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Enantioselective synthesis of herbertane sesquiterpenes: synthesis of (–)-α-formylherbertenol

Antonio Abad,* Consuelo Agulló, Ana C. Cuñat and Remedios H. Perni

Departamento de Química Orgánica, Facultad de Químicas, Universidad de Valencia C/Dr. Moliner 50, E-46100 Burjassot, Valencia, Spain

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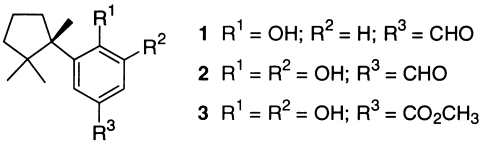
Abstract

The synthesis of 4-hydroxy-3-[(1*S*)-1,2,2-trimethylcyclopentyl]benzaldehyde [(–)-α-formylherbertenol **1**], a herbertane-type sesquiterpene isolated from the leafy liverwort *Herberta adunca*, from β-cyclogeraniol is described. The synthesis is based on the previously described preparation of an enantiopure 1,2,2-trimethylcyclopentane synthon from which the characteristic aromatic moiety of **1** is elaborated, using a Robinson annulation and a palladium-catalysed methoxycarbonylation of an aryl triflate as key synthetic steps. The synthesis of the natural sesquiterpene (–)-α-herbertenol, also a natural sequiterpene, using the same methodology is also described.

1. Introduction

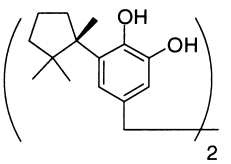
(–)-α-Formylherbertenol **1** constitutes one of the few examples of herbertanes, a group of aromatic sesquiterpenoids characterised by a 1,2,2-trimethyl-1-*m*-tolylcyclopentane structure that have been isolated from *Herbertus* species and other liverworts,[1,2] functionalised at the methyl aromatic group. This compound, isolated from the methanolic extracts of the leafy liverwort *Herberta adunca* (Dicks.) S. Gray, shows a strong antifungal activity.[3] Other related herbetane-type sesquiterpene phenols recently isolated are 1,2-dihydroxyherberten-12-al **2**,[4] methyl 1,2-dihydroxyherberten-12-oate **3**[4] and the bis-side-chain coupled analogue mastigophorene D **4**.[5]



1 $R^1 = OH$; $R^2 = H$; $R^3 = CHO$

2 $R^1 = R^2 = OH$; $R^3 = CHO$

3 $R^1 = R^2 = OH$; $R^3 = CO_2CH_3$



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* Corresponding author.

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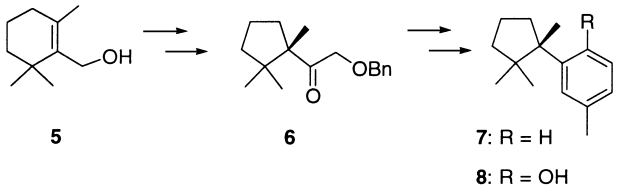
The interesting biological properties of the herbertanes and their unique carbon framework, in particular the two adjacent quaternary carbon atoms, have stimulated extensive synthetic efforts from many research teams.[6] In recent years we have developed a general approach to the enantioselective synthesis of herbertane-type compounds. This approach, based on the enantioselective preparation of the 1,2,2-trimethylcyclopentane nucleus from readily available β-cyclogeraniol **5** followed by elaboration of the aromatic six-membered ring (Scheme 1), has been successfully used for the preparation of two representative members of this group of sesquiterpenes, (–)-herbertene **7** and (–)-α-herbertenol **8**.[7] In connection with this work we describe in this paper a new and more efficient procedure for the elaboration of the aromatic moiety of these systems which has allowed us to complete very efficiently the first enantioselective synthesis of (–)-α-formylherbertenol **1**† and opens an alternative way to the preparation of other related herbertanes.



