured into H_2O (400 mL). The resultant mixture was extracted with diethyl ether and the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by distillation under reduced pressure (bp 85−87 °C/1.0 mbar) to give 20.24 g (87%) of **4b** as colorless liquid: ^1H NMR ($CDCl_3$) δ = 1.23 [s, 9H, $C(CH_3)_3$], 3.78 (s, 6H, $O-CH_3$), 5.46 [s, 1H, $CH(CO)_2$]; ^{13}C NMR ($CDCl_3$) δ = 26.6 [q, $C(CH_3)_3$], 38.5 [s, $C(CH_3)_3$], 52.9 (q, $O-CH_3$), 71.1 [d, $CH(CO)_2$], 164.8 [s, $CH(CO)_2$], 176.7 [s, $O=C-C(CH_3)_3$]. Anal. Calcd for $C_{10}H_{16}O_6$ (232.23): C, 51.72; H, 6.95. Found: C, 51.59; H, 7.10.

(+)-2-[4-[(*S*)-1-Carboxyethyl]-(1*S*,4*R*)-cyclohex-2-enyl]-2-(2,2-dimethylpropionyloxy)malonic Acid Dimethyl Ester [(+)-(5)]. A suspension of $Pd(OAc)_2$ (74.0 mg, 0.33 mmol) and 1,2-bis(diphenylphosphino)ethane (197 mg, 0.50 mmol) in dry THF (40 mL) was stirred at room temperature for 2 h under an argon atmosphere until a clear, yellow solution resulted, and (+)-**3** (7.82 g, 51.4 mmol, > 99.9% ee) was added to give solution A. Sodium hydride (95%, 2.00 g, 87.0 mmol) was suspended in dry THF (130 mL) and ester **4b** (23.85 g, 103.0 mmol) was added. Upon stirring at room temperature a clear, colorless solution resulted which was transferred into solution A. The reaction mixture was heated at reflux for 3 h. After cooling, 6 N HCl (100 mL) was added, and the mixture was extracted repeatedly with diethyl ether (5 × 200 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (40 × 5 cm) using petroleum ether/ethyl acetate 9:1 (0.5% HOAc) as eluent gave **5** (17.41 g, 88%) as a colorless, viscous oil: $[\alpha]^{20}_D$ = +26.7 (*c* 2.8, $CHCl_3$, >99.9% ee); ^1H NMR ($CDCl_3$) δ 1.15 (d, *J* = 6.4 Hz, 3 H, CH_3CH), 1.23 [s, 9 H, $C(CH_3)_3$], 1.55−173 (m, 4H, CH_2), 2.34−2.41 (m, 2 H, $CHCHCH_3$), 2.93 (m_c, 1 H, $OCCHCH=$), 3.75 (s, 6 H, OCH_3), 5.63−5.66 (m, 1 H, =CH), 5.76−5.80 (m, 1 H, =CH), 9.5−11.2 (bs, COOH); ^{13}C NMR ($CDCl_3$) δ 14.8 (q, CH_3), 20.1 (t, CH_2), 22.6 (t, CH_2), 26.8 [q, $C(CH_3)_3$], 36.2 (d, $CHCHCH_3$), 38.7 [s, $C(CH_3)_3$], 41.6 (d, $OCCHCH=$), 43.5 (d, $CHCHCH_3$), 52.7, 52.8 (2q, OCH_3), 83.6 [s, $OC(COOCH_3)_2$], 125.8 (d, =CH), 132.3 (d, =CH), 166.5 (s, 2 $COOCH_3$), 177.1 [s, $O=CC(CH_3)_3$], 181.9 (s, COOH). Anal. Calcd for $C_{19}H_{28}O_8$ (384.43): C, 59.36; H, 7.34. Found: C, 59.38; H 7.34.

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(21) In addition, [(methylthio)alkyl]phosphonic acid esters were used as acylanion equivalents (Corey, E. J.; Shulman, J. I. *J. Org. Chem.* **1970**, *35*, 777−790). The lithium derivative of [3-methyl-1-(methylthio)-butyl)-phosphonic acid diethyl ester gave incomplete conversion and side products. One of the side reactions was transesterification of the methyl to the ethyl ester. Accordingly, [3-methyl-1-(methylthio)-butyl]-phosphonic acid dimethyl ester was probed. The alkenyl sulfide **11** was obtained in 40% yield. One of the reasons for the low yield was incomplete deprotonatiom of the phosphonate with *s*-BuLi as demonstrated by quenching with D_2O.

