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Stereoselective Total Synthesis of (±)-Tochuinyl Acetate and (±)-Dihydrotochuinyl Acetates

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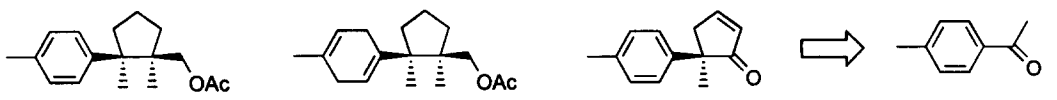
Abstract: Details of the first total synthesis of the marine natural product dihydrotochuinyl acetate is described. Cyclopentenone annulation of p-methylacetophenone via a Claisen rearrangement-Wacker oxidation based sequence generated the cyclopentenone **3**, a known precursor for the sesquiterpenes cuparene, laurene, α-cuparenone and β-cuparenones. Conversion of the ketone moiety into a carboxylate followed by stereoselective alkylation and reduction transformed the cyclopentenone **3** into the primary alcohol **19**. Birch reduction of the alcohol **19** followed by acetylation furnished (±)-dihydrotochuinyl acetate, whereas direct acetylation of **19** furnished (±)-tochuinyl acetate.

The skin extracts of several nudibranches contain interesting secondary metabolites and a majority of them were found to be sesquiterpenoids and diterpenoids. The dendronotid nudibranch *Tochuina tetraquetra* is commonly found from the Kuril Islands (USSR) to Santa Cruz Islands (USA). In 1987, Andersen and Williams reported[1] the isolation and structure elucidation of the marine natural products, tochuinyl acetate (**1**) and dihydrotochuinyl acetate (**2**), belonging to the *cuparane* class of sesquiterpenes, from the skin extracts of *T. tetraquerta*, collected from the Port Hardy, British Columbia. Subsequently, the acetates **1** and **2** were also isolated,[1] as minor components, from the extracts of the soft coral *Gersemia rubiformis*, which was found to be a feed for *T. tetraquerta*. The acetates **1** and **2** were the first examples of cuparanes to be isolated from a soft coral. The presence of two vicinal stereogenic quaternary carbon atoms in a cyclopentane ring makes the acetates **1** and **2** intriguing synthetic targets. The first synthesis of (±)-tochuinyl acetate (**1**) was achieved by Ishibashi and coworkers[2] *via* a thiochromane approach, and later Taber and coworkers[3] exploited rhodium catalysed intramolecular C-H insertion of a diazo ketone for the synthesis of (±)-**1**. Herein we describe the details of the first total synthesis[4] of (±)-dihydrotochuinyl acetate (**2**) along with the synthesis of (±)-tochuinyl acetate (**1**) starting from p-methylacetophenone (**4**) via the cyclopentenone **3**, which is a known precursor of the sesquiterpenes cuparene, laurene, α-cuparenone and β-cuparenone.