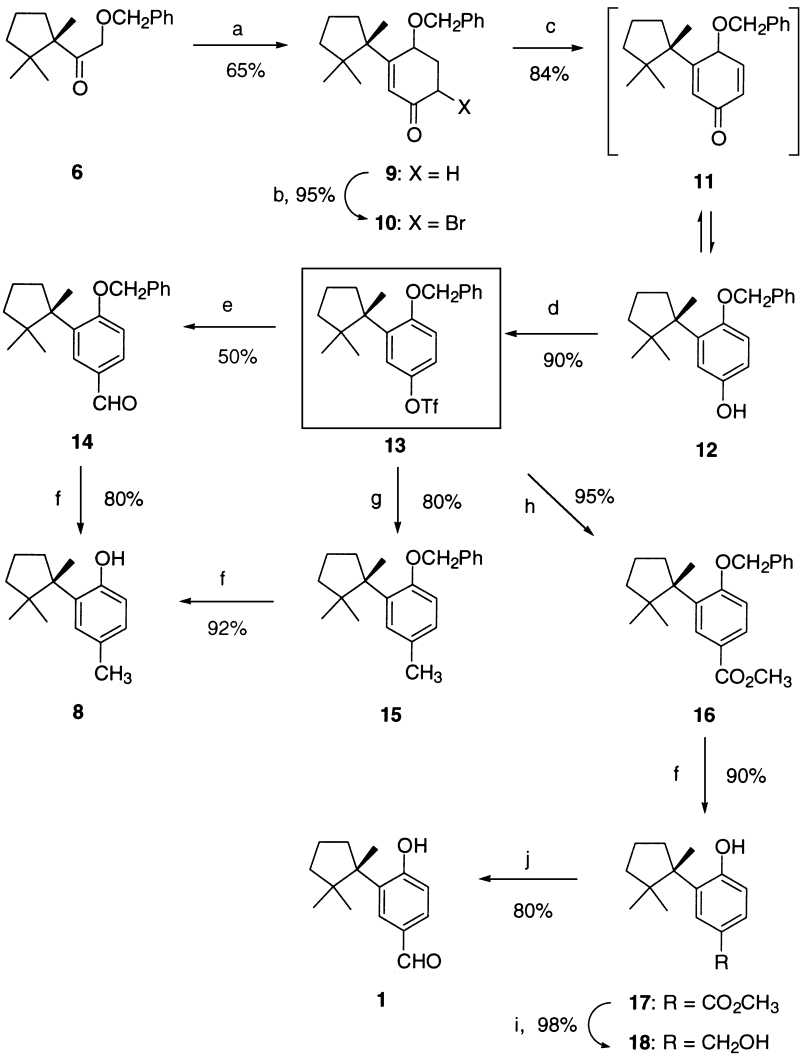
Scheme 1.

2. Results

As in the previous synthesis, the enantiomerically pure ketone **6** was prepared from β-cyclogeraniol in three synthetic steps (Sharpless asymmetric epoxidation, benzylation of the hydroxyl group and pinacollic rearrangement) in 67% overall yield. Michael addition of the sodium enolate, obtained by treatment of **6** with *N*-sodiohexamethyldisilazane (NaHMDS), to α-(trimethylsilyl)vinyl ketone followed by KOH promoted intramolecular aldol reaction afforded cyclohexenone **9** in 65% overall yield, as an equimolecular mixture of epimers at C-4 (Scheme 2). In order to complete the functionalisation of the target herbertane we first proceeded to the aromatisation of the cyclohexane-ring moiety. Towards this end we set out to transform **9** into phenol **12** via the tautomeric cyclohexadienone **11**. The standard selenium-based methodology unfortunately gave rise to low yields of **12** (ca. 40% yield after α-selenenylation, oxidation and loss of benceneselenenic acid). However, **12** was prepared in good yield by α-bromination/dehydrobromination of **9**. Thus, treatment of **9** with trimethylsilyl triflate and triethylamine, followed by in situ reaction of the resulting silyl enol ether with *N*-bromosuccinimide (NBS), yielded the α-bromoketone **10**,‡ which, upon heating to 110°C in toluene with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and a small amount of hydroquinone, afforded phenol **12** in 84% overall yield.

† A preliminary communication of this work was presented at the 16th International Symposium on Synthesis in Organic Chemistry, Churchill College, Cambridge, UK, July 1999.

‡ Reaction of the silyl enol ether with palladium(II) acetate in acetonitrile gave a complex reaction mixture from which the phenol **12** could be isolated in very low yield.



Scheme 2. (a) (i) NaHMDS, –78°C then 3-TMS-buten-2-one; (ii) KOH, MeOH–H_2O, 120°C. (b) TMSOTf, Et_3N, Et_2O, –78°C then NBS, THF. (c) DBU, toluene, 110°C. (d) Tf_2O, Et_3N, CH_2Cl_2, –70→–30°C. (e) $Pd(OAc)_2$, dppp, Et_3N, $(C_8H_{17})_3SiH$, CO, DMF, 70°C. (f) Pd/C, H_2, EtOH. (g) $PdCl_2(PPh_3)_2$, LiCl, Me_4Sn, DMF, 88°C. (h) $Pd(OAc)_2$, dppp, Et_3N, CO, DMF–MeOH, 70°C. (i) DIBALH, THF, –78°C. (j) 4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate, silica gel, CH_2Cl_2