(+)-2-(4-[(*S*)-2-Hydroxymethylethyl]-(1*S*,4*R*)-cyclohex-2-enyl(propane-1,2,3-triol [(+)-6]. A solution of **5** (3.69 g, 9.60 mmol, >99.9% ee) in dry THF (15 mL) was added dropwise to a stirred, cold (0 °C) suspension of lithium aluminum hydride (3.65 g, 96.1 mmol) in dry THF (70 mL). The reaction mixture was heated at reflux for 5 h. After cooling, the mixture was diluted with diethyl ether (200 mL) and cooled to 0 °C. Then water (3.7 mL), NaOH (3.7 mL, *c* = 15%), and water (11 mL)[16] were added slowly with vigorous stirring. After further stirring for 12 h, the white precipitate of aluminum salts was filtered off and washed with THF extracted twice with boiling THF (100 mL). The THF solutions were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Recrystallization from acetone/*n*-hexane yielded 1.59 g (72%) of **6** as white solid: mp 95−97 °C; $[\alpha]^{20}_D$ = +9.57 (*c* 3.8, CH_3OH, >99.9% ee); ^1H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.50−1.70 (m, 5 H, C*H*CH_3, CH_2CH_2), 2.01−2.15 (m_c, 1 H, OCC*H*CH=), 2.44 (m_c, 1 H, C*H*CHCH$_3$), 3.42 (dd, *J* = 10.7, 6.6 Hz, 1 H, CH_2CHCH$_3$), 3.55−3.65 [m, 5 H, CH_2-CHCH$_3$, C(CH_2OH)$_2$], 5.74−5.84 (m, 2 H, HC=CH); ^{13}C NMR ($CDCl_3$) δ 14.9 (q, CH_3), 21.7, 24.4 (t, CH_2−CH_2), 37.1 [d, *C*HC-(CH_2OH)$_2$], 40.2 (d, *C*HCHCH$_3$), 41.2 (d, CH*C*HCH$_3$), 64.9, 65.3 [t, C(*C*H_2OH)$_2$], 66.4 (t, H_3CCHCH_2OH), 77.0 [s, *C*(CH_2OH)$_2$], 128.6 (d, =CH), 133.5 (d, =CH). Anal. Calcd for $C_{12}H_{22}O_4$ (230.30): C, 62.58; H, 9.63. Found: C, 62.38; H, 9.93.

(+)-(4*R*)-4-[(*S*)-2-Hydroxy-1-methylethyl]cyclohex-1-enecarboxylic Acid Methyl Ester [(+)-7]. A solution of **6** (991 mg, 4.3 mmol, >99.9% ee) in water (40 mL) was added to a solution of $NaIO_4$ (2.76 g, 13.0 mmol) in water (20 mL). The mixture was stirred for 2 h at room temperature and then acidified with 6 N HCl. The resultant suspension was repeatedly extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. This was dissolved in diethyl ether (20 mL) and treated with a ethereal solution of diazomethane until the yellow color persisted. The solvent was removed and the residue was dissolved in methanol (4 mL) and the solution added to a solution of NaOMe in methanol (5 mL). After stirring for 1.5 h at room temperature, water was added and the mixture was extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (20 × 3 cm) using petroleum ether/ethyl acetate 9:1 as eluent gave **7** (460 mg, 54%) as pale yellow oil: $[\alpha]^{20}_D$ = +91.4 (*c* 2.96, $CHCl_3$, >99.9% ee); ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.7 Hz, 3 H, HCC*H*$_3$), 1.11−1.24 (m, 1 H, CH_2), 1.48−1.62 (m, 2 H, C*H*C*H*CH$_3$), 1.75−2.44 (m, 5 H, CH_2), 3.47 (dd, *J* = 10.6, 6.2 Hz, 1 H, CH_2OH), 3.59 (dd, *J* = 10.6, 5.4 Hz, 1H, CH_2OH), 3.67 (s, OCH_3), 6.90−6.92 (m, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ 13.2 (q, C*C*H$_3$), 24.3 (t, CH_2), 24.4 (t, CH_2), 30.1 (t, CH_2), 34.2 (d, *C*HCHCH$_3$), 39.3 (d, CH*C*HCH$_3$), 51.3 (q, OCH_3), 65.7 (t, CH_2OH), 129.9 (s, =*C*COOCH$_3$), 139.3 (d, =CH), 167.7 (s, *C*OOCH$_3$). Anal. Calcd for $C_{11}H_{18}O_3$ (198.26): C, 66.64; H, 9.15. Found: C, 66.30; H, 9.28.

