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Efficient Synthesis of Octandrenolone and Related Dipyranoacetophenones

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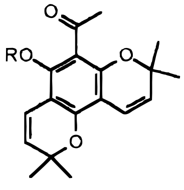
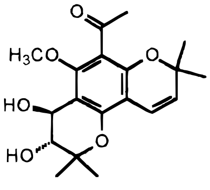
Octandrenolone (**1**) was prepared in high yield by condensation of 2′,4′,6′-trihydroxyacetophenone with 3-chloro-3-methylbut-1-yne in the presence of a catalytic amount of copper(I) iodide. Methylation of **1** afforded *O*-methyloctandrenolone (**2**). Oxidation of **2** with *m*-chloroperoxybenzoic acid followed by hydrolysis gave the racemic *trans*-(+)-1-(9,10-dihydro-9,10-dihydroxy-5-methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-6-yl)ethanone (**3**), which confirmed the structure of the natural product previously isolated from *Melicope erromangensis*.

Isolation of the dimethylpyran acetophenone octandrenolone (**1**), together with four novel related compounds, including *O*-methyloctandrenolone (**2**) and *trans*-(+)-1-(9,-10-dihydro-9,10-dihydroxy-5-methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-6-yl)ethanone (**3**), from the roots of *Melicope erromangensis* was reported earlier.[1] Fused dimethylpyran rings biogenetically arising from condensation of a phenol with an isoprenyl unit are commonly encountered in *Rutaceae* secondary metabolites, and the syntheses of dimethylpyranocoumarins,[2,3] dimethylpyranotyramine amides,[4] dimethylpyranocarbazoles,[5,6] dimethylpyranoquinolones,[7,8] dimethylpyranofuroquinolines,[9] and dimethylpyranoacridones[10−12] are well documented. However, the synthesis of dimethylpyranoacetophenones has been considerably less explored. The only previous synthesis of octandrenolone (**1**), by condensation of chloroacetophenone with 3-hydroxy-3-methylbutanal dimethylacetal, gave only 20% yield, due to formation of byproducts.[13]



1 R = H
2 R = CH_3



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Several series of natural products or structural analogues, including a dimethylpyran-derived system, exhibit interesting biological activities, exemplified by the cytotoxic and antitumor activities of acronycine[14] and related pyranophenanthridine[15] derivatives, and by the anti-AIDS activity of seselin derivatives.[16] The potential interest of dipyranoacetophenones prompted us to develop a convenient methodology for the synthesis of octandrenolone derivatives. We describe here an efficient synthesis of octandrenonelone (**1**) and *O*-methyloctandrenolone (**2**), and the conversion of this latter compound into the *trans*-diol **3**, which permitted us to confirm the structure of this natural product.

We selected the Claisen rearrangement[10] of dimethylpropargyl ethers, obtained by alkylation of a suitable phenol with 3-chloro-3-methylbut-1-yne,[17] as the most appropriate way to obtain octandrenolone (**1**). Thus, reaction of 3-chloro-3-methylbut-1-yne with commercially available 2′,4′,6′-trihydroxyacetophenone was first carried out in refluxing acetone, in the presence of potassium carbonate and potassium iodide, resulting in the formation of six major products within 24 h (Scheme 1). The first one (25% yield) was identified as octandrenolone (**1**), identical with the natural product. The second and third products were the propargylic ethers **4** (19%) and **5** (8%), which were subsequently converted almost quantitatively into **1** by refluxing in dimethylformamide for 5 h. The last three compounds were side products with one or two fused dimethylfuran rings, resulting from cyclization of products of *C*-alkylation of 2′,4′,6′-trihydroxyacetophenone with 3-chloro-3-methylbut-1-yne.[18,19] Their structures were established as 1-(2,8-diyliden-5-hydroxy-2,3,8,9-tetrahydro-3,3,9,9-tetramethylbenzo[1,2-*b*:3,4-*b*′]difuran-6-yl)ethanone (**6**), 1-(2,3-dihydro-5-hydroxy-3,3,8,8-tetramethyl-2-yliden-8*H*-benzo[1,2-*b*]furan-[3,4-*b*′]pyran-6-yl)ethanone (**7**), and 1-(8,9-dihydro-5-hydroxy-2,2,9,9-tetramethyl-8-yliden-2*H*-benzo[3,4-*b*]furan-[1,2-*b*′]pyran-6-yl)ethanone (**8**) on the basis of their spectral data. Of particular interest was the presence of ^{1}H NMR signals characteristic of *exo*-methylene groups, appearing as systems of two doublets ($J = 2.9$ Hz), at about δ 4.30 and 4.70.[18] In **7** and **8**, the relative positions of the fused pyrano and furano rings on the acetophenone basic core could be unambiguously deduced from ^{1}H−^{13}C correlations observed in the COLOC spectra.