With the phenol **12** in hand, we proceeded to its conversion into aryl triflate **13**. This transformation was readily effected in excellent yield by treatment of **12** with triflic anhydride in the presence of triethylamine. Compound **13** was considered a key intermediate in the synthesis of herbertane sesquiterpenes of the type shown above due to the easy substitution of the trifluoromethanesulfonate group by formyl, alkoxycarbonyl or alkyl groups through palladium-catalysed reactions.[8] We first examined the formylation of **13**. When a mixture of the aryl triflate, triethylamine, trioctylsilane and catalytic amounts of palladium(II) acetate and 1,3-bis(diphenylphosphino)propane (dppp) in DMF was stirred at 70°C under a carbon monoxide atmosphere,

the aldehyde **14** was obtained in 50% yield after chromatographic purification.[§] Completion of the synthesis of α-formylherbertenol **1** from **14** only required deprotection of the phenolic moiety. Unfortunately, under a variety of reaction conditions hydrogenolysis of the benzyl group of **14** always took place with simultaneous reduction of the aldehyde group followed by hydrogenolysis of the resulting benzylic alcohol, thus also affording the natural α-herbertenol **8**. In fact, conversion of **14** into **8** could be effected in very high yield by hydrogenation using Pd on carbon in EtOH.[¶]

In order to circumvent this problem we decided to effect a methoxycarbonylation of the triflate **13** as an indirect way to arrive at **1**. Treatment of **13** with triethylamine and catalytic amounts of palladium acetate(II) and dppp in MeOH and DMF at 70°C under carbon monoxide atmosphere for two days resulted in the isolation of the methyl ester **16** in excellent yield (95%). Hydrogenolysis of the benzyl group of **16**, using palladium on carbon in EtOH, cleanly afforded the phenol-ester **17**. Final reduction of the ester moiety to an aldehyde group was effected in two steps. First, the ester moiety of **17** was reduced in nearly quantitative yield to the benzylic alcohol **18** by treatment with DIBALH in THF at low temperature. Subsequent oxidation of **18** with 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate[9] in CH_2Cl_2 in the presence of silica gel provided, after column chromatography, the target compound **1** in 80% yield.[‖] The spectroscopic properties of the synthetic material were identical in all respects with those of the naturally occurring compound.[3b] The overall yield of (–)-α-formylherbertenol **1** from β-cyclogeraniol **5** was 20–21% in 12 synthetic steps.

3. Experimental

3.1. General

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined using a 5 cm path length cell. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. All ^{1}H spectra were recorded in $CDCl_3$ at 300 or 400 MHz, and all ^{13}C at 75 MHz. Carbon substitution degrees were established by DEPT pulse sequence. Mass spectra were obtained by electron impact (EI) at 70 eV. IR spectra were measured as KBr pellets or liquid films. All reactions were carried out under an inert atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–400 mesh.

[§] Given the difficulties found for the transformation of **14** into **1**, see below, this formylation was effected only once and so the yield is not optimised.

[¶] An alternative and more efficient synthesis of **8** from aryl triflate **13** was also completed using a palladium-catalysed Stille coupling reaction to introduce the methyl group. Thus, coupling of **13** with Me_4Sn in the presence of LiCl and a catalytic amount of $PdCl_2(PPh_3)_2$ in DMF afforded the compound **15** (see Scheme 2) in 80% yield, which, upon hydrogenolysis of the benzyl group using Pd on carbon in EtOH, gave α-herbertenol **8** in 92% yield. This enantioselective synthesis of α-herbertenol from β-cyclogeraniol via aryl triflate **13** (11 steps, ca. 23% overall yield) constitutes the most efficient enantioselective synthesis described so far for this compound.

[‖] The use of the oxoammonium salt as oxidant in this transformation was essential. Attempts to run the reaction with other oxidants afforded a much lower yield of **1** (e.g. TPAP 43%, PCC on alumina 50%) or even complex reaction mixtures (Magtrieve™, $BaMnO_4$ or Swern oxidation) from which **1** could not be isolated.

3.2. 4-Benzyloxy-6-bromo-3[(1S)-1,2,2-trimethylcyclopentyl]-2-cyclohexen-1-one **10**