[3-Methyl-1-(methylthio)butyl]diphenylphosphine Oxide (10). Under an argon atmosphere, a solution of (3-methylbutyl)diphenylphosphine oxide (4.50 g, 16.4 mmol) and freshly distilled TMEDA (2.9 mL, 19.3 mmol) in dry THF (80 mL) was cooled to −78 °C. Then *n*-butyllithium (12.7 mL, 19.4 mmol, *c* = 1.6 M in *n*-hexane) was added slowly. The resultant orange solution was stirred for 60 min and then treated at −78 °C with a solution of dimethyl disulfide (1.70 mL 19.2 mmol) in dry THF (15 mL). The resultant mixture was stirred for 60 min at −78 °C and allowed to warm to room temperature. Then 2 N NaOH (90 mL) was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Recrystallization from ethyl acetate yielded 3.63 g (68%) **10** as colorless needles: mp 144−145 °C; ^1H NMR ($CDCl_3$) δ 0.87 [d, *J* = 6.5 Hz, 3 H, CH(CH_3)$_2$], 0.90 [d, *J* = 6.7 Hz, 3 H, CH(CH_3)$_2$], 1.46−1.52 (m, 1 H, CH_2), 1.76−1.77 (m, 1 H, CH_2), 2.00 (s, 3 H, SCH_3), 2.02−2.06 [m, 1 H, C*H*(CH_3)$_2$], 3.02−3.10 (m, 1 H, P−CH), 7.43−7.54 (m, 6 H, Ar−H), 7.79−7.91 (m, 4 H, Ar−H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q, SCH_3), 20.7 [q, CH(*C*H_3)$_2$], 23.4 [q, CH(*C*H_3)$_2$], 24.8 [d, *C*H(CH_3)$_2$], 35.4 (t, CH_2), 40.9 (dd, *J* = 71.5 Hz, P−CH), 128.3, 128.4, 128.5, 128.6, 131.1, 131.2, 131.5, 131.6, 131.7 (Ar−C); ^{31}P NMR ($CDCl_3$) δ 33.3. Anal. Calcd for $C_{18}H_{23}OPS$ (245.32): C, 67.87; H, 7.28; P, 9.79; S, 10.08. Found: C, 67.77; H, 7.23; P, 9.73; S, 9.90.

(+)-(4*R*)-[(*S*)-Methyl-2-oxo-ethyl]-cyclohex-1-enecarboxylic Acid Methyl Ester [(+)-8]. A solution of **7** (397 mg, 2.00 mmol, >99.9% ee) in CH_2Cl_2 (5 mL) was added to a suspension of Dess−Martin periodinane (933 mg, 2.2 mmol) in CH_2Cl_2 (10 mL). After the mixture was stirred at room temperature for 45 min, a mixture of $Na_2S_2O_3$ (4 g) and saturated $NaHCO_3$ solution (15 mL) was added and the reaction mixture was stirred for 20 min. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (25 × 3 cm) using petroleum ether/ethyl acetate 9:1 as eluent gave (+)-**8** (342 mg, 87%) as a colorless oil: $[\alpha]^{21}_D$ = +121.8 (*c* 2.57, $CHCl_3$, >99.9% ee); ^1H NMR ($CDCl_3$) δ 1.09 (d, *J* = 7.1 Hz, 3 H, CCH_3), 1.26−1.40 (m, 1 H, CH_2), 1.66−1.80 (m, 1 H, CH_2), 1.90−2.48 (m, 6 H, CH_2, C*H*CHCH$_3$, C*H*CH_3), 3.71 (s, 3 H, OCH_3), 6.91−6.93 (m, 1 H, C=CH), 9.66−9.67 (m, 1 H, HC=O); ^{13}C NMR ($CDCl_3$) δ 10.1 (q, C*C*H_3), 24.1 (t, CH_2), 24.6 (t, CH_2), 30.0 (t, CH_2), 33.3 (d, *C*HCHCH$_3$), 50.3 (d, H*C*CH$_3$), 51.6 (q, O*C*H$_3$), 130.2 (s, *C*=CH), 138.2 (s, C=*C*H), 167.6 (s, *C*OOCH$_3$), 204.6 (d, HC=O). Anal. Calcd for $C_{11}H_{16}O_3$ (196.25): C, 67.32; H, 8.22. Found: C, 67.03; H, 8.12.

