Structural Amendment and Stereoselective Synthesis of Mutisianthol

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cis-1-(5-Acetoxy-3,6-dimethyl-1-indanyl)-2-methyl-1-propene synthesized from 3,6-dimethyl-1-indanone was found to be different from mutisianthol by spectral comparison. The presence of a high-field signal in the NMR spectrum of the final product and various intermediates, characteristic of the cis-1,3-dialkyldiananes but absent in the spectrum of the natural terpene, suggests a revision of the structure of mutisianthol to the trans isomer. The trans-indane which was subsequently obtained indeed exhibits data fully agreeable with mutisianthol. A similar stereochemical revision for jungianol is also indicated.

The isolation of the phenolic sesquiterpene mutisianthol \(1c\) from the roots of Mutisia homeoantha was reported, and its structural assignment was made on the basis of spectroscopic data.\(^1\) Mutisianthol is plausibly derived in nature from an \(\alpha\)-curcumene-type precursor by cyclization to form the indane nucleus. Interestingly, an isomer of mutisianthol, jungianol \((2c)\), was found in \(J\) unga malvafoia\(^2\) and apparently arises from intramolecular ortho-alkylation of the same biogenetic precursor (eq 1). The most intriguing aspect of these terpene molecules is the cis-relationship assigned for the two side chains in the five-membered ring of mutisianthol and of jungianol. This feature, suggesting a congested folding of the precursor for the cyclization, attracted our attention to investigate them synthetically.

We proposed to approach both molecules from a central intermediate. Accordingly, the introduction of the oxygen function would be delayed, and the subtart of our synthesis was a cis-1,5-dimethylindan-3-ylacetic ester (Scheme 1). It was hoped that the corresponding carboxylic acid might direct acylation at the peri position and that insertion of an oxygen atom between the acyl group and the aromatic ring would pave the way to jungianol. Alternatively, intermolecular acylation would deliver a ketone suitable for elaboration of mutisianthol.

The starting point of our synthesis was 3,6-dimethyl-1-indanone \(3\) which had been prepared from Rupe's acid.\(^3\) For a shorter ketone preparation we intended to effect benzylic deoxygenation and cyclization of \(3\)-hydroxy-3-(4-methylphenyl)butanoic acid in a tandem fashion,\(^4\) using triethylsilane and trifluoroacetic anhydride. However, the attempt failed as \(p\)-cymene was the only detected product, thus indicating that decarboxylation proceeded far more rapidly than reduction. The primary product of dehydrocymene underwent reduction under the reaction conditions.

By the Reformatsky reaction the indanone was converted into a mixture of the tertiary alcohol \(4\) and two isomeric unsaturated esters \(5\) and \(6\). It was later found that the in situ dehydration could be avoided if the Reformatsky reaction was carried out in an ultrasonic bath at temperatures below 30 °C; but when the temperature was maintained between 50 to 60 °C, the product was \(5\). The transformation of the Reformatsky reaction products involved dehydration of the alcohol/alkene mixtures and catalytic hydrogenation or ionic hydrogenolysis of the alcohol. The two-step procedure furnished only the cis compound \(7\) which was required for the synthesis of the proposed structures of the natural terpenes, whereas the ionic process \((\text{CF}_3\text{COOH/Et}_3\text{SiH})\)\(^5\) led to a mixture still in favor of the cis-isomer \((\text{cis:trans} = 10:1)\).

The structure of the major product was confirmed by NOE experiments. Concerning the four hydrogen atoms on the five-membered ring, two one-proton multiplets for the methine hydrogens appeared at \(\delta 3.00–3.12\) and \(3.40–3.50\), respectively, one of the methylene hydrogen resonated at \(\delta 2.57\), and the other one was hidden under the methyl signals \((\delta 1.18–1.30)\), as clearly indicated by integration. Such a relationship was delineated by a \(\mathbf{H}–\mathbf{H}\) COSY experiment, showing coupling of the \(\delta 2.57\) peak to the \(\delta 1.18–1.30\) multiplet. As nuclear Overhauser effects were also observed on the two methine hydrogens in the same experiment, the \(\delta 2.57\) peak can be assigned to the hydrogen cis to them. The other

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\(^1\) This paper is dedicated to Professor Dr. D. Seebach on the occasion of his 60th birthday.


methylenic hydrogen atom is cis to the methyl group and the acetic ester side chain and shifted upfield due to the strong shielding presumably arising from these two substituents.