To a solution of diastereomeric ketones **9**[7] (591 mg, 1.89 mmol) in anhydrous Et_2O (12 mL) were added triethylamine (0.79 mL, 5.68 mmol) and TMS triflate (0.55 mL, 3.03 mmol) at –78°C. The reaction mixture was stirred at the same temperature for 2 h and then treated with a solution of recently purified NBS[10] (1.35 g, 7.58 mmol) in THF (10 mL). The reaction mixture was allowed to warm to –30°C over 30 min and then poured into 5% hydrochloric acid and extracted with ethyl acetate. The organic extracts were washed with 5% aqueous $NaHCO_3$ solution and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent under vacuum afforded an oily residue which was chromatographed on silica gel, using hexane:ethyl acetate 9:1 as eluent, to give the bromoketone **10** as a mixture of four diastereomers (708 mg, 95%). Although this mixture was directly used in the next reaction (see below), the diastereomers could be partially separated by MPLC and their spectroscopic data were determined independently. However, unequivocal assignment of each set of data to a particular diastereomer was not possible. We give here the spectroscopic data of the main diastereomer. IR (KBr): 2958, 2873, 1681, 1610, 1063, 698, 449 cm^{-1}; ^1H NMR δ 7.5–7.3 (5H, m, H_5-Ar), 6.10 (1H, s, H-2), 4.85 (1H, d, $J=10.4$ Hz, OCH_2), 4.48 (1H, dd, $J=5.6$ and 2.7 Hz, H-6), 4.38 (1H, d, $J=10.4$ Hz, $OCH_{2'}$), 4.32 (1H, dd, $J=2.8$ and 2.7 Hz, H-4), 3.04 (ddd, $J=16$, 2.8 and 2.7 Hz, H-5), 2.46 (ddd, $J=16$, 5.6 and 2.8 Hz, H-5′), 1.16 (3H, s, Me-1′α), 1.01 and 0.78 (3H each, each s, Me-2′α and Me-2′β); ^{13}C NMR δ 192.65 (C1), 168.19 (C3), 137.14 (C1″), 128.49, 128.35 and 127.79 (C2″/C6″, C3″/C5″ and C4″), 126.21 (C2), 71.07 (OCH_2), 70.71 (C4), 52.66 (C1′), 45.07 (C2′), 40.13 (C6), 40.11 (C3′), 36.69 (C5′), 31.84 (C5), 26.40 (Me-1′), 25.15 (Me-2′β), 21.50 (Me-2′α), 19.37 (C4′); MS (EI) m/z 393 (M^++2, 2), 391 (M^+, 2), 312 (2), 286 (2), 285 (15), 283 (14), 221 (12), 207 (18), 206 (17), 205 (47), 91 (100); HRMS calcd for $C_{21}H_{28}BrO_2$: 391.1273; found: 391.1270.

3.3. 4-Benzyloxy-3-[(1S)-1,2,2-trimethylcyclopentyl]phenol **12**

A solution of the above mixture of bromoketones **10** (384 mg, 0.98 mmol), DBU (0.58 mL, 3.88 mmol) and a few crystals of hydroquinone in anhydrous toluene (10 mL) was heated at 105–110°C in a sealed tube for 2 h. The reaction mixture was poured into 5% hydrochloric acid and extracted with ethyl acetate. The combined organic extracts were washed with 5% aqueous $NaHCO_3$ solution and brine, dried over anhydrous sodium sulfate and evaporated under vacuum. Chromatography of the residue, using hexane:ethyl acetate 85:15 as eluent, yielded phenol **12** (259 mg, 84%) as a colourless oil. $[\alpha]_D^{19}$ –48.7 (*c* 1.2, $CHCl_3$); IR (KBr) 3349, 1211, 1023, 803, 741, 697 cm^{-1}; ^1H NMR δ 7.5–7.3 (5H, m, H_5-Ar), 6.87 (1H, d, $J=3.1$ Hz, H-2), 6.77 (1H, d, $J=8.6$ Hz, H-6), 6.60 (1H, dd, $J=8.6$ and 3.1 Hz, H-5), 5.0 (2H, s, OCH_2), 4.41 (1H, s, OH), 2.52 (1H, m, H-5′), 1.39, 1.05, 0.74 (3H each, each s, Me-1′, Me-2′α and Me-2′β); ^{13}C NMR δ 152.5 (C4), 148.7 (C1), 137.8 (C3), 137.7 (C1″), 128.4 and 127.5 (C3″/C5″ and C2″/C6″), 127.6 (C4″), 116.6, 113.9 and 112.5 (C2, C5 and C6), 71.2 (OCH_2), 51.4 (C1′), 44.5 (C2′), 41.5 (C3′), 39.7 (C5′), 20.4 (C4′), 27.3, 25.8 and 23.2 (Me-1′, Me-2′α and Me-2′β); MS (EI) m/z 310 (M^+, 100), 219 (43), 91 (84); HRMS calcd for $C_{21}H_{26}O_2$: 310.1933; found: 310.1935.

