Formal Total Synthesis of (±)-Herbertene-1,13-diol and (±)-α-Herbertenol via Ireland Ester Claisen Rearrangement and RCM Reaction Sequence

A. Srikrishna,* B. Vasantha Lakshmi

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India
E-mail: ask@orgchem.iisc.ernet.in

Received 25 January 2005

Abstract: A combination of Ireland ester Claisen rearrangement and ring-closing metathesis (RCM) reactions has been employed for efficient formal total syntheses of herbertene-1,13-diol and α-herbertenol, sesquiterpenes containing two vicinal quaternary carbon atoms on a cyclopentane ring.

Key words: (±)-herbertene-1,13-diol, (±)-α-herbertenol, Ireland ester Claisen rearrangement

Herbertanes are a small group of sesquiterpenes, which are considered as chemical markers for the liverworts belonging to the genus *Herbertus*.[1] Isolation of the first members of the herbertane group **1a**–**e** and **2a** from *Herberta adunca* was reported earlier by Matsuo and coworkers.[2] Recently, Asakawa and coworkers reported a number of herbertanes, e.g. **2b**–**5**, carrying oxygen functionality not only in the aromatic portion of the molecule but more unusually on the methyl groups (C-13 to C-15) attached to cyclopentane ring.[1] The phenolic herbertanes, e.g. **1b**–**d**, **2**–**5**, have been shown to possess interesting biological properties such as growth inhibiting and antilipid peroxidation activities (Figure 1).[2,3]

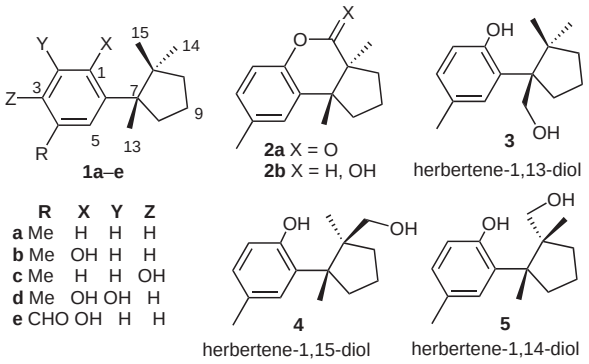


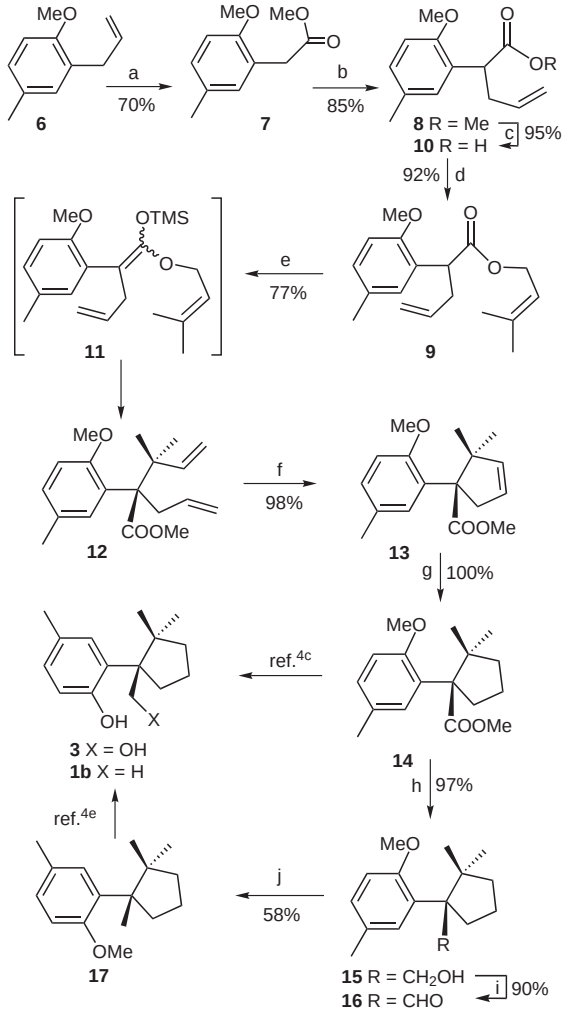
Figure 1

The sesquiterpenes cuparanes and herbertanes are interesting synthetic targets owing to the presence of a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane moiety, and the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring. The significant biological properties of the phenolic herbertanes made them important synthetic targets of current interest.[4] Herein, we wish to describe formal total synthesis of (±)-herbertene-1,13-diol **3** and (±)-α-herbertenol **1b** employing a combination of Ireland ester Claisen rearrangement[5] and ring-closing metathesis reactions.[6]