At this stage we noticed a possible discrepancy in the NMR data between our synthetic intermediate and those reported for mutisianthol and jungianol. In the described spectra, the signals at the highest field belong to the benzylic methyl group only, and the methylene group appears to absorb at 1.93 or 1.98. It seems highly unlikely that the presence of a remote hydroxyl group in the aromatic ring could cause a convergence of the methylene group from that of the magnetically non-equivalent situation we observed. Consequently we examined the spectral data of the natural products more carefully and concluded that these sesquiterpenes might indeed possess the indane skeleton, with the relative configuration of the two side chains revised to trans. To resolve this problem, we continued our synthesis work toward 1c and/or 2c.

Ester 7 was saponified, and cyclization of the corresponding acid was attempted to deliver a precursor of jungianol. However, the intramolecular acylation was foiled, presumably due to excessive strain of the ring system. The use of a mixed anhydride to induce peri-acetylation also failed. We then tried to convert the ester to the tertiary alcohol by a Grignard reaction and treat the alcohol with formic acid and concentrated sulfuric acid, expecting the formation of a less strained α-tetralone system. Unfortunately, the Koch–Haaf reaction did not proceed, only dehydoration and double bond migration to give an isobutylideneindane were observed.

We redirected our focus to the synthesis of structure 1c. Accordingly, ester 7 was acetylated to give mainly the 6-acetyl derivative 8. Reaction of this ketone with m-chloroperbenzoic acid led to partial hydrolysis, and the product mixture was recrystallized to afford 9. Methyl-lithium attacked both ester functions of the acetic acid, and it was best to resubmit the product to acetic anhydride treatment to facilitate its isolation as the acetate 10. Finally, the dehydoration of 10 by refluxing with catalytic amount of p-toluenesulfonylic acid in toluene under a Dean–Stark trap led to 11 (Scheme 2).

The stereochemical structure of 11 was unambiguously established by NMR, including NOE and 1H–1H COSY experiments. There are marked differences in the spectra for this product and mutisianthol, although our compound is the α-acetyl derivative of structure 1c. Since the overall NMR spectral features of mutisianthol support the conclusion of it being an indane having substituents identical to those previously proposed, our results strongly suggest a reassignment of the configuration of C-1 and C-3 of the indane skeleton.

The entry into the trans-series was far from straightforward. Numerous attempts at reducing the unsaturated ester to give the trans-1,3-disubstituted indane were thwarted; at best an equimolar mixture of the cis and trans compounds was generated. Finally, we considered that the template effect of a tricarbonylchromium complex might be exploited to provide a solution to the stereoselective reduction leading to the desired intermediate. Accordingly, the light-sensitive derivative 12 of the unsaturated ester 5 was prepared following a standard protocol; the apparently exclusive formation of one complex was both satisfying and rather surprising (Scheme 3). This complex was reduced with magnesium in methanol. The interesting observation of trans-esterification under the mild reduction condition to furnish the chromium complex 13 may indicate interaction of the chromium with the ester enolate intermediate, enabling elimination of an alkoxide ion with the formation of a ketene. Such a pathway is possible only when the ester enolate chain is cis to the metal. On treatment of 13 with iodine the desired trans-ester 14 was obtained. The upfield region of the NMR spectrum of this ester was more consistent with that reported for mutisianthol and jungianol. Synthetic progression toward 15 then followed the same protocol as described for the cis-series, i.e., 14 → 15 → 16 → 17.

Thus, our work established the relative stereochemical feature of mutisianthol, and by extension jungianol should now be considered to have a trans-1,3-indane structure. This synthesis exploited a template effect to exert stereocontrol in the key reduction step. Interestingly, we could isolate only one α-complex 12 in 52% yield, with a structure assigning the bulky metal moiety on the face of the aromatic ring opposite to the benzylic methyl group, by inference from the steric course of the reduction.