3.4. 4-Benzyloxy-3-[(1S)-1,2,2-trimethylcyclopentyl]phenyl trifluoromethanesulfonate **13**

A solution of **12** (386 mg, 1.25 mmol) in CH_2Cl_2 (4 mL) was treated with Et_3N (0.39 mL, 2.8 mmol). After cooling to –70°C trifluoromethanesulfonic anhydride (0.246 mL, 1.46 mmol) was

added dropwise. The reaction mixture was stirred for 1 h from –70 to –30°C, poured into 5% hydrochloric acid and extracted with ethyl acetate. The organic extracts were washed with 5% aqueous $NaHCO_3$ solution and brine, and dried over anhydrous sodium sulfate. Column chromatography of the residue left after evaporation of the solvent, using hexane:ethyl acetate 8:2, afforded the triflate **13** (495 mg, 90%) as a colourless oil. $[\alpha]_D^{19}$ –40 (*c* 2.1, $CHCl_3$); IR (KBr) 2960, 2876, 1489, 1423, 1248, 1212, 1143, 1059, 1012, 866, 807 cm^{-1}; ^1H NMR δ 7.4–7.3 (5H, m, H_5-Ar), 7.24 (1H, d, $J=2.7$ Hz, H-2), 7.04 (1H, dd, $J=2.7$ and 9.0 Hz, H-6), 6.89 (1H, d, $J=9.0$ Hz, H-5), 5.06 (2H, s, OCH_2), 2.46 (1H, m, H-5′), 1.39, 1.03 and 0.71 (3H each, each s, Me-1′, Me-2′α and Me-2′β); ^{13}C NMR δ 157.4 (C4), 142.8 (C1), 136.4 (C3), 138.6 (C1″), 128.6 and 127.6 (C2″/C6″ and C3″/C5″), 128.1 (C4″), 122.1 (C6), 119.1 (C2), 118.8 (q, $J=319$ Hz), 113.1 (C5), 71.0 (OCH_2), 51.6 (C1′), 44.7 (C2′), 41.3 (C3′), 39.7 (C5′), 20.2 (C4′), 26.9, 25.6 and 22.8 (Me-1′, Me-2′α and Me-2′β); MS (EI) *m/z* 442 (M^+, 19), 351 (33), 91 (100); HRMS calcd for $C_{22}H_{25}O_4F_3S$: 442.1426; found: 442.1425.

3.5. 4-Benzyloxy-3-[(1S)-1,2,2-trimethylcyclopentyl]benzaldehyde **14**

A mixture of the triflate **13** (90.6 mg, 0.205 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol) and dppp (16 mg, 0.04 mmol) in DMF (1 mL) was heated at 70°C. Carbon monoxide was bubbled into the solution over 15 min and then Et_3N (72 μL, 0.52 mmol) and trioctylsilane (189 μL, 0.42 mmol) were added dropwise. The reaction mixture was stirred under a CO balloon at the same temperature overnight, diluted with water and extracted with ether. The organic extracts were washed with 5% $NaHCO_3$ aqueous solution and brine and dried over anhydrous sodium sulfate. Column chromatography of the residue left after evaporation of the solvent, using hexane:ether 9:1 as eluent, gave the aldehyde **14** (33 mg, 50%) as a colourless solid. Mp 81–82°C (from pentane); $[\alpha]_D^{20}$ –56 (*c* 1.7, $CHCl_3$); IR (KBr) 2866, 2722, 1687, 1593, 1246, 808, 746, 699 cm^{-1}; ^1H NMR δ 9.91 (1H, s, CHO), 7.95 (1H, d, $J=2.4$ Hz, H-2), 7.72 (1H, dd, $J=8.4$ and 2.4 Hz, H-6), 7.5–7.3 (5H, m, H_5-Ar), 7.05 (1H, d, $J=8.4$ Hz, H-5), 5.19 (2H, s, OCH_2), 2.65 (1H, m, H-5′), 1.43 (3H, s, Me-1′), 1.08 and 0.74 (3H each, each s, Me-2′α and Me-2′β); ^{13}C NMR δ 191.4 (CHO), 163.1 (C4), 137.0 (C3), 136.0 (C1″), 130.8 and 130.1 (C2 and C6), 129.3 (C1), 128.7 and 127.8 (C2″/C6″ and C3″/C5″), 128.2 (C4″), 112.4 (C5), 70.7 (OCH_2), 51.4 (C1′), 44.4 (C2′), 41.7 (C3′), 39.9 (C5′), 27.3, 25.9 and 22.8 (Me-1′, Me-2′α and Me-2′β), 20.3 (C4′); MS (CI) *m/z* 322 (M^+, 39), 231 (91), 215 (30), 149 (72), 91 (100); HRMS calcd for $C_{22}H_{26}O_2$: 322.1933; found: 322.1928.

