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Facile Total Synthesis of (±)-α-Herbertenol, (±)-α-Cuparenone and (±)-HM-1 Methyl Ether Involving Alkylation of Hindered Esters

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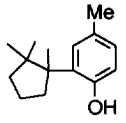
Abstract : The total syntheses of (±)-α-herbertenol **1**, (±)-α-cuparenone **4** and (±)-HM-1 methyl ether **3** have been successfully accomplished involving α,α-dimethylation of the esters **8a**, **17** and **8b** respectively as key steps.

(-)-α-Herbertenol **1**, a sesquiterpene phenol, exhibits significant antifungal properties and was isolated by Matsuo and co-workers[1] from the liverwort *Herberta adunca,* along with several closely related phenols. Recently, HM-1 **2** and three other phenols possessing skeletal features similar to **1** have been isolated by Nohara *et al*[2] from the phytopathogenic fungus *Helicobasidium mompa*. The total syntheses of **1** and **2** present interesting problems in view of the steric congestion associated with two vicinal quaternary centres in a cyclopentane ring. The related sesquiterpene ketone α-cuparenone **4** has attracted[3] considerable attention as a challenging synthetic target. In connection with our studies on alkylation of hindered esters,



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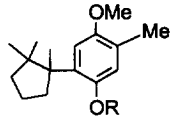
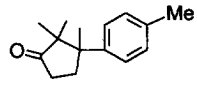


2, R = H
3, R = Me



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we have accomplished the total syntheses of (±)-α-herbertenol **1**, (±)-HM-1 methyl ether **3**, and (±)-α-cuparenone **4** involving α,α-dimethylation of the esters **8a, 8b** and **17** respectively as key steps.

The tetralones **5a** and **5b** were condensed with malononitrile to provide the unsaturated dinitriles **6a,**[4] m.p. 93-94°C and **6b**, m.p. 131-132°C in near quantitative yields (Scheme 1). Conjugate addition of MeMgI to **6a** afforded **7a** (89%) which on hydrolysis, decarboxylation, and esterification furnished the methyl ester **8a** in 82% yield. The dinitrile **6b** was similarly converted into the methyl ester **8b** in 74% overall yield. The ester **8a** was alkylated with MeI at -78°C using LDA (1 equiv.) as the base to provide the ester **9a** as a diastereoisomeric mixture in 95% yield. Alkylation of **9a** with MeI in the presence of LDA (1.7 equiv.) and HMPA (2 equiv.) at 0°C afforded the ester **10a** (92%). α,α-Dimethylation of **8b** was similarly carried out to provide **10b** (87%). The transformation of **8a** into **10a** could also be accomplished in 90% yield in a one-pot process employing a sequential methylation without isolating the monomethyl derivative **9a**. Oxidation of **10a** and **10b** with CrO_3 gave the keto-esters **11a**, m.p. 76-77°C and **11b**, m.p. 97-98°C in 75% and 78% yields respectively. Baeyer-Villiger reaction of **11a** and **11b** afforded the lactones **12a** (84%) and **12b** (88%). Alkaline hydrolysis of **12a** followed by treatment with Me_2SO_4 and esterification with CH_2N_2 furnished the diester **13a** (85%). The lactone **12b** was similarly converted into the diester **13b** (85%).