Tochuinyl acetate (**1**) Dihydrotochuinyl acetate (**2**) **3** **4**

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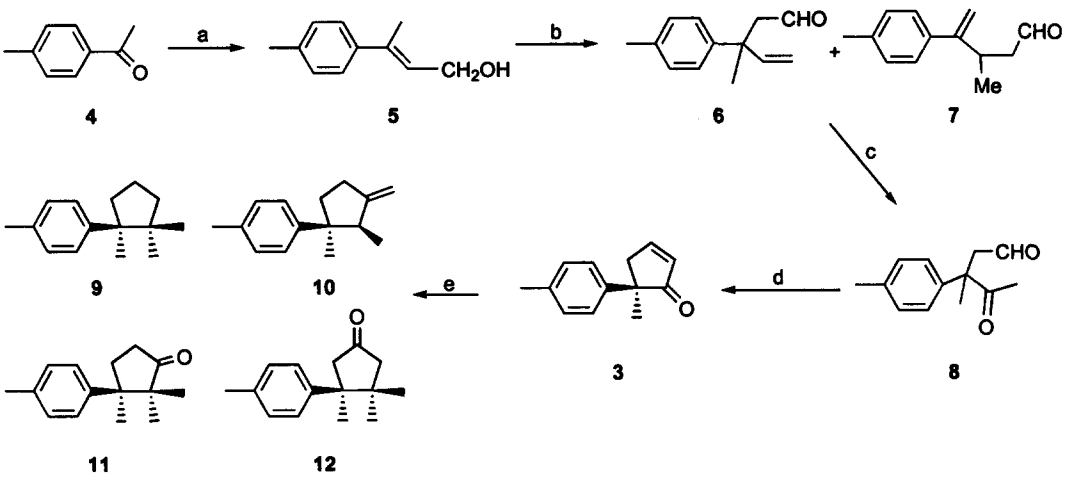
For the synthesis of the key intermediate, the cyclopentenone **3**, a Claisen rearrangement-Wacker oxidation based cyclopentenone annulation was chosen. The sequence starting from p-methylacetophenone (**4**) is depicted in Scheme 1. Horner-Wadsworth-Emmons reaction of p-methylacetophenone with triethyl phosphonoacetate and sodium hydride in refluxing THF followed by reduction of the resulting cinnamate with lithium aluminium hydride at low temperature in diethyl ether generated the requisite precursor for the Claisen rearrangement, the cinnamyl alcohol **5**. The first quaternary carbon atom was created employing a one pot Claisen rearrangement.[5] Thermal activation of the cinnamyl alcohol **5** and ethyl vinyl ether in the presence of a catalytic amount of mercuric acetate in a sealed tube at 170-180 °C furnished the aldehyde **6**. Depending upon the exact variation of the temperature of the reaction, the Claisen product **6** was accompanied by varying amount of the further rearranged product, the aldehyde **7**, which was formed by an intramolecular ene reaction followed by a retroene reaction sequence.[6] Since the Wacker reaction is known to be regiospecific, presence of the aldehyde **7** along with the aldehyde **6** has no consequence. Thus, oxidation of a mixture of the aldehydes **6** and **7** using Wacker conditions[7] ($PdCl_2$, CuCl, O_2, DMF, H_2O) followed by purification on a silica gel column furnished the keto-aldehyde **8**. Base catalysed intramolecular aldol condensation transformed the keto-aldehyde **8** into the key intermediate of the sequence, the cyclopentenone **3**, a known precursor of the sesquiterpenes cuparene (**9**), laurene (**10**), α-cuparenone (**11**) and β-cuparenone (**12**).[8]

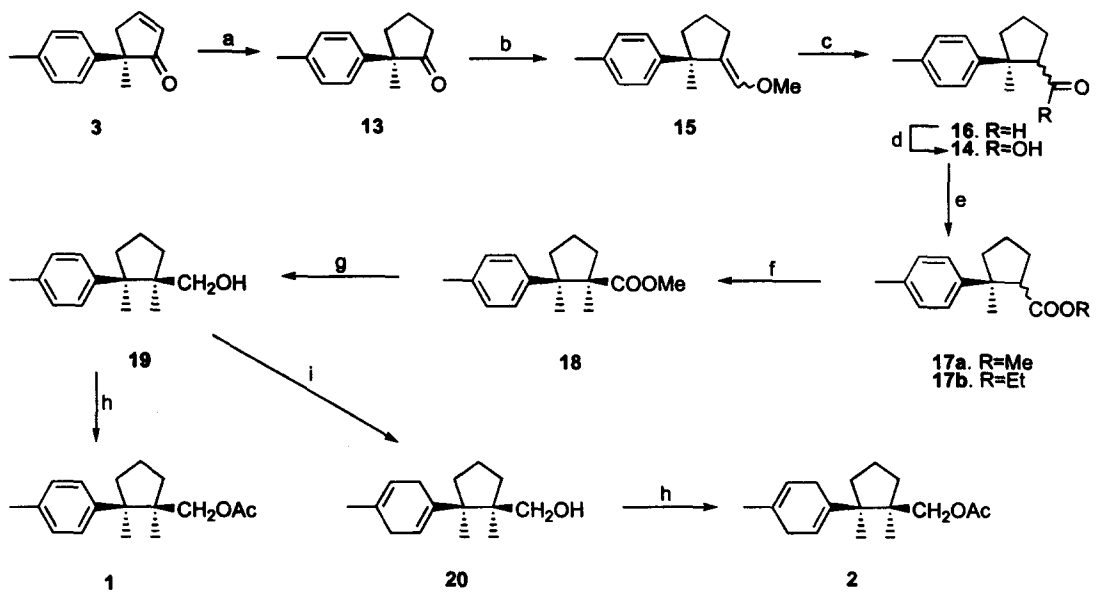
Further elaboration of the enone **3** into tochuinyl acetate (**1**) and dihydrotochuinyl acetate (**2**) is depicted in Scheme 2. Hydrogenation of the enone **3** in ethyl acetate using 10% Pd on carbon as the catalyst furnished the cyclopentanone **13**. The second quaternary carbon atom was created employing a stereoselective alkylation reaction. Accordingly, the cyclopentanone **13** was converted into the cyclopentane carboxylic acid **14** *via* methoxymethylene Wittig reaction followed by hydrolysis and oxidation. Thus, reaction of the cyclopentanone **13**

