Pergamon

Tetrahedron Letters 41 (2000) 7563–7566

TETRAHEDRON LETTERS

New total synthesis of (±)-herbertene, (±)-β-herbertenol and (±)-herbertenediol

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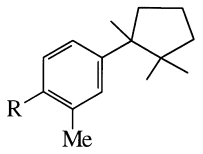
Received 5 June 2000; accepted 28 July 2000

Abstract

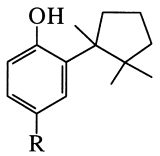
The total syntheses of the herbertane sesquiterpenes (±)-herbertene (**1**), (±)-β-herbertenol (**2**) and (±)-herbertenediol (**5**) have been successfully accomplished involving copper-catalysed conjugate addition of Grignard reagents to unsaturated compounds and α,α-dimethylation of primary esters as key reactions.

Keywords: terpenes; phenols; Grignard reagents; alkylation; cyclopentanones.

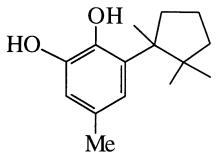
From the liverwort *Herberta adunca*, Matsuo and co-workers[1] isolated several biologically active sesquiterpene phenols, e.g. **2**–**5**, together with the parent hydrocarbon (−)-herbertene (**1**). The sesquiterpene phenols **2**–**5** possess significant antifungal properties and recently, Fukuyama et al. have found[2] that herbertenediol (**5**) exhibits potent *anti*-lipid peroxidation activity. The total syntheses of the herbertane sesquiterpenes present interesting problems in view of the difficulty associated with the construction of the vicinal quaternary centres on the five-membered ring. In connection with our studies on conjugate addition of Grignard reagents to unsaturated cyano-esters and unsaturated dinitriles, we have accomplished the total syntheses of the sesquiterpenes (±)-herbertene (**1**),[3] (±)-β-herbertenol (**2**)[4] and (±)-herbertenediol (**5**)[2] involving copper-catalysed conjugate addition of appropriate Grignard reagents to the unsaturated compounds **7a**, **7b** and **15**, respectively, as key steps (Fig. 1).



Herbertene (**1**), R=H
β-Herbertenol (**2**), R=OH



α-Herbertenol (**3**), R=Me
α-Formylherbertenol (**4**), R=CHO



Herbertenediol (**5**)

Figure 1.

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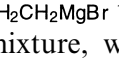
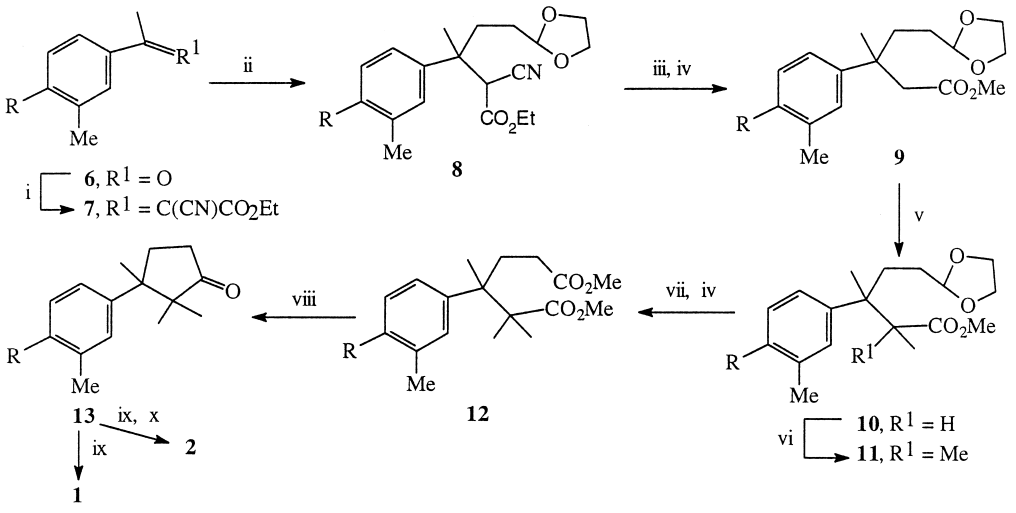
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01298-3