3.6. 1-Benzyloxy-4-methyl-2-[(1S)-1,2,2-trimethylcyclopentyl]benzene **15**

A mixture of previously dried LiCl (26.0 mg, 0.61 mmol), $PdCl_2(PPh_3)_2$ (28.8 mg, 0.04 mmol) and a few crystals of 2,6-di*tert*-butyl-4-methylphenol under argon was dissolved in degassed DMF (1.4 mL). To this mixture was added Me_4Sn (113 μL, 0.82 mmol) followed by a solution of the triflate **13** (90.5 mg, 0.205 mmol) in the same DMF (1.2 mL) and the mixture was heated at 88°C during 1 h. The resulting black mixture was poured into 10% hydrochloric acid and extracted with ether. The organic extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated. Chromatography on silica gel, using pentane:ether 9:1 as eluent, afforded compound **15** (50.5 mg, 80%) as an oil. IR (film) 2956, 2972, 1604, 1497, 1463, 1223, 802, 736, 696 cm^{-1}; ^1H NMR δ 7.5–7.3 (5H, m, H_5-Ar), 7.15 (1H, d, $J=2.1$ Hz, H-3), 6.93 (1H, dd, $J=8.3$ and 2.1 Hz, H-5), 6.79 (1H, d, $J=8.3$ Hz, H-6), 5.03 (2H, s, OCH_2), 2.55 (1H, m, H-5′), 2.28 (3H, s,

Me-Ar), 1.40 (3H, s, Me-1′), 1.05 and 0.73 (3H each, each s, Me-2′α and Me-2′β); ^{13}C NMR δ 156.0 (C1), 137.7 (C1″), 135.9 (C2), 129.8, 128.4, 127.6, 127.5 and 127.0 (C3, C5, C2″/C6″, C3″/C5″ and C4″), 129.0 (C4), 112.8 (C6), 70.6 (O*C*H$_2$), 51.2 (C1′), 44.4 (C2′), 41.6 (C3′), 39.7 (C5′), 27.3, 25.8 and 23.3 (Me-1′, Me-2′α and Me-2′β), 20.9 (Me-4), 20.4 (C4′). MS (CI) *m*/*z* 308 (M$^+$, 23), 223 (16), 217 (38), 161 (20), 135 (49), 91 (100); HRMS calcd for $C_{22}H_{28}O$: 308.2140; found: 308.2141.

3.7. 4-Methyl-2-[(1S)-1,2,2-trimethylcyclopentyl]phenol (α-herbertenol **8**)

A mixture of 10% palladium on carbon (7 mg) and the benzyl ether **15** (35 mg, 0.11 mmol) in absolute EtOH (2 mL) was stirred vigorously at rt under an atmosphere of hydrogen overnight. Removal of the palladium catalyst by filtration through Celite, followed by evaporation of the filtrate, afforded compound **8** (22.7 mg, 92%) as a colourless oil: $[\alpha]_D^{19}$ –48 (*c* 5.9, $CHCl_3$) (lit.[3b] $[\alpha]_D$ –55); IR (film) 3525, 1665, 1507, 810 cm^{-1}; ^{1}H NMR δ 7.1 (1H, s, H-3), 6.86 (1H, d, *J* = 7.9 Hz, H-5), 6.57 (1H, d, *J* = 7.9 Hz, H-6), 4.63 (1H, s, OH), 2.26 (3H, s, Me-4), 1.41 (3H, s, Me-1′), 1.18 (3H, s, Me-2′β), 0.76 (3H, s, Me-2′α); ^{13}C NMR δ 152.2 (C1), 138.0 (C2), 133.0 (C4), 130.0 (C5), 127.2 (C3), 116.7 (C6), 50.9 (C1′), 44.6 (C2′), 41.2 (C3′), 39.4 (C5′), 26.9 (Me-1′), 25.5 and 23.9 (Me-2′α and Me-2′β), 20.8 (*Me*-Ar), 20.3 (C4′); MS (CI) *m*/*z* 218 (M$^+$, 88), 203 (11), 161 (8), 149 (11), 148 (26), 111 (100); HRMS calcd for $C_{15}H_{22}O$: 218.1671; found: 218.1667.