Optimization of the process by addition of a catalytic amount of copper(I) iodide[20] when alkylating 2′,4′,6′-trihydroxyacetophenone (Scheme 1) permitted isolation of octandrenolone (**1**) in 78% yield, after only 3 h of reaction. It should be noted that intermediate propargylic ethers could not be isolated from the reaction mixture under such conditions.

Methylation of **1** (Scheme 1) with iodomethane in refluxing acetone afforded **2** in excellent yield. Finally, conversion of **2** to the corresponding racemic *trans*-dihydrodiol **3** gave confirmation of the structure of natural *trans*-(+)-1-(9,10-dihydro-9,10-dihydroxy-5-methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-6-yl)ethanone isolated from *M. erromangensis*.[1] Thus, oxidation of **2** with *m*-chloroperoxybenzoic acid, followed by hydrolysis, led to the expected racemic *trans*-diol **3**, whose UV, IR, MS,

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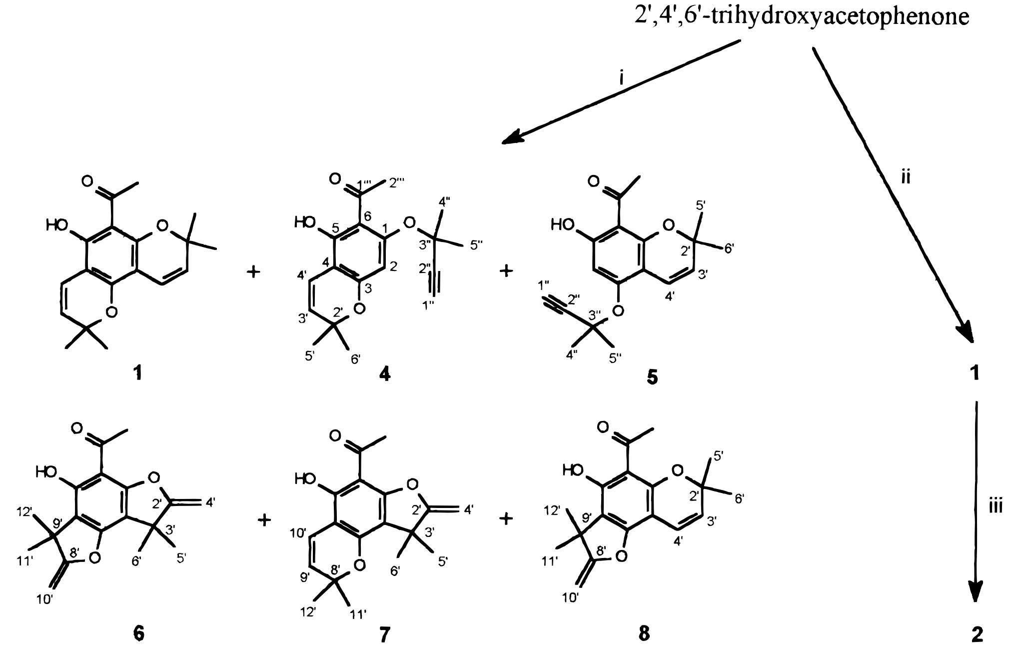
Scheme 1. Synthetic Routes to **1** and **2**[a]



[a] Key: (i) 3-chloro-3-methylbut-1-yne, Me_2CO, reflux; (ii) 3-chloro-3-methylbut-1-yne, CuI, Me_2CO, reflux; (iii) CH_3I, KOH, Me_2CO, reflux.

NMR, and TLC data were identical with those of natural *trans*-(+)-1-(9,10-dihydro-9,10-dihydroxy-5-methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-6-yl)ethanone.

Experimental Section

General Experimental Procedures. Spectra were recorded on the following apparatuses: UV, Shimadzu UV-160A; MS, Nermag R10-10H in electron impact (70 eV); NMR, Bruker AC200, ^1H NMR (200 MHz) and a Bruker AC300, ^{13}C NMR (75 MHz). Chemical shifts are given in δ with TMS as an internal standard. Coupling constants (J) are given in Hertz. Multiple-pulse experiments ($^1H-^1H$ COSY and $^{13}C-^1H$ HETCOR and COLOC) were performed on Bruker AC300, using the Bruker standard microprograms.

Column chromatography was conducted with Si gel (Merck; 20−63 μm). Elution was performed either with *n*-hexane containing increasing amounts of EtOAc (purification of compounds **1**, **2**, **6**−**10**) or with $CHCl_3$ containing increasing amounts of EtOAc (purification of compound **3**).