Scheme 1



Reagents and Conditions: *(a) i. NaH, $(EtO)_2P(O)CH_2COOEt$, THF, reflux, 8 h; ii. $LiAlH_4$, Et_2O, -70 °C, 2 h; (b) CH_2=CH-OEt, sealed tube, 170-180 °C, 48 h; (c) $PdCl_2$, CuCl, O_2, DMF, H_2O, rt, 24 h; (d) 5% aq. KOH, THF, Et_2O, rt, 6 h; (e) reference 8.*

Scheme 2



Reagents and Conditions: *(a) 10% Pd-C, H_2, EtOAc, rt, 1 h; (b) $MeOCH_2P^+Ph_3\ Cl^-$, $K^+\ ^tAmO^-$, THF, rt, 6 h; (c) 3 N aq. HCl, THF, rt, 16 h; (d) Jones reagent, $Me_2C{=}O$, rt, 2 h; (e) CH_2N_2, Et_2O, rt, 2 h (for 17a) or EtOH, H_2SO_4, reflux, 16 h (for 17b); (f) LDA, THF, HMPT, MeI, −70 °C→rt, 4 h; (g) $LiAlH_4$, THF, rt, 3 h; (h) Ac_2O, py, DMAP, rt, 2 h; (i) Li, liquid NH_3, ^tBuOH, THF, 6 h.*

with methoxymethylenetriphenylphosphorane followed by acid catalysed hydrolysis of the resulting enol ether **15** furnished the cyclopentane carboxaldehyde **16**. Oxidation of the aldehyde **16** with Jones reagent in acetone generated the carboxylic acid **14**,[9] which on treatment with an excess of ethereal diazomethane furnished the methyl ester **17a**. Generation of the lithium enolate of the ester **17a** with LDA in THF and HMPT followed by treatment with methyl iodide furnished the alkylated product **18** in a highly stereoselective manner via the approach of the reagent from the less hindered face. In the ^1H NMR spectrum, the upfield shift of the resonance due to the ester methyl (δ 3.25 ppm) due to the shielding by the *cis* aryl group, and the absence of an upfield shifted methyl singlet typical for methyl *cis* to the aromatic ring in cuparenes, established the stereochemistry at the newly created quaternary carbon atom in the ester **18**.[10] For the completion of the synthesis, first the ester moiety in **18** was reduced using lithium aluminium hydride to furnish the primary alcohol **19**. Treatment of the alcohol **19** with acetic anhydride in pyridine in the presence of a catalytic amount of DMAP furnished the tochuinyl acetate **1**. Since the Birch reduction of tochuinyl acetate (**1**) furnished a mixture of the alcohols **19** and **20** along with only small amount of the acetates, dihydrotochuinyl acetate (**2**) was prepared from the alcohol **19**. Thus, Birch reduction of the alcohol **19** furnished the dihydroalcohol **20**, which on acetylation using acetic anhydride, pyridine and DMAP furnished dihydrotochuinyl acetate (**2**). The ^1H NMR (270 MHz) and ^{13}C NMR (50 MHz) spectra of tochuinyl acetate (**1**) and dihydrotochuinyl acetate (**2**) obtained in this study were found to be identical with those of the natural products.