3.8. Methyl 4-benzyloxy-3-[(1S)-1,2,2-trimethylcyclopentyl]benzoate **16**

A mixture of triflate **13** (213 mg, 0.483 mmol), Et_3N (0.40 mL, 2.90 mmol), $Pd(OAc)_2$ (32 mg, 0.145 mmol), dppp (60 mg, 0.145 mmol) in DMF (3.5 mL) and MeOH (2 mL) was purged for several minutes with carbon monoxide. The reaction mixture was heated with stirring in a 70°C oil bath under a CO balloon for two days. After this time, the reaction mixture was cooled down and then quenched with brine and extracted with ether. Usual work up followed by column chromatography of the residue on silica gel, using hexane:ether 9:1 as eluent, gave unreacted starting material **13** (10 mg, 6%) followed by methyl ester **16** (153 mg, 90%) as a colourless oil. $[\alpha]_D^{25}$ –55 (*c* 1.9, $CHCl_3$); IR (film) 1717, 1600, 1495, 1256, 1121, 771, 745, 699 cm^{-1}; ^{1}H NMR δ (400 MHz) 8.08 (1H, d, *J* = 2.3 Hz, H-2), 7.84 (1H, dd, *J* = 8.8 and 2.3 Hz, H-6), 7.4–7.3 (5H, m, H_5-Ph), 6.91 (1H, d, *J* = 8.8 Hz, H-5), 5.1 (2H, s, OCH_2), 3.9 (3H, s, CO_2CH_3), 2.60 (1H, m, H-5′), 1.38, 1.03 and 0.69 (3H each, each s, Me-1′, Me-2′α and Me-2′β); ^{13}C NMR δ 167.3 (*C*O$_2$), 161.7 (C4), 136.4 and 136.0 (C3 and C1″), 128.6 and 127.8 (C2″/C6″ and C3″/C5″), 130.8, 129.1 and 128.0 (C2, C6 and C4″), 121.8 (C1), 111.9 (C5), 70.5 (O*C*H$_2$), 51.8 (CO_2CH_3), 51.3 (C1′), 44.4 (C2′), 41.6 (C3′), 39.8 (C5′), 27.3, 25.9 and 22.9 (Me-1′, Me-2′α and Me-2′β), 20.3 (C4′); MS (EI) *m*/*z* 352 (M$^+$, 17), 261 (71), 179 (47), 91 (100); HRMS calcd for $C_{23}H_{28}O_3$: 352.2038; found: 352.2044.

3.9. Methyl 4-hydroxy-3-[(1S)-1,2,2-trimethylcyclopentyl]benzoate **17**

A mixture of **16** (112.1 mg, 0.318 mmol) and 10% palladium on carbon (20 mg) in ethanol (4 mL) was shaken at rt under an H_2 atmosphere overnight. Removal of the palladium catalyst by filtration through a pad of silica gel followed by evaporation of the filtrate under reduced pressure afforded the phenol **17** (75 mg, 90%) as a white solid. Mp 193.7–194.7°C (from benzene–ether); $[\alpha]_D^{20}$ –49 (*c* 1.9, $CHCl_3$); IR (KBr) 3373, 1694, 1601, 1512, 1288, 1262, 827, 769 cm^{-1};

^{1}H NMR δ 8.06 (1H, d, J=2.4 Hz, H-2), 7.77 (1H, dd, J=8.1 and 2.4 Hz, H-6), 6.70 (1H, d, J=8.1 Hz, H-5), 5.4 (1H, s, OH), 3.9 (3H, s, CO_2CH_3), 2.64 (1H, m, H-5′), 1.41, 1.20 and 0.74 (3H each, each s, Me-1′, Me-2′α and Me-2′β); ^{13}C NMR δ 167.0 (CO_2), 158.8 (C4), 133.3 (C3), 131.6 and 129.0 (C6 and C2), 122.0 (C1), 116.7 (C5), 51.8 CO_2Me), 51.0 (C1′), 44.7 (C2′), 41.3 (C3′), 39.5 (C5′), 26.9, 25.5 and 22.6 (Me-1′, Me-2′α and Me-2′β), 20.2 (C4′); MS (EI) m/z 262 (M^+, 38), 247 (5), 192 (100), 179 (50), 161 (3); HRMS calcd for $C_{16}H_{22}O_3$: 262.1569; found: 262.1569.

3.10. 4-Hydroxymethyl-2-[(1S)-1,2,2-trimethylcyclopentyl]phenol **18**

A solution of methyl ester **17** (72.8 mg, 0.278 mmol) in THF (3 mL) was treated with DIBALH (1.39 mL of a 1 M solution in cyclohexane, 1.39 mmol) at –78°C. The reaction mixture was stirred for 2 h at the same temperature, treated with MeOH (1 mL) and then poured into 5% hydrochloric acid. Extraction with CH_2Cl_2 and work up as usual gave a residue which was purified by chromatography using hexane:ethyl acetate 7:3 as eluent to afford alcohol **18** (63.7 mg, 98%) as an amorphous solid that could not be induced to crystallise. $[\alpha]_D^{24}$ –37 (c 1.3, $CHCl_3$); IR (KBr) 3316, 1258, 891, 820 cm^{-1}; ^{1}H NMR δ 7.29 (1H, d, J=2.1 Hz, H-3), 7.06 (1H, dd, J=8.1 and 2.1 Hz, H-5), 6.66 (1H, d, J=8.1 Hz, H-6), 5.1 (1H, br s, OH), 4.6 (2H, s, OCH_2), 2.60 (1H, m, H-5′), 1.42 (3H, s, Me-1′), 1.19 and 0.75 (3H each, each s, Me-2′α and Me-2′β); ^{13}C NMR δ 154.4 (C1), 133.6 (C2), 132.2 (C4), 128.9 and 126.1 (C3 and C5), 116.9 (C6), 65.6 (CH_2OH), 51.1 (C1′), 44.7 (C2′), 41.3 (C3′), 39.4 (C5′), 27.0, 25.6 and 22.8 (Me-1′, Me-2′α and Me-2′β), 20.3 (C4′); MS (EI) m/z 234 (M^+, 55), 164 (100), 151 (76), 147 (69), 91 (35); HRMS calcd for $C_{15}H_{22}O_2$: 234.1619; found: 234.1614.