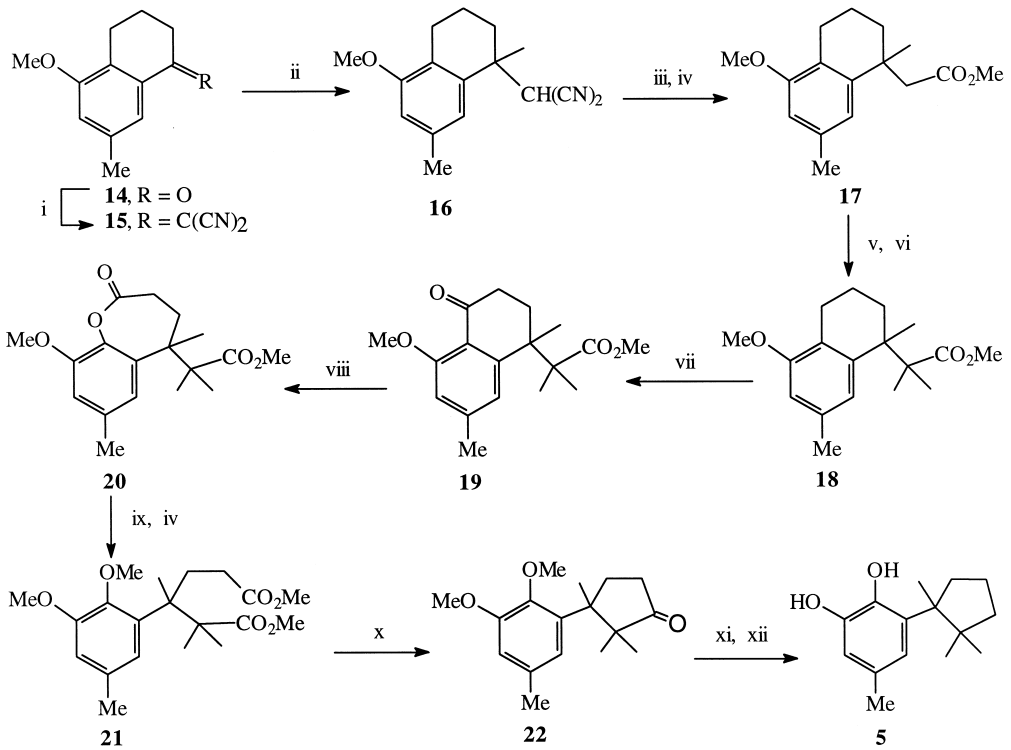
The acetophenones **6a** and **6b** were condensed with ethyl cyanoacetate to provide the unsaturated cyano-esters **7a** and **7b** in 79 and 74% yields, respectively. Conjugate addition of 
to **7a** in the presence of $CuBr{\cdot}S(CH_3)_2$[5] afforded **8a**[6] (62%) as a diastereoisomeric mixture, which on hydrolysis, decarboxylation and esterification furnished the methyl ester **9a** in 75% yield (Scheme 1). The cyano-ester **7b** was similarly converted into the methyl ester **9b** in 45% overall yield. Alkylation of **9a** with MeI at −78°C using LDA (1 equiv.) as the base provided the monomethyl ester **10a** as a diastereoisomeric mixture in 94% yield. The ester **10a** was alkylated with MeI at 0°C in the presence of LDA (1.7 equiv.) and HMPA (2 equiv.) to give the dimethyl ester **11a**[7] (89%). α,α-Dimethylation of the ester **9b** was similarly carried out to provide **11b**[7] (84%). The conversion of **9a** into **11a** could also be accomplished in 82% yield in a one pot process employing a sequential methylation without isolating the monomethyl ester **10a**. Deacetalisation of **11a** followed by oxidation of the resulting aldehyde with Jones reagent and esterification with CH_2N_2 furnished the diester **12a** in 75% overall yield. The ester **11b** was similarly converted into the diester **12b** (75%). Dieckmann cyclisation of the diesters **12a** and **12b** followed by decarbomethoxylation of the resulting crude β-keto-esters afforded the cyclopentanones **13a**[7] and **13b**[7] in 74 and 72% yields, respectively. Huang–Minlon reduction[8] of **13a** furnished (±)-herbertene (**1**)[7] (81%). Huang–Minlon reduction of **13b** followed by demethylation with BBr_3 afforded (±)-β-herbertenol (**2**)[7] (72%), mp 83–84°C. The spectral data of **1** and **2** agreed very well with those reported in the literature.