**Experimental Section**

3,6-Dimethyl-1-indanone (3). To a magnetically stirred solution of phosphorus pentoxide (7.27 g) in methanesulfonic acid (72.70 g) was added Rupe’s acid (4.00 g, 22.5 mmol) at room temperature. After reaction overnight the mixture was

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quenched with water (150 mL), and after 2 h the organic material was extracted from the aqueous phase with dichloromethane thrice. The combined extracts were washed with brine, dried, evaporated in a rotary evaporator, and chromatographed (eluent: EtOAc/hexane 1:19) to afford the indanone (2.70 g; 75%). IR (film) 1705, 1608 cm⁻¹; ¹H NMR δ 1.36 (3H, d, J = 4.75 Hz), 2.23 (1H, dd, J = 12.7, 2.2 Hz), 2.37 (3H, s), 2.90 (1H, dd, J = 12.7, 4.9 Hz), 3.38 (1H, m), 3.77 (1H, d, J = 5 Hz), 7.41 (1H, d, J = 5 Hz), 7.50 (1H, s); ¹³C NMR δ 21.0, 21.4, 32.4, 45.7, 123.3, 124.9, 135.9, 136.6, 137.3, 157.4, 206.5; MS m/z 248 (M⁺, 59.8), 140 (100), 132 (16.5), 117 (23.7). HRMS (EI) 248.1407 (248.1411 calcd for C₁₅H₂₀O₃).

**Ethyl (3,6-Dimethyl-1-hydroxyindanyl)acetate (4).** A mixture of indanone (2.00 g, 12.5 mmol), ethyl bromoacetate (2.1 mL, 18.75 mmol), and iodine (0.60 g) in dichloromethane (25 mL) was put in a flask under nitrogen and irradiated in an ultrasonic bath (Branson). The bath temperature was kept below 30 °C by occasional addition of ice. After 16 h, the reaction mixture was poured into 150 g of crushed ice containing hydrochloric acid (10 mL). Extraction, evaporation, and chromatography gave the hydroxy ester (2.48 g, 80%). IR (film) 3492, 1726 cm⁻¹; ¹H NMR δ 2.91 (1H, t, J = 7.1 Hz), 1.31 (3H, d, J = 6.8 Hz), 1.82 (1H, dd, J = 12.8, 9.2 Hz), 2.33 (3H, s), 2.53 (1H, dd, J = 12.8, 7.1 Hz), 2.61 (1H, d, J = 15.6 Hz), 2.74 (1H, d, J = 15.6 Hz), 3.03 (1H, s), 3.79 (1H, d, J = 7.3 Hz), 4.18 (2H, q, J = 7.1 Hz), 4.35 (1H, br s), 7.08 (2H, br s), 7.15 (1H, s); ¹³C NMR δ 14.0, 19.7, 21.1, 35.4, 44.0, 49.6, 60.6, 79.6, 123.0, 123.1, 129.2, 136.4, 143.5, 146.1, 171.2; MS m/z 248 (M⁺, 0.3), 230 (80), 162 (79), 156 (100). HRMS (EI) 248.1411 (248.1413 calcd for C₁₀H₁₅O₃).