3.11. 4-Hydroxy-3-[(1S)-1,2,2-trimethylcyclopentyl]benzaldehyde (α-formylherbertenol **1**)

To a solution of **18** (50 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (3.2 mL) were added silica gel (70 mg, previously activated at 120°C during 1 h), and 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate[9] (70 mg, 0.22 mmol). The bright yellow slurry was stirred at room temperature for 25 min. The slurry was then filtered through a pad of silica gel eluting with CH_2Cl_2. The filtrates and washings were evaporated under vacuum to give nearly pure **1** (39.5 mg, 80%) as a white solid: mp 133–134°C (from benzene–ether) (lit.[3b] mp 134–135°C); $[\alpha]_D^{25}$ –72 (c 1.2, $CHCl_3$) (lit.[3b] $[\alpha]_D$ –65.8); IR (KBr) 3251, 1667, 1582, 1508, 1423, 1377, 1270, 825 cm^{-1}; ^{1}H NMR δ 9.83 (1H, s, CHO), 7.88 (1H, d, J=2 Hz, H-2), 7.63 (1H, dd, J=8.1 and 2 Hz, H-6), 6.83 (1H, d, J=8.1 Hz, H-5), 6.1 (1H, br s, OH), 2.65 (1H, m, H-5′), 1.43 (3H, s, Me-1′), 1.21 and 0.75 (3H each, each s, Me-2′α and Me-2′β); ^{13}C NMR δ 191.6 (CHO), 160.4 (C4), 134.2 (C3), 132.3 (C2), 129.7 (C6), 129.1 (C1), 117.4 (C5), 51.1 (C1′), 44.6 (C2′), 41.3 (C3′), 39.5 (C5′), 27.0, 25.5 and 22.5 (Me-1′, Me-2′α and Me-2′β), 20.2 (C4′); MS (EI) m/z 232 (M^+, 49), 217 (8), 215 (6), 203 (3), 189 (6), 174 (14), 162 (100); HRMS calcd for $C_{15}H_{20}O_2$: 232.1463; found: 232.1465.

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References

1. Asakawa, Y. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, Ch., Eds.; Springer: Wien, 1995; Vol. 65, p. 1.
2. Connolly, J. D.; Hill, R. A. In *Dictionary of Terpenoids*, 1st ed.; Chapman and Hall: London, 1991; Vol. 1, p. 299. Also see: Fraga, B. M. *Nat. Prod. Rep*. **1992**, *9*, 217; *ibid* **1993**, *10*, 397; *ibid* **1994**, *11*, 533; *ibid* **1995**, *12*, 303; *ibid* **1996**, *13*, 307; *ibid* **1997**, *14*, 145; *ibid* **1998**, *15*, 73.
3. (a) Matsuo, A.; Yuki, S.; Nakayama, M.; Hayashi, S. *Chem. Lett*. **1982**, 463. (b) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701.
4. Buchanan, M. S.; Connolly, J. D.; Rycroft, D. S. *Phytochemistry* **1996**, *43*, 1245.
5. Fukuyama, Y.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737.
6. For recent published syntheses of herbertane-type sesquiterpenoids, see: (a) Tse-Lo, H.; Chang, M. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2479. (b) Pal, A.; Gupta, P. D.; Roy, A.; Mukherjee, D. *Tetrahedron Lett*. **1999**, *40*, 4733. (c) Bringmann, G.; Pabst, T.; Rycroft, D. S.; Connolly, J. D. *Tetrahedron Lett*. **1999**, *40*, 483. (d) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc*. **1999**, *121*, 2762.
7. Abad, A.; Agulló, C.; Cuñat, A. C.; Perni, R. H. *J. Org. Chem*. **1999**, *64*, 1741 and references cited therein.
8. (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *The Stille Reaction*; Paquete, L. A., Ed. Organic reaction. John Wiley: New York, 1997; Vol. 50. (b) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235. (c) Titter, K. *Synthesis* **1993**, 735.
9. Bobbitt, J. M. *J. Org. Chem*. **1998**, *63*, 9367.
10. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988; p. 105.