Alkylation of 2′,4′,6′-Trihydroxyacetophenone by 3-Chloro-3-methylbut-1-yne. To a solution of 2′,4′,6′-trihydroxyacetophenone, KI (12 g), and K_2CO_3 (10.5 g) in dry acetone (180 mL) was added 3-chloro-3-methylbut-1-yne (34 g, 0.34 mol) dropwise. The reaction mixture was refluxed for 24 h and then evaporated. The solid residue was extracted with chloroform. Concentration of the chloroform solution gave an orange oil, the TLC analysis of which showed four major products. The residue was purified on column chromatography to give **1**, **4**, **5**, **6**, **7**, and **8** in 25%, 19%, 8%, 22%, 20%, and 5% yield, respectively.

Octandrenolone (1). Spectral data are identical with those previously published.[36]

1-(5-Hydroxy-1-3-methylbutyn-3-oxy-2*H*-benzo[3,4-*b*]-pyran-6-yl)ethanone(4): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.49 (6H, s, 2 × CH_3), 1.73 (6H, s, 2 × CH_3), 2.65 (1H, s, H-1″), 2.67 (3H, s, CH_3-2‴), 5.41 (1H, d, J = 10.0 Hz, H-3′), 6.52 (1H, d, J = 10.0 Hz, H-4′), 6.70 (1H, s, H-2), 13.65 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.8 (C-5′), 27.8 (C-6′), 29.5 (C-4″), 29.5 (C-5″), 33.2 (C-2‴), 75.1 (C-2′), 77.8 (C-1″), 84.6 (C-3″), 98.1 (C-2″), 104.8 (C-3), 106.1 (C-5), 117.1 (C-1), 124.6 (C-3′), 124.6 (C-4′), 156.3 (C-2), 157.4 (C-4), 165.1 (C-6), 203.4 (C-1‴); EIMS m/z 300 $[M]^+$, 287, 285; HREIMS m/z 300.1372 (calcd for $C_{18}H_{20}O_4$ 300.1362).

1-(5-Hydroxy-3-3-methylbutyn-3-oxy-2*H*-benzo[1,2-*b*]-pyran-6-yl)ethanone (5): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.51 (6H, s, 2 × CH_3), 1.70 (6H, s, 2 × CH_3), 2.62 (1H, s, H-1″), 2.65 (3H, s, CH_3-2‴), 5.44 (1H, d, J = 10.0 Hz, H-3′), 6.57 (1H, d, J = 10.0 Hz, H-4′), 6.72 (1H, s, H-4), 13.70 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.8 (C-5′), 27.8 (C-6′), 29.8 (C-4″), 29.8 (C-5″), 32.9 (C-2‴), 77.0 (C-2′), 78.1 (C-1″), 83.9 (C-3″), 98.2 (C-2″), 104.1 (C-1), 106.1 (C-5), 115.5 (C-3), 116.6 (C-4′), 127.6 (C-3′), 155.3 (C-4), 157.4 (C-2), 168.2 (C-6), 204.3 (C-1‴); EIMS m/z 300 $[M]^+$, 287, 285; HREIMS m/z 300.1359 (calcd for $C_{18}H_{20}O_4$ 300.1362).

1-(2,8-Diyliden-5-hydroxy-2,3,8,9-tetrahydro-3,3,9,9-tetramethylbenzo[1,2-*b*:3,4-*b*′]difuran-6-yl)ethanone (6): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.51 (6H, s, 2 × CH_3), 1.53 (6H, s, 2 × CH_3), 2.68 (3H, s, CH_3-2‴), 4.29 (1H, d, J = 2.9 Hz, H-4′), 4.32 (1H, d, J = 2.9 Hz, H-10′), 4.72 (1H, d, J = 2.9 Hz, H-4′), 4.74 (1H, d, J = 2.9 Hz, H-10′), 13.17 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz)_δ 28.3 (C-5′), 28.3 (C-6′), 28.3 (C-11′), 28.3 (C-12′), 31.1 (C-2‴), 42.8 (C-4′), 42.8 (C-10′), 83.5 (C-3′ or C-9′), 84.0 (C-3′ or C-9′), 101.0 (C-3 or C-5), 101.8 (C-3 or C-5), 115.7 (C-1), 155.8 (C-2 or C-4), 156.5 (C-2 or C-4), 161.1 (C-6), 172.9 (C-2′ or C-8′), 173.1 (C-2′ or C-8′), 201.4 (C-1‴); EIMS m/z 300 $[M]^+$, 285; HREIMS m/z 300.1348 (calcd for $C_{18}H_{20}O_4$ 300.1362).