**Ethyl (3,6-Dimethyl-1-indanyl)acetate (5) and Ethyl (3,6-Dimethyl-1-indenyl)acetate (6).** To the magnetically stirred chloroform-methanol-activated zinc dust (1.64 g, 25 mmol) in anhydrous tetrahydrofuran (20 mL) was added from a dropping funnel a solution of ethyl bromoacetate (2.10 mL, 18.75 mmol) and indanone (2.00 g, 12.5 mmol) in tetrahydrofuran (20 mL) during 5 min. The reaction was refluxed for 2.5 h, cooled, and concentrated in vacuo. The residue was suspended in dichloromethane (20 mL), placed in an ice bath, and acidified with concd HCl. Layers were separated, the aqueous solution was extracted three more times with the same solvent, and the combined extracts were dried and evaporated. ¹H NMR showed the presence of hydroxy ester and unsaturated ester; therefore, the mixture was dehydrated in refluxing benzene (30 mL) in the presence of catalytic amount of p-toluenesulfonic acid under a Dean–Stark trap for 8 h. The cooled reaction mixture was diluted with ether (20 mL), washed twice with 5% aqueous sodium hydroxide and brine, dried, and concentrated in vacuo. Silica gel chromatography gave 5 and 6 in a combined yield of 70%. The ratio of 5 and 6 was 2:1. The spectral data for 5: IR (film) 1699, 1627 cm⁻¹; ¹H NMR δ 1.27–1.35 (6H, m), 2.35 (3H, s), 2.77 (1H, d, J = 19.4, 3.7, 2.8 Hz), 3.20–3.40 (1H, m), 3.58 (1H, d, J = 19.4, 7.7, 2.6 Hz), 4.20 (2H, q, J = 7.1 Hz), 6.25 (1H, t, J = 7.5 Hz), 7.19 (2H, s), 7.36 (1H, s); ¹³C NMR δ 14.4, 21.2, 21.4, 2.9, 40.7, 59.7, 107.4, 121.7, 124.1, 132.1, 136.6, 139.4, 151.4, 161.8, 167.6; MS m/z 230 (M⁺, 100), 201 (75), 183 (24), 156 (88); HRMS (EI) 230.1311 (230.1307 calcd for C₁₀H₁₉O₂).

The spectral data for 6: IR (film) 1731 cm⁻¹; ¹H NMR δ 1.26 (3H, t, J = 7.1 Hz), 1.28 (3H, d, J = 7.3 Hz), 2.39 (3H, s), 3.45 (1H, q, J = 7.3 Hz), 3.53 (1H, br s), 4.18 (2H, q, J = 7.3 Hz), 6.34 (1H, s), 7.03 (1H, d, J = 7.5 Hz), 7.14 (1H, s), 7.28 (1H, d, J = 7.5 Hz); ¹³C NMR δ 14.1, 16.1, 21.5, 33.9, 43.5, 60.6, 119.9, 122.3, 125.8, 134.8, 135.9, 136.9, 143.8, 146.7, 171.0; HRMS (EI) 232.1310 (232.1307 calcd for C₁₀H₁₅O₂).

The following experiment led to 5 only. Zinc dust (1.64 g, 25 mmol), ethyl bromoacetate (2.10 mL, 18.75 mmol), and indanone (2.00 g, 12.5 mmol), and a small grain of iodine in anhydrous dioxane (25 mL) was placed under nitrogen in an ultrasonic bath. Irradiation continued for 18 h while the bath temperature was kept between 50–60 °C. The reaction mixture was poured into ice–conc HCl, extracted with dichloromethane (3 x 20 mL), dried, and evaporated. Silica gel chromatography gave 5 (1.73 g, 60%).
Ethylic ester of methyl-3,6-dimethyl-1-indanyl-2-propynoic acid (10). A solution of ketone (0.060 g, 2.07 mmol) in anhydrous ether (4 mL) under nitrogen was added during 10 min to a solution of methyllithium (1 M in ether, 5 mL) at -78° C. The resulting mixture was stirred at room temperature for 8 h, quenched with saturated NH₄Cl solution (5 mL), and diluted with ether (20 mL). The product obtained from workup of the organic layer was dissolved in dichloromethane (5 mL) and immediately acetylated with acetic anhydride (0.25 g) and pyridine (0.20 g) overnight. Final workup in the same way as for the isolation of ketone afforded the tert-butyl ester (0.343 g, 60%). (RI) film 1754 cm⁻¹; 1H-NMR δ 1.17–1.25 (1H, m), 2.25–2.40 (3H, m), 3.60 (1H, m), 3.61 (1H, m), 3.83 (1H, d), 3.93 (3H, s), 4.01 (2H, t), 7.27 (1H, d), 7.66 (1H, d), 7.74 (1H, d). HRMS (EI) 290.1520 (290.1519) for C₁₇H₂₄O₃. 