In conclusion, we have achieved the first total synthesis of dihydrotochuinyl acetate along with the synthesis of tochuinyl acetate, wherein the first quaternary carbon atom was created employing a Claisen rearrangement and the second one was created employing a stereoselective alkylation reaction.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H (90, 200 and 270 MHz) and ^{13}C NMR (25 and 100 MHz) spectra were recorded on Jeol FX-90Q, FX-100, Brucker ACF-200, WH-270 and AMX-400 spectrometers. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra off-resonance multiplicities, when recorded are given in parentheses. Low and High resolution mass measurements were carried out using a Jeol JMS-DX 303 GC-MS instrument using a direct inlet mode. Relative intensities of the ions are given in parentheses. Acme's silica gel (100-200 mesh) was used for column chromatography. All small scale dry reactions were carried out using standard syringe-septum technique. Anhydrous solvents were obtained by standard procedures. All the commercial reagents, obtained from Fluka or Merck and were used without further purification.

3-Methyl-3-(4-methylphenyl)pent-4-enal (6): A solution of the allylic alcohol[5] **5** (972 mg, 6 mmol), ethyl vinyl ether (2.6 g, 3.4 ml, 36 mmol) and mercuric acetate (10-15 mg) was placed in a sealed tube and heated to 170-180 °C for 2 days. The reaction mixture was cooled, diluted with ether (30 ml), washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate-hexane (0:1 to 1:33) as eluent furnished a 3:2 mixture of the aldehyde[5] **6** and the rearranged aldehyde **7** (770 mg, 69%). IR (neat): ν_{max}/cm^{-1} 2730, 1710, 1625, 1505, 1015, 895, 915, 815. ^{1}H NMR (90 MHz, $CDCl_3$): δ 9.55 (1 H, t, *J* 3.5 Hz, H-C=O), 6.9-7.4 (4 H, m, aromatic H), 6.07 (1 H, dd, *J* 17.4, 10.7 Hz, C*H*=CH_2), 5.14 (1 H, d, *J* 10.7 Hz) and 5.02 (1 H, d, *J* 17.4 Hz) [C=CH_2], 2.74 (2 H, d, *J* 3.5 Hz, CH_2CHO), 2.32 (3 H, s, Ar-CH_3), 1.53 (3 H, s, *tert*-CH_3). Peaks due to the rearranged aldehyde **7**: δ 9.7 (1 H, t, *J* 1.8 Hz, H-C=O), 4.97 (1 H, s) and 5.16 (1 H, s) [C=CH_2], 1.9-2.6 (3 H, m), 2.35 (3 H, s, Ar-CH_3), 1.17 (3 H, d, *J* 6.3 Hz, *sec*-CH_3).

3-Methyl-3-(4-methylphenyl)-4-oxopentanal (8): A suspension of palladium chloride (26 mg) and cuprous chloride (213 mg) in DMF (2.5 ml) and water (0.87 ml) was magnetically stirred in an oxygen atmosphere, created via evacuative displacement of air using an oxygen balloon, for 1 h at RT. A solution of a 3:2 mixture of the aldehydes **6** and **7** (552mg, 2.93 mmol) in 1 ml of DMF was then added, and the reaction mixture was stirred for 24 h at RT in the oxygen atmosphere. 3 N Aq. HCl (5 ml) was added to the reaction mixture, and extracted with ether (3 x 15 ml). The ether layer was washed with saturated aq. $NaHCO_3$ followed by brine and dried (Na_2SO_4). Evaporation of the solvent and careful chromatography of the residue on a silica gel column using ethyl acetate-hexane (1:50 to 1:25) as eluent, furnished first the unreacted aldehyde **7** (197 mg, 35.7%). Further elution of the column with ethyl acetate-hexane (1:10 to1:5) furnished the keto aldehyde **8** (290 mg, 48.5%, 75.3% based on the consumed starting material). IR (neat): ν_{max}/cm^{-1} 2740, 1720, 1705, 1512, 1350. ^{1}H NMR (90 MHz, $CDCl_3$): δ 9.62 (1 H, t, *J* 2.3 Hz, H-C=O), 7.19 (4 H, s, aromatic H), 2.97 and 2.72 (2 H, d of AB q, *J* 17.1 and 2.3 Hz, H-2), 2.35 (3 H, s, Ar-CH_3), 1.97 (3 H, s, CH_3C=O), 1.69 (3 H, s, *tert*-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.1 (C=O), 201.3 (H-C=O), 137.9, 137.4, 129.8 (2 C) and 126.0 (2 C) (aromatic C), 53.8 (quaternary C), 52.1