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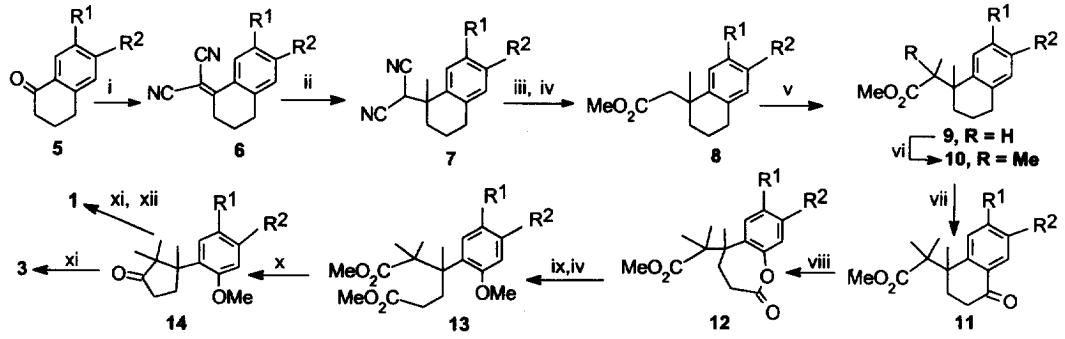
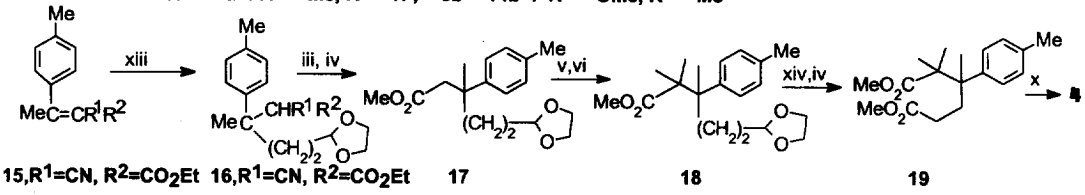


Scheme 1 : **5a– 14a : R^1 = Me, R^2 = H ; 5b – 14b : R^1 = OMe, R^2 = Me**



Scheme 2

Reagents and Conditions : i, $CH_2(CN)_2$, NH_4OAc, AcOH, C_6H_6, reflux; ii, MeMgI, CuI, THF, 25°C then reflux; iii, KOH, $HOCH_2CH_2OH$, H_2O, reflux, then H_3O^+; heat (190°C); iv, CH_2N_2, Et_2O, 0°C; v, LDA (1 equiv.), THF, -20°C; MeI, HMPA, -78°C; vi, LDA (1.7 equiv.), HMPA (2 quiv.), THF, 0°C; MeI, 0°C; vii, CrO_3, AcOH, 10-25°C; viii, MCPBA, CH_2Cl_2, CF_3CO_2H, 0-25°C; ix, aq. NaOH, MeOH, reflux; then Me_2SO_4, 50-55°C, H_3O^+; x, *t*-BuOK, C_6H_6 reflux, then H_3O^+; DMSO, NaCl, 150°C; xi, N_2H_4, $N_2H_4.2HCl$, $(HOCH_2CH_2)_2O$, 130°C; KOH, 210°C; xii, BBr_3, CH_2Cl_2, 0-25°C; xiii,  $CHCH_2CH_2MgBr$, CuBr.Me_2S, THF, -10-25°C; xiv, AcOH, H_2O, 25-60°C; then Jones reagent, Me_2CO, 0-25°C.

Dieckmann cyclisation of the diesters **13a** and **13b** followed by decarbomethoxylation of the resulting crude β-ketoesters afforded the ketones **14a** and **14b** in 75% and 72% yields respectively. Huang-Minlon reduction[5] of **14b** furnished (±)-HM-1 methyl ether **3** (78%). Huang-Minlon reduction of **14a** followed by demethylation with BBr_3 afforded (±)-α-herbertenol **1** (72%). The identities of synthetic **1** and **3** were secured through ^1H NMR, ^{13}C NMR, IR and microanalytical data.

Conjugate addition of $CHCH_2CH_2MgBr$ to the unsaturated cyano-ester **15** afforded **16** (50%) which on hydrolysis, decarboxylation, and esterification furnished the ester **17** in 75% yield (Scheme2). α,α-Dimethylation of **17** as described for **10a** gave the ester **18** (88%). Deacetalisation of **18** followed by oxidation of the resulting aldehyde with Jones reagent and esterification with CH_2N_2 furnished the diester **19** in 73% overall yield. Dieckmann cyclisation of **19** and subsequent decarbomethoxylation of the resulting β-ketoester afforded (±)-α-cuparenone **4** in 75% yield.

The spectral data of **1** and **4** agreed very well with those reported in the literature.[1,3]

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References and Notes

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