1-(2,3-Dihydro-5-hydroxy-3,3,8,8-tetramethyl-2-yliden-8*H*-benzo[1,2-*b*]furan[3,4-*b*′]pyran-6-yl)ethanone (7): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.48 (6H, s, 2 × CH_3), 1.50 (6H, s, 2 × CH_3), 2.66 (3H, s, CH_3-2‴), 4.29 (1H, d, J = 2.9 Hz, H-4′), 4.71 (1H, d, J = 2.9 Hz, H-4′), 5.47 (1H, d, J' = 10.0 Hz, H-9′), 6.66 (1H, d, J' = 10.0 Hz, H-10′), 13.45 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.8 (C-11′), 27.8 (C-12′), 28.3 (C-5′), 28.3 (C-6′), 31.3 (C-2‴), 42.9 (C-3′), 77.9 (C-8′), 83.5 (C-4′), 101.3 (C-3), 103.1 (C-5), 112.0 (C-10′), 116.2 (C-1), 125.4 (C-9′), 155.9 (C-2), 158.3 (C-4), 159.4 (C-6), 172.3 (C-2′), 201.7 (C-1‴); EIMS m/z 300 $[M]^+$, 285; HREIMS m/z 300.1371 (calcd for $C_{18}H_{20}O_4$ 300.1362).

1-(8,9-Dihydro-5-hydroxy-2,2,9,9-tetramethyl-8-yliden-2*H*-benzo[3,4-*b*]furan[1,2-*b*′]pyran-6-yl)ethanone (8): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.51 (6H, s, 2 × CH_3), 1.52 (6H, s, 2 × CH_3), 2.66 (3H, s, CH_3-2‴), 4.28 (1H, d, J = 2.9 Hz, H-10′), 4.70 (1H, d, J = 2.9 Hz, H-10′), 5.48 (1H, d, J' = 10.0 Hz, H-3′), 6.46 (1H, d, J' = 10.0 Hz, H-4′), 13.68 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.8 (C-5′), 27.8 (C-6′), 28.3 (C-11′), 28.3 (C-12′), 32.1 (C-2‴), 43.0 (C-10′), 76.7 (C-2′), 83.5 (C-9′), 100.9 (C-3), 102.4 (C-5), 115.3 (C-4′), 117.2 (C-1), 127.2 (C-3′), 151.1

(C-2), 155.9 (C-4), 156.5 (C-6), 173.2 (C-8′), 200.6 (C-1′′′); EIMS m/z 300 $[M]^+$, 285; HREIMS m/z 300.1342 (calcd for $C_{18}H_{20}O_4$ 300.1362).

Copper(I) Iodide Catalyzed Alkylation of 2′,4′,6′-Trihydroxyacetophenone by 3-Chloro-3-methylbut-1-yne. To a solution of 2′,4′,6′-trihydroxyacetophenone (6.4 g, 38 mmol) with KI (11.5 g) and K_2CO_3 (9.4 g) in dry acetone (40 mL) was added CuI (60 mg, 0.3 mmol). The reaction mixture was stirred at reflux for 15 min. Then 3-chloro-3-methylbut-1-yne (34.9 g, 340 mmol) was added dropwise over 1.5 h. The reaction mixture was stirred for 3 h at reflux. After cooling, water (150 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 120 mL). The organic layer was washed successively with 2 N HCl, 2 N NaOH, and H_2O; dried over Na_2SO_4; and concentrated under reduced pressure. The residue was crystallized from *n*-hexane, yielding **1** (8.9 g, 78%) as yellow needles.

Methylation of 1. A solution of **1** (2.8 g, 9.3 mmol), KOH (1 g), and MeI (6.2 mL, 86 mmol) in dry acetone (200 mL) was heated under reflux for 1.5 h. After cooling, water (100 mL) was added, and the reaction mixture was extracted with $CHCl_3$ (3 × 150 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified on column chromatography to give **2** (2.8 g) as yellow oil in 95% yield. Spectral data of **2** were identical with those previously published.[1]

Oxidation of 2. To a solution of **2** (262 mg, 0.8 mmol) in $CHCl_3$ (7 mL), *m*-chloroperoxybenzoic acid (182 mg, 1.2 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, then hydrolyzed with saturated aqueous $NaHCO_3$ and stirred again for 10 min. The mixture was extracted with Et_2O (12 mL), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (3 × 8 mL) and H_2O (3 × 6 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in dioxane (5 mL) and 0.5 N KOH (5 mL); the mixture was stirred at room temperature for 30 min, then acidified with 20% HCl, and further stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure to give a solution that was extracted with EtOAc. The EtOAc layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Column chromatography of the residue led to the isolation of **3** in 2% yield.

***trans*-(+)-1-(9,10-Dihydro-9,10-dihydroxy-5-methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-6-yl)ethanone (3).** Spectral data were identical with those previously published.[1]

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