(CH_2CHO), 25.1 (CH_3-C=O), 21.2 and 20.9 (2 x CH_3). Mass: m/z 204 (M^+, 4%), 161 (34), 144 (32), 132 (100), 117 (33), 105 (40), 93 (30). HRMS: m/z for $C_{13}H_{16}O_2$, calcd. 204.1150; Found, 204.1143.

5-Methyl-5-(4-methylphenyl)-cyclopent-2-en-1-one (3): To a solution of the keto aldehyde **8** (380 mg, 1.86 mmol) in dry THF (1.02 ml) and ether (2.02 ml) was added 5% aq. KOH (2.15 ml, 1.93 mmol). The reaction mixture was stirred for 6 h at RT. It was then extracted with ether (3 x 10 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10 to 1:5) as eluent furnished the enone **3** (277 mg, 80%) as an oil which was identified by comparison of the spectral data with that reported in the literature.[8] IR (neat): ν_{max}/cm^{-1} 1700, 1590, 1515. ^1H NMR (270 MHz, $CDCl_3$): δ 7.78 (1 H, t of d, *J* 5.8 and 2.7 Hz, H-3), 7.16 and 7.12 (4 H, AB q, *J* 8.2 Hz, aromatic H), 6.25 (1 H, t of d, *J* 5.8 and 2.1 Hz, H-2), 3.12 and 2.85 (2 H, t of AB q, *J* 19.4 and 2.3 Hz, H-4), 2.31 (3 H, s, Ar-CH_3), 1.52 (3 H, s, *tert*-CH_3). ^{13}C NMR (25 MHz, $CDCl_3$): δ 211.7 (C=O), 162.4 (C-3), 132.1 (C-2), 140.4, 135.8, 129.0 (2 C) and 125.6 (2 C) [aromatic C], 49.9 (C-5), 47.8 (C-4), 24.3 (*tert*-CH_3), 21.0 (Ar-CH_3).

2-Methyl-2-(4-methylphenyl)-cyclopentanone (13): To a pre-activated suspension of 10% Pd-C (25 mg) in 3.5 ml of dry ethyl acetate was added the enone **3** (227 mg, 1.22 mmol) in 1 ml of ethyl acetate. The reaction mixture was stirred at RT for 3 h in a hydrogen atmosphere, created *via* evacuative displacement of air using a hydrogen balloon and then the catalyst was filtered off. Evaporation of the solvent and purification of the residue on a silica gel column, using ethyl acetate-hexane (1:40 to 1:20) as eluent, furnished the cyclopentanone **13** (228 mg, 99.3%) as an oil. IR (neat): ν_{max}/cm^{-1} 1740, 1515. ^1H NMR (270 MHz, $CDCl_3$): δ 7.24 and 7.14 (4 H, AB q, *J* 8.1 Hz, aromatic H), 2.45-2.6 (1 H, m), 2.32 (3 H, s, Ar-CH_3), 2.3 (1 H, m), 1.7-2.1 (4 H, m), 1.37 (3 H, s, *tert*-CH_3). ^{13}C NMR (25 MHz, $CDCl_3$): δ 220.2 (C=O), 139.5, 136.1, 129.2 (2 C) and 126.1 (2 C) (aromatic C), 52.9 (quaternary C), 38.4 (CH_2C=O), 37.7, 25.5, 21.1, 18.9. Mass: m/z 188 (M^+, 20%), 145 (18), 132 (100), 117 (19), 91 (12).