(+)-(4*R*)-[(*S*)-1,5-Dimethyl-3-oxo-hexyl]cyclohex-1-enecarboxylic Acid Methyl Ester [(+)-Juvabione] [(+)-1a]. A solution of *n*-butyllithium (1.1 mL, 1.8 mmol, *c* = 1.6 M in *n*-hexane) was added slowly to a cooled solution (−78 °C) of 621 mg (1.95 mmol) of **10** in dry THF (10 mL). After being stirred for 90 min, the mixture was allowed to warm to room temperature and added dropwise to a cooled solution (−78 °C) of 294 mg (1.5 mmol, >99.9% ee) of the aldehyde **8** in dry THF (10 mL). The reaction mixture was stirred at −78 °C for 6 h treated with sadt. NH_4Cl solution (40 mL) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. A solution of the residue in 20 mL of diethyl ether was added to aqueous $HClO_4$ (35%, 20 mL,). After stirring for 2 h at room temperature and neutralization with solid $NaHCO_3$, the mixture was extracted with diethyl ether and the organic layer dried over Na_2SO_4. After concentration in vacuo flash chromatography on silica gel (35 × 3 cm), using petroleum ether/ethyl acetate 98:2 as eluent, gave (+)-juvabione (**1**) (201 mg, 50%) as a colorless oil: $[\alpha]^{25}_D$ = +66.9 (*c* 2.57, C_6H_6, >99.9% ee) (lit.[8] $[\alpha]_D^{25}$ = +62.7 (*c* 0.45, C_6H_6)); ^1H NMR[22] ($CDCl_3$) δ 0.86 (d, *J* = 6.8 Hz, 3 H, 1′−CH_3), 0.89 [d, *J* = 6.6 Hz, 3 H, CH(CH_3)$_2$], 0.90 [d, *J* = 6.6 Hz, 3 H, CH(CH_3)$_2$], 1.12−1.20 (m, 1 H, CH_2), 1.35−1.39 (m, 1 H, 4-H), 1.72−1.85 (m, 1 H, CH_2), 1.90−2.46 [sh, 10 H, 1′-H, C*H*(CH_3)$_2$, CH_2], 3.67 (s, 3 H, OCH_3), 6.89−6.91 (m, 1 H, C=CH); ^{13}C NMR ($CDCl_3$) δ 16.5 (q, 1′-*C*H$_3$), 22.5 [q, CH(*C*H_3)$_2$], 22.6 [q, CH(*C*H_3)$_2$], 24.5 [d, *C*H(CH_3)$_2$], 24.7 (t, CH_2), 24.8 (t, CH_2), 29.7 (t, =CH*C*H$_2$), 32.6 (d, C-1′), 37.7 (d, C-4), 47.8 (t, C-2′), 51.4 (q, OCH_3), 52.4 [t, *C*H$_2$CH(CH$_3$)], 130.1 (s, *C*=CH), 139.2 (d, C=*C*H), 167.7 (s, *C*OOCH$_3$), 210.4 (s, CH$_2$*C*OCH$_2$).

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(22) The assignment of the resonances is based on ^1H−^1H COSY, HMQC and HMBC experiments.