The synthetic sequence starting from the anisole[7] **6** is depicted in Scheme 1. An ozonolysis followed by Criegee fragmentation[8] was employed for the oxidative degradation of the allyl group in **6**. Thus, ozonolysis of the allylanisole **6** in methanol-methylene chloride followed by treatment of the resultant methoxyhydroperoxide with triethylamine, acetic anhydride and a catalytic amount of 4-dimethylaminopyridine (DMAP) in refluxing benzene furnished the arylacetate **7** in 70% yield. Generation of the lithium enolate of the ester **7** with lithium diisopropylamide (LDA) and treatment with allyl bromide furnished the pentenoate **8** in 85% yield. A dicyclohexylcarbodiimide (DCC) mediated coupling reaction was contemplated for the conversion of the ester **8** into the dimethylallyl ester **9**. Thus, hydrolysis of the ester **8** with aqueous sodium hydroxide in methanol furnished the acid **10**. Coupling of the acid **10** with dimethylallyl alcohol employing DCC and DMAP generated the key intermediate of the sequence the ester **9**, in 92% yield.[9] The Ireland ester Claisen rearrangement of the ester **9** was then addressed. After exploring a few reaction conditions[10] it was found that generation of the TMS enol ether **11** of the ester **9** with LDA, trimethylsilyl chloride and triethylamine in THF at –70 °C followed by refluxing the reaction mixture for 2 hours resulted in the Ireland ester Claisen rearrangement. Hydrolysis of the reaction mixture with dilute hydrochloric acid followed by esterification with ethereal diazomethane furnished the ester **12** in 77% yield, whose structure was deduced from its spectral data.[9] Treatment of the dieneester **12** with 5 mol% of Grubbs' first-generation catalyst [$Cl_2Ru(PCy_3)_2$=CHPh] in methylene chloride for 5 hours at room temperature cleanly furnished the cyclopentene carboxylate **13**, mp 62–65 °C, in near quantitative yield.[9] Hydrogenation of the eneester **13** in ethanol using 10% palladium on charcoal as the catalyst at one atmospheric pressure of hydrogen quantitatively furnished the ester **14**, which exhibited spectral data identical to that of an authentic sample reported earlier.[4c] On the other hand, reduction of the ester **14** with lithium aluminum hydride (LAH) furnished herbertene-1,13-diol monomethyl ether **15** in 97% yield. Oxidation of the primary alcohol in **15** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride at room temperature furnished the

SYNLETT 2005, No. 7, pp 1173–1175
Advanced online publication: 14.04.2005
DOI: 10.1055/s-2005-865223; Art ID: D02005ST

aldehyde **16**. Finally, Wolff–Kishner reduction of the aldehyde **16** with hydrazine hydrate, diethylene glycol (digol) and potassium hydroxide at 190 °C furnished the methyl ether **17** of α-herbertenol **1b**, which exhibited spectral data identical to that of an authentic sample.[4e] Since the ester **14** and the ether **17** have already been converted into herbertene-1,13-diol **3** and α-herbertenol **1b**, respectively, the present sequence constitutes formal total synthesis of these herbertenoids.



Scheme 1 *Reagents and conditions*: (a) O_3/O_2, MeOH–CH_2Cl_2 (1:9), $NaHCO_3$ (catalytic), –70 °C; Ac_2O, Et_3N, C_6H_6, DMAP (catalytic), reflux, 7 h; (b) LDA, THF; CH_2=$CHCH_2Br$, –70 °C to r.t., 7 h; (c) 5% NaOH, MeOH–H_2O (1:1), reflux, 7 h; (d) DCC, DMAP (catalytic), Me_2C=$CHCH_2OH$, CH_2Cl_2, r.t., 4 h; (e) i. LDA, THF; TMSCl, Et_3N, –70 °C, 30 min, r.t, 5 h, reflux, 2 h; ii. dil. HCl, 40 min; iii. CH_2N_2, Et_2O, 0 °C, 30 min; (f) $Cl_2Ru(PCy_3)_2$=CHPh (5 mol%), CH_2Cl_2, 5 h; (g) 10% Pd/C, H_2, EtOH, 1 atm., 5 h; (h) LAH, Et_2O, 0 °C to r.t., 2 h; (i) PCC, silica gel, CH_2Cl_2, r.t., 30 min; (j) $NH_2NH_2 \cdot H_2O$, KOH, digol, 190 °C, 10 h.