2-Methyl-2-(4-methylphenyl)cyclopentanecarboxylic acid (14): To a magnetically stirred solution of potassium *tert*-amylate (2.82 mmol) in dry THF (4 ml) at RT was added methoxymethyltriphenyphosphonium chloride (1.1 g, 3.23 mmol), and the resulting red coloured solution was stirred at RT for 15 min. To the phosphorane thus formed, was added a solution of the ketone **13** (208 mg, 1.11 mmol) in 1ml of dry THF and stirred at RT for 6 h. The reaction mixture was then diluted with water (5 ml) and extracted with ether (3 x 10 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Careful evaporation of the solvent and purification of the residue over a neutral alumina column using ethyl acetate-hexane (1:40 to 1:20) as eluent furnished a E,Z mixture of the enol ether **15** as a colourless oil contaminated with small amount of triphenylphosphine. [IR (neat): ν_{max}/cm^{-1} 1685, 1510]. A solution of the enol ether **15** in THF (5 ml) and 3 N HCl (10 ml) was stirred for 16 h at RT. The reaction mixture was extracted with ether (3 x 10 ml), washed with water, saturated aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column, using ethyl acetate-hexane (1:50 to 1:20) as eluent, furnished the aldehyde **16** (212 mg, 95.%) as an oil. IR (neat): ν_{max}/cm^{-1} 2720, 1715, 1510. ^1H NMR (200 MHz, $CDCl_3$, Peaks due to the major isomer): δ 9.16 (1 H, d, *J* 3.5 Hz. CHO), 7.0-7.4 (5 H, m, aromatic-H), 2.89 (1 H, dd, *J* 7.4, 4.8 Hz, C*H*CHO), 1.7-2.5 (5 H, m), 2.29 (3 H, s, Ar-CH_3), 1.35-1.5 (1 H, m), 1.35 (3 H, s, *tert*-CH_3). Peaks due to the minor isomer: 9.75 (1 H, d, *J* 3.0 Hz, CHO), 3.08 (1 H, t, *J* 7.9 Hz, C*H*CHO), 2.32 (3 H, s, Ar-CH_3), 1.29 (3 H, s, *tert*-CH_3). To a solution of the aldehyde **16**

(212 mg, 1.05 mmol) in dry acetone (2.6 ml) was added a freshly prepared solution of Jones reagent (2.62 ml of 1.6 M, 4.2 mmol). The resultant reaction mixture was stirred for 2 h. It was then treated with isopropanol (2.5 ml) to consume the excess reagent. The solvent was evaporated under reduced pressure and extracted with ether (3 x 10 ml). The ether extract was washed with saturated aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent furnished the acid **14**, which was used in the next step without purification. A small sample of the acid **14** was esterified with ethanol and sulfuric acid for comparison purpose.[9] IR (neat): ν_{max}/cm^{-1} 2970, 1725, 1510, 1445, 1370, 1340, 1155, 1035, 1015, 810. ^1H NMR (270 MHz, $CDCl_3$, 3:2 diastereomeric mixture) δ 6.9-7.4 (4 H, m, aromatic), 4.15 (2 H, q, J=7.2 Hz, O-C*H*$_2$CH$_3$), 3.73 (1 H, dd, J=7.2, 5.9 Hz, C*H*COOEt), 2.32 & 2.33 (3 H, s, Ar-CH_3), 1.7-2.65 (5 H, m), 1.37 & 1.36 (3 H, s, *tert*-CH_3), 1.26 (3 H, t, J=7.3 Hz) & 0.91 (3 H, t, J=7.0 Hz) (O-CH_2C*H*$_3$), 1.1-1.5 (1 H, m).