cis-1-(5-Acetoxy-3,6-dimethyl-1-indanyl)-2-methyl-1-propane (11). A solution of alcohol 10 (0.276 g, 1 mmol) and p-toluenesulfonic acid (0.05 g) in toluene (40 mL) was refluxed under a Dean–Stark trap for 12 h. The cooled reaction mixture was diluted with ether (20 mL), washed with 5% NaOH and brine, and worked up. Silica gel chromatography (eluent: EtOAc/Hexane 1:9) furnished 11 (0.198 g, 80%). (RI) film 1754 cm⁻¹; 1H-NMR δ 1.18–1.34 (1H, m), 1.26 (3H, d, J = 10 Hz), 1.27 (3H, s), 1.78 (3H, s), 2.12 (3H, s), 2.30 (3H, s), 2.59–2.68 (1H, m), 3.00–3.13 (1H, m), 6.78 (1H, s); 13C-NMR δ 16.2, 19.2, 20.8, 29.7, 30.4, 38.1, 39.4, 45.6, 49.1, 71.2, 116.2, 125.3, 127.4, 145.2, 147.2, 148.1, 169.6; MS m/z 276 (M⁺, 4), 258 (15), 216 (59), 201 (100), 161 (47); (RI) film 276.1719 (276.1726 calculated for C₁₇H₂₂O₃). 

Methyl trans-(3,6-Dimethyl-1-indanyl)acetate (12). A mixture of 5 (0.24 g, 1.04 mmol), chromium hexacarbonyl (0.26 g, 1.18 mmol), and dioxane (6 mL) was placed in a round-bottomed flask equipped with a condenser. After evacuation and filling with nitrogen in three cycles, the flask was heated in a 150°C bath for 3 h. On cooling to room temperature the content of the flask was filtered, and the filtrate was evaporated to afford a residue which was chromatographed over silica gel. Elution with 1:10 EtOAc/hexane gave the complex 12 (0.2 g, 52% yield) and unreacted ester (0.05 g). (RI) film 1754 cm⁻¹; 1H-NMR δ 1.22 (3H, d, J = 7.5 Hz), 1.30 (3H, t, J = 2.1 Hz), 1.93 (3H, s), 2.90–2.96 (1H, m), 3.12–3.30 (2H, m), 4.21 (2H, q, J = 7.1 Hz), 7.34 (6H, m), 7.46 (1H, d, J = 6.5 Hz); 13C-NMR δ 1.16, 1.81, 19.0, 20.8, 25.8, 37.9, 42.7, 44.0, 116.2, 126.1, 127.5, 127.76, 132.8, 144.7, 147.3, 148.1, 169.7; MS m/z m/z 258 (M⁺, 15.5), 216 (35), 201 (100), 173 (14); (RI) film 258.1626 (258.1621 calculated for C₁₇H₂₀O₂). 

Methyl trans-(3,6-Dimethyl-1-indanyl)acetate (12). A mixture of 5 (0.24 g, 1.04 mmol), chromium hexacarbonyl (0.26 g, 1.18 mmol), and dioxane (6 mL) was placed in a round-bottomed flask equipped with a condenser. After evacuation and filling with nitrogen in three cycles, the flask was heated in a 150°C bath for 3 h. On cooling to room temperature the content of the flask was filtered, and the filtrate was evaporated to afford a residue which was chromatographed over silica gel. Elution with 1:10 EtOAc/hexane gave the complex 12 (0.2 g, 52% yield) and unreacted ester (0.05 g). (RI) film 1754 cm⁻¹; 1H-NMR δ 1.22 (3H, d, J = 7.5 Hz), 1.30 (3H, t, J = 2.1 Hz), 1.93 (3H, s), 2.90–2.96 (1H, m), 3.12–3.30 (2H, m), 4.21 (2H, q, J = 7.1 Hz), 7.34 (6H, m), 7.46 (1H, d, J = 6.5 Hz); 13C-NMR δ 1.16, 1.81, 19.0, 20.8, 25.8, 37.9, 42.7, 44.0, 116.2, 126.1, 127.5, 127.76, 132.8, 144.7, 147.3, 148.1, 169.7; MS m/z m/z 258 (M⁺, 15.5), 216 (35), 201 (100), 173 (14); (RI) film 258.1626 (258.1621 calculated for C₁₇H₂₀O₂).
6.6 Hz), 1.52 (6H, s), 1.8–2.4 (6H, m), 2.12 (3H, s), 2.31 (3H, s), 3.24 (1H, m), 6.77 (1H, s), 6.99 (1H, s); $^{13}$C-NMR δ 20.5, 22.6, 26.4, 26.9, 37.8, 38.6, 42.8, 46.5, 82.4, 116.8, 126.0, 127.8, 144.8, 147.5, 148.2, 169.6; MS m/z 276 (M$^+$, 6), 260 (80), 243 (60), 218 (30), 202 (100); HRMS (EI) 276.1721 (276.1726 calcd for C$_{16}$H$_{24}$O$_3$).