In conclusion, starting from the allylmethylanisole **6**, we have developed efficient synthesis of (±)-herbetene-1,13-diol **3** (the ester **14** obtained in 7 steps in an overall yield of 39.8%) and α-herbertenol **1b** (α-herbertenyl methyl ether **17** obtained in 10 steps in an overall yield of 19.8%). Ireland ester Claisen rearrangement was strategically exploited for the generation of the two vicinal quaternary carbon atoms, and an efficient RCM reaction for the generation of the cyclopentene ring. Extension of this methodology for the enantioselective synthesis of these sesquiterpenoids is currently under progress.

Acknowledgment

We thank Prof. Asakawa for providing the copies of the spectra of natural herbertene-1,13-diol and α-herbertenols, and the Council of Scientific and Industrial Research, New Delhi for the financial support and a fellowship to BVL.

References

(1) Irita, H.; Hashimoto, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **2000**, *55*, 247.

(2) (a) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Chem. Commun.* **1981**, 864. (b) Matsuo, A.; Yuki, S.; Nakayama, M.; Hayashi, S. *Chem. Lett.* **1982**, 463. (c) Asakawa, Y.; Matsuda, R.; Schofield, W. B.; Gradstein, S. R. *Phytochemistry* **1982**, *21*, 2471. (d) Matsuo, A.; Yuki, S.; Nakayama, M. *Chem. Lett.* **1983**, 1041. (e) Matsuo, A.; Nakayama, N.; Nakayama, M. *Phytochemistry* **1985**, *24*, 777. (f) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701.

(3) (a) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Tetrahedron Lett.* **1996**, *37*, 1261. (b) Fukuyama, Y.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737.

(4) (a) Boxall, R. J.; Ferris, L.; Grainger, R. S. *Synlett* **2004**, 2379. (b) Ng, D.; Yang, Z.; Garcia-Garibay, M. A. *Org. Lett.* **2004**, *6*, 645. (c) Srikrishna, A.; Satyanarayana, G. *Tetrahedron Lett.* **2003**, *44*, 1027. (d) Srikrishna, A.; Rao, M. S. *Eur. J. Org. Chem.* **2004**, 499. (e) Srikrishna, A.; Babu, N. C.; Rao, M. S. *Tetrahedron* **2004**, *60*, 2125; and references cited therein.

(5) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650. (c) Gilbert, J. C.; Yin, J.; Fakhreddine, F. H.; Karpinski, M. L. *Tetrahedron* **2004**, *60*, 51.

(6) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3013. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(7) Achari, B.; Bandyopadhyay, S.; Basu, K.; Pakrashi, S. C. *Tetrahedron* **1985**, *41*, 107.

(8) (a) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363. (b) Criegee, R. *Ber. Bunsen-Ges. Phys. Chem.* **1944**, *77*, 722.

(9) Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H NMR and ^{13}C NMR and MS) consistent with their structures.
Selected Spectral Data.
3-Methylbut-2-enyl 2-(2-methoxy-5-methylphenyl)pent-4-enoate (**9**): IR (neat): ν_{max} = 1733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 6.99 (1 H, s), 6.95 (1 H, d, *J* = 8.2 Hz), 6.69 (1 H, d, *J* = 8.2 Hz), 5.71 (1 H, ddt, *J* = 17.1, 10.2, 6.7 Hz), 5.26 (1 H, br t, *J* = 7.2 Hz), 5.01 (1 H, d, *J* = 17.1 Hz), 4.93 (1 H, d, *J* = 10.2 Hz), 4.55 (1 H, dd, *J* = 12.4, 6.9 Hz), 4.49 (1 H, dd, *J* = 12.4, 7.2 Hz), 3.97 (1 H, t, *J* = 8.1 Hz), 3.77 (3 H, s), 2.71 (1 H, dt, *J* = 14.1, 8.1 Hz), 2.40 (1 H, dt, *J* = 14.1, 6.7 Hz), 2.27 (3 H, s), 1.72 (3 H, s), 1.66 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 173.4 (C), 154.6 (C), 137.9 (C), 136.1 (CH), 129.5 (C), 129.1 (CH), 128.3 (CH), 127.3 (C), 119.3 (CH), 116.4 (CH_2), 110.6 (CH), 61.3 (CH_2),