Methyl *cis*-1,2-dimethyl-2-(4-methylphenyl)cyclopentanecarboxylate (18): To a magnetically stirred solution of the acid **14**, obtained above, was added a cold, ethereal diazomethane solution (30 ml) and stirred for 2 h at RT. Careful evaporation of excess diazomethane and solvent, and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 1:15) as eluent furnished the ester **17a** (164 mg, 67.5% from the aldehyde) as an oil. IR (neat): ν_{max}/cm^{-1} 1730 (COOMe), 1510, 1155, 810. ^1H NMR (90 MHz, $CDCl_3$, *ca* 3:1 mixture of epimers): δ 6.9-7.4 (4 H, m, aromatic H), 3.28 & 3.67 (3 H, s, O-CH_3), 2.7-3.0 (1 H, m, C*H*-COOMe), 2.27 & 2.31 (3 H, s, Ar-CH_3), 1.7-2.2 (6 H, m), 1.32 & 1.26 (3 H, s, *tert*-CH_3). To a cold (-90 °C) magnetically stirred solution of LDA [prepared from diisopropylamine (232 mg, 0.32 ml, 2.3 mmol) and n-BuLi (2.21 mmol, 1.38 ml of a 1.6 M solution in hexane)] in 2.5 ml of dry THF was added HMPT (356 mg, 0.35 ml, 2.21 mmol) followed by a solution of the ester **17** (124 mg, 0.53 mmol) in 1.2 ml of dry THF over a period of 10 min. The reaction mixture was stirred for 40 min at the same temperature. Methyl iodide (1.6 g, 0.7 ml, 11.2 mmol) was added to the reaction mixture, slowly warmed up to RT and stirred for 8 h. It was then diluted with water (2 ml) and extracted with ether (3 x 10 ml). The combined organic extract was washed with 3 N HCl (2 ml), saturated $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20 to 1:15) as eluent furnished the ester **18** (85 mg, 65%) as an oil. IR (neat): ν_{max}/cm^{-1} 1715, 1515, 810. ^1H NMR (200 MHz, $CDCl_3$): δ 7.1 and 6.99 (4 H, AB q, *J* 8.0 Hz, aromatic H), 3.2 (3 H, s, O-CH_3), 2.22 (3 H, s, Ar-CH_3), 1.4-2.6 (6 H, m), 1.34 (3 H, s) and 1.25 (3 H, s) (2 x *tert*-CH_3). ^{13}C NMR (25 MHz, $CDCl_3$): δ 175.6 (C=O), 143.5, 135.9, 128.4 (2 C) and 126.8 (2 C) (aromatic C), 57.0 (C-2), 51.9 (C-1), 51.2 (O-CH_3), 38.4, 36.3, 24.7, 21.6, 21.1, 20.8. Mass: m/z 246 (M^+, 40%), 215 (30), 186 (80), 158 (70), 145 (90), 131 (100), 119 (85).

***cis*-1,2-Dimethyl-2-(4-methylphenyl)cyclopentanemethanol (19):** To a cold (-90 °C) magnetically stirred solution of the ester **18** (40 mg, 0.163 mmol) in 3 ml of dry THF was added LAH (38 mg, 1.0 mmol) and slowly warmed up to RT and stirred for 3 h. The reaction mixture was then quenched by careful addition of water and extracted with ether (3 x 5 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 1:5) as eluent furnished the alcohol[2,3] **19** (25 mg, 70.6%) as an oil. IR (neat): ν_{max}/cm^{-1} 3340, 1515, 1450, 1375, 1025, 815. ^1H NMR (200 MHz, $CDCl_3$): δ 7.29 and 7.12 (4 H, AB q, *J* 8.2 Hz, aromatic H), 3.12 and 3.07 (2 H, close AB q, *J* 11.2 Hz, C*H*$_2$-OH), 2.32 (3 H, s, Ar-CH_3), 1.5-2.5 (6 H, m), 1.31 (3 H, s) and 1.13 (3 H, s) [2 x *tert*-CH_3].