Scheme 1. **6a–13a**: R = H; **6b–13b**: R = OMe. Reagents and conditions: i, $CH_2(CN)CO_2Et$, NH_4OAc, AcOH, C_6H_6, reflux; ii,
, $CuBr{\cdot}Me_2S$, THF, Et_2O, −5 to 25°C; iii, KOH, $HOCH_2CH_2OH$, H_2O, reflux; AcOH, 0°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 equiv.), THF, 0°C; MeI, 0°C; vii, AcOH–H_2O (4:1), 25 to 60°C; Jones reagent, Me_2CO, 0 to 20°C, CH_2N_2; viii, *t*-BuOK, C_6H_6, reflux, then H_3O^+; DMSO, NaCl, 155°C; ix, N_2H_4, $N_2H_4{\cdot}2HCl$, $(HOCH_2CH_2)_2O$, 125°C; KOH, 210°C; x, BBr_3, CH_2Cl_2, 0 to 25°C.

The synthesis of herbertenediol (**5**) is outlined in Scheme 2. The tetralone **14**[9] was condensed with malononitrile to provide the unsaturated dinitrile **15**, mp 122–123°C in near quantitative yield. Conjugate addition of MeMgI to **15** in the presence of CuI afforded **16** (88%), mp 136–137°C, which on hydrolysis, decarboxylation, and esterification furnished the methyl ester **17** in 80% yield. α,α-Dimethylation of **17** as described for **11a** afforded the ester **18** (85%).

Oxidation of **18** with CrO_3 gave the keto-ester **19**, mp 99–100°C, in 74% yield. Baeyer–Villiger reaction of **19** provided the lactone **20** (82%), mp 105–106°C. Alkaline hydrolysis of **20** followed by treatment with Me_2SO_4 and esterification with CH_2N_2 gave the diester **21** (82%). Dieckmann cyclisation of **21** and subsequent decarbomethoxylation of the resulting β-keto-ester furnished the ketone **22**[7] (73%), mp 70–71°C. Huang–Minlon reduction[8] of **22** followed by demethylation with BBr_3 afforded (±)-herbertenediol (**5**)[7] (70%) whose spectral data were identical to those of the natural product.



Scheme 2. Reagents and conditions: i, $CH_2(CN)_2$, NH_4OAc, AcOH, C_6H_6, reflux; ii, MeMgI, CuI, Et_2O, 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 equiv.), THF, 0°C; MeI, 0°C; vii, CrO_3, AcOH–H_2O (4:1), 10 to 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, H_3O^+; DMSO, NaCl, 155°C; xi, N_2H_4, $N_2H_4{\cdot}2HCl$, $(HOCH_2CH_2)_2O$, 125°C; KOH, 210°C; xii, BBr_3, CH_2Cl_2, −78 to 0°C.

Acknowledgements

We are grateful to the CSIR, New Delhi, for financial support (Grant No. 01(1534)/98/EMR-II). One of us (P. D. G.) thanks the CSIR for a fellowship.