55.5 (CH_3), 44.1 (CH), 36.8 (CH_2), 25.8 (CH_3), 20.7 (CH_3), 18.1 (CH_3). MS: *m/z* (%) = 288 (17) [M^+], 220 (36), 179 (28), 175 (100), 160 (28), 145 (16), 128 (15), 121 (23), 105 (28). HRMS: *m/z* calcd for $C_{18}H_{24}O_3Na$ [M + Na]: 311.1623; found: 311.1630.

Methyl 2-allyl-3,3-dimethyl-2-(2-methoxy-5-methylphenyl)pent-4-enoate (**12**): IR (neat): ν_{max} = 1738, 1198, 911 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 7.00 (1 H, dd, *J* = 8.4, 1.5 Hz), 6.92 (1 H, d, *J* = 1.5 Hz), 6.73 (1 H, d, *J* = 8.4 Hz), 6.25 (1 H, dd, *J* = 17.4, 10.8 Hz), 5.84 (1 H, ddt, *J* = 17.4, 10.2, 7.2 Hz), 5.03–4.85 (4 H, m), 3.70 (3 H, s), 3.55 (3 H, s), 2.88 (1 H, dd, *J* = 15.0, 6.6 Hz), 2.81 (1 H, dd, *J* = 15.0, 7.2 Hz), 2.31 (3 H, s), 1.22 (3 H, s), 1.06 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 174.1 (C, C=O), 155.3 (C), 146.7 (CH), 136.7 (CH), 131.4 (CH), 129.3 (C), 128.2 (C), 128.1 (CH), 116.2 (CH_2), 111.4 (CH_2), 111.2 (CH), 56.1 (C), 55.1 (CH_3), 50.5 (CH_3), 43.8 (C), 39.9 (CH_2), 24.7 (CH_3), 24.1 (CH_3), 21.0 (CH_3). MS: *m/z* (%) = 302 (2) [M^+], 233 (43), 201 (98), 173 (100), 158 (47), 145 (26), 128 (20), 115 (19). HRMS: *m/z* calcd for $C_{19}H_{26}O_3Na$ [M + Na]: 325.1780; found: 325.1783.

Methyl 2,2-dimethyl-1-(2-methoxy-5-methylphenyl)cyclopent-3-enecarboxylate (**13**): mp 62–65 °C. IR (neat): ν_{max} = 1741, 1252, 1235 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 7.24 (1 H, s), 6.96 (1 H, d, *J* = 8.4 Hz), 6.70 (1 H, d, *J* = 8.4 Hz), 5.61 (1 H, d, *J* = 6.0 Hz), 5.55 (1 H, d, *J* = 6.0 Hz), 3.70 (3 H, s), 3.58 (3 H, s), 3.04 (1 H, d, *J* = 16.5 Hz), 2.80 (1 H, d, *J* = 16.5 Hz), 2.27 (3 H, s), 1.23 (3 H, s), 0.93 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 175.2 (C), 155.0 (C), 142.1 (CH), 130.7 (C), 129.6 (CH), 128.6 (C), 128.0 (CH), 124.6 (CH), 111.1 (CH), 61.1 (C), 55.3 (CH_3), 51.2 (CH_3), 50.2 (C), 42.3 (CH_2), 25.8 (CH_3), 24.2 (CH_3), 21.1 (CH_3). MS: (%) = 274 (47) [M^+], 243 (16), 242 (100), 227 (27), 215 (62), 199 (32), 173 (11), 159 (20), 145 (19), 135 (21). HRMS: *m/z* calcd for $C_{17}H_{22}O_3Na$ [M + Na]: 297.1467; found: 297.1462.

(10) Generation of the lithium enolate of the ester **6** with LDA and warming up the reaction (or refluxing), or quenching with *t*-butyldimethylsilyl chloride and heating the resultant TBDMS enol ether, however, failed to generate the Ireland ester Claisen rearrangement product.[4d]