(±)-Tochuinyl acetate (1): To a magnetically stirred solution of the alcohol **19** (15 mg, 0.071 mmol) in CH_2Cl_2 (2 ml) was sequentially added pyridine (0.012 ml, 0.15 mmol), acetic anhydride (0.014 ml, 0.15 mmol) and a catalytic amount of DMAP, and stirred for 2 h at RT. The reaction mixture was then quenched with 1.5 N aq. HCl (3 ml) and extracted with CH_2Cl_2 (2 x 5 ml). The combined organic phase was washed with saturated aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:40) as eluent furnished tochuinyl acetate (**1**, 15.2 mg, 85%) which exhibited ^1H and ^{13}C NMR spectra identical to those of the natural product.[1] IR (neat): ν_{max}/cm^{-1} 1740 (C=O), 1515, 1465, 1380, 1240, 1030, 815. ^1H NMR (270 MHz, $CDCl_3$): δ 7.16 and 7.01 (4 H, 2 x AB q, *J* 8.2 Hz, aromatic H), 3.53 and 3.29 (2 H, AB q, *J* 11.0 Hz, C*H*$_2$-OAc), 2.26-2.44 (1 H, m), 2.23 (3 H, s, Ar-CH_3), 1.87 (3 H, s, CH_3-COO), 1.44-1.8 (5 H, m), 1.26 (3 H, s) and 1.06 (3 H, s) [2 x *tert*-CH_3]. ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.1 (C=O), 143.1, 135.4, 128.7 (2 C) and 126.8 (2 C) [aromatic C], 70.7 (*C*H$_2$-OAc), 50.0, 47.7, 37.8, 35.0, 25.1 (2 C), 20.9 (Ar-CH_3), 20.3, 19.7. Mass: m/z 260 (M^+, 25%), 185 (8), 158 (40), 145 (45), 132 (100), 119 (75), 105 (32), 99 (15), 43 (53).

(±)-Dihydrotochuinyl acetate: **Step 1, Reduction**: To a solution of lithium (30 mg, 4.3 mmol) in 30 ml of freshly distilled ammonia was added dropwise, a solution of the alcohol **19** (23 mg, 0.106 mmol) and *tert*-butanol (0.2 ml) in 1 ml of dry THF over a period of 5 min. The reaction mixture was stirred for 6 h and then quenched with ammonium chloride. Ammonia was evaporated, the reaction mixture was diluted with water and extracted with ether (3 x 5 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the dihydro alcohol **20**, which was immediately used for the acetylation step. IR (neat): ν_{max}/cm^{-1} 3355, 1370, 1020, 950, 810. ^1H NMR (90 MHz, $CDCl_3$): δ 5.63 (1 H, br s) and 5.4 (1 H, br s) (olefinic H), 3.44 and 3.15 (2 H, AB q, *J* 11.6 Hz, C*H*$_2$-OH), 2.69 (4 H, br s, 2 x allylic CH_2), 1.64 (3 H, s, olefinic CH_3), 1.4-2.5 (6 H, m), 1.06 (3 H, s) and 1.01 (3 H, s) (2 x *tert*-CH_3). **Step 2, Acetylation**: To a magnetically stirred solution of the alcohol **20** (20 mg, 0.095 mmol) in CH_2Cl_2 (2 ml) was sequentially added pyridine (0.015 ml, 0.2 mmol), acetic anhydride (0.02 ml, 0.2 mmol) and a catalytic amount of DMAP, and stirred for 2 h at RT. The reaction mixture was then quenched with 1.5 N aq. HCl (0.5 ml) and extracted with CH_2Cl_2 (2 x 5 ml). The combined organic phase was washed with saturated aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and rapid purification of the residue on a silica gel column using ethyl acetate-hexane (1:40) as eluent furnished the dihydrotochuinyl acetate (**2**, 20 mg, 72.5% from the alcohol **19**) which exhibited ^1H and ^{13}C NMR spectra identical to those of the natural product.[1] IR (neat): ν_{max}/cm^{-1} 1740 (C=O), 1380, 1235, 1030, 800. ^1H NMR (270 MHz, $CDCl_3$): δ 5.54 (1 H, br s) and 5.39 (1 H, br s) (olefinic H), 3.81 and 3.74 (2 H, AB q, *J* 10.9 Hz, C*H*$_2$-OAc), 2.6-2.8 (4 H, m, 2 x allylic CH_2), 2.02 (3 H, s, CH_3-COO), 1.4-2.5 (6 H, m), 1.65 (3 H, s, olefinic CH_3), 1.07 (3 H, s) and 1.04 (3 H, s) (2 x *tert*-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 181.8 (C=O), 138.7 and 130.6 (olefinic C), 119.3 and 119.2 (olefinic *C*H), 70.2 (*C*H$_2$-OAc), 50.5 and 47.1 (quaternary C), 37.1, 35.4, 32.1, 28.5, 22.9, 22.7, 21.0, 20.2, 19.7.

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References and Notes

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