**trans-1-(5-Acetoxy-3,6-dimethyl-1-indanyl)-2-methyl-1-propene (18).** A solution of alcohol 17 (0.03 g, 0.11 mmol) and p-toluenesulfonic acid (0.005 g) in benzene (10 mL) was refluxed under a Dean–Stark trap for 12 h. The cooled reaction mixture was diluted with ether (20 mL), washed with 5% NaOH and brine, and worked up. Silica gel chromatography (eluent: hexane/EtOAc 10:1) furnished 18 (0.024 g, 85%). IR (film) 1760 cm$^{-1}$; $^1$H-NMR δ 1.20 (3H, d, J = 6.6 Hz), 1.73 (3H, s), 1.74 (3H, s), 1.77–1.96 (2H, m), 2.10 (3H, s), 2.29 (3H, s), 3.18 (1H, sx, J = 7.2 Hz), 3.99 (1H, q, J = 8.7 Hz), 5.11 (1H, br d, J = 8.7 Hz), 6.78 (1H, s); $^{13}$C-NMR δ 20.53, 22.63, 26.39, 26.91, 37.78, 38.59, 42.82, 46.49, 82.36, 116.80, 126.03, 127.75, 144.83, 147.45, 148.18, 169.56; MS m/z 258 (M$^+$, 50), 218 (36), 216 (85), 210 (100); HRMS (EI) 258.1628 (258.1620 calcd for C$_{17}$H$_{22}$O$_2$).

**Mutisianthol (1t).** A solution of acetate 18 (0.024 g, 0.1 mmol) in anhydrous ether (2 mL) was added to a suspension of lithium aluminum hydride (0.076 g, 0.2 mmol) in ether (2 mL). After stirring at room temperature for 20 min excess reagent was destroyed by addition of EtOAc. The resulting mixture was diluted with ether and treated with 10% HCl. The organic layer was separated, dried, and evaporated. The product was purified by silica gel chromatography (elucent: EtOAc/hexane 1:10) to give 1t (0.02 g, 92%). IR (film) 3600–3000 cm$^{-1}$; $^1$H-NMR δ 1.19 (3H, d, J = 7.5 Hz), 1.73 (3H, s), 1.76 (3H, d, J = 4.5 Hz), 1.93 (2H, m), 2.19 (3H, s), 3.18 (1H, sx, J = 5.1 Hz), 3.95 (1H, q, J = 9 Hz), 4.69 (1H, br s), 5.10 (1H, br d, J = 10.5 Hz), 6.60 (1H, s), 6.79 (1H, s); $^{13}$C-NMR δ 15.8, 18.1, 20.9, 25.8, 38.0, 41.5, 42.4, 45.1, 110.1, 121.7, 126.3, 128.6, 131.2, 138.6, 147.8, 152.7; MS m/z 216 (M$^+$, 45), 201 (100), 161 (20), 159 (10), 145 (6); HRMS (EI) 216.1522 (216.1514 calcd for C$_{15}$H$_{20}$O).

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**Supporting Information Available:** Copies of $^1$H and $^{13}$C-NMR spectra (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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