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6. Satisfactory spectroscopic and microanalytical data were obtained for all new compounds.
7. Selected spectral data for: **11a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3H), 1.14 (s, 3H), 1.38 (s, 3H), 1.22–1.75 (m, 3H), 2.33 (s, 3H), 2.32–2.45 (m, 1H), 3.50 (s, 3H), 3.82–3.97 (m, 4H), 4.84 (t, 1H, J=4.6 Hz), 6.98–7.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.24, 21.71, 21.77, 22.11, 28.80, 29.26, 45.43, 49.79, 51.16, 64.70, 64.84, 104.95, 125.43, 126.66, 127.13, 129.15, 136.57, 142.50, 177.18. **11b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 3H), 1.12 (s, 3H), 1.36 (s, 3H), 1.24–1.73 (m, 3H), 2.19 (s, 3H), 2.26–2.39 (m, 1H), 3.51 (s, 3H), 3.80 (s, 3H), 3.80–3.94 (m, 4H), 4.84 (t, 1H, J=4.7 Hz), 6.72 (d, 1H, J=8.4 Hz), 7.00 (d, 1H, J=2.5 Hz), 7.01 (dd, 1H, J=8.4, 2.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.44, 21.29, 21.77, 22.11, 28.84, 29.24, 44.86, 49.84, 51.13, 55.09, 64.66, 64.81, 104.96, 108.63, 124.83, 126.64, 130.75, 134.00, 155.80, 177.29. **13a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.62 (s, 3H), 1.19 (s, 3H), 1.26 (s, 3H), 1.88–1.96 (m, 1H), 2.37 (s, 3H), 2.35–2.74 (m, 3H), 7.05–7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.45, 21.70, 22.07, 25.31, 29.58, 33.69, 48.48, 53.14, 123.52, 126.95, 127.18, 128.01, 137.54, 144.91, 222.44. **13b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.62 (s, 3H), 1.16 (s, 3H), 1.24 (s, 3H), 1.86–1.92 (m, 1H), 2.24 (s, 3H), 2.38–2.70 (m, 3H), 3.83 (s, 3H), 6.80 (d, 1H, J=9 Hz), 7.15–7.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.50, 18.32, 22.08, 25.32, 29.72, 33.70, 47.88, 53.18, 55.16, 109.40, 124.63, 125.90, 128.84, 136.44, 156.06, 222.67. **1**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.56 (s, 3H), 1.07 (s, 3H), 1.26 (s, 3H), 1.51–1.83 (m, 5H), 2.34 (s, 3H), 2.45–2.54 (m, 1H), 6.98–7.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.70, 21.78, 24.29, 24.41, 26.48, 36.76, 39.75, 44.19, 50.45, 124.09, 126.05, 127.32, 127.81, 136.71, 147.53. **2**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.56 (s, 3H), 1.04 (s, 3H), 1.23 (s, 3H), 1.52–1.80 (m, 5H), 2.24 (s, 3H), 2.40–2.48 (m, 1H), 4.74 (bs, 1H), 6.68 (d, 1H, J=8.4 Hz), 7.05 (dd, 1H, J=8.4, 2.3 Hz), 7.09 (d, 1H, J=2.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.13, 19.69, 24.25, 24.50, 26.49, 36.92, 39.70, 44.17, 49.91, 113.92, 122.29, 125.61, 129.69, 139.81, 151.44. **19**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (s, 3H), 1.18 (s, 3H), 1.47 (s, 3H), 1.85–1.97 (m, 1H), 2.17–2.26 (m, 1H), 2.39 (s, 3H), 2.53–2.63 (m, 1H), 2.70–2.82 (m, 1H), 3.60 (s, 3H), 3.88 (s, 3H), 6.71 (s, 1H), 6.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.40, 23.10, 23.77, 26.05, 32.82, 37.16, 42.16, 49.42, 51.59, 55.96, 111.08, 120.97, 121.43, 143.70, 149.47, 159.06, 177.04, 197.72. **22**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (s, 3H), 1.27 (s, 3H), 1.34 (s, 3H), 2.07–2.16 (m, 1H), 2.32 (s, 3H), 2.39–2.46 (m, 2H), 2.66–2.78 (m, 1H), 3.81 (s, 3H), 3.85 (s, 3H), 6.67 (d, 1H, J=1.5 Hz), 6.76 (d, 1H, J=1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.10, 21.66, 22.20, 24.42, 31.70, 34.11, 49.60, 53.60, 55.67, 60.26, 111.78, 120.73, 132.34, 138.15, 146.33, 152.99, 223.18. **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (s, 3H), 1.18 (s, 3H), 1.41 (s, 3H), 1.49–1.79 (m, 5H), 2.22 (s, 3H), 2.55–2.66 (m, 1H), 5.11 (bs, 1H), 5.37 (s, 1H), 6.56 (s, 1H), 6.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.26, 21.14, 22.80, 25.40, 26.83, 39.20, 40.92, 44.82, 51.09, 113.39, 121.87, 128.25, 133.45, 140.94, 143.32.
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