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An RCM based approach to (±)-herbertene-1, 14-diol and (±)-tochuinyl acetates†

A Srikrishna* & M Sreenivasa Rao

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

E-mail: ask@orgchem.iisc.ernet.in

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A sequence comprising of Johnson's ortho ester Claisen rearrangement, alkylation and RCM reactions has been developed for the synthesis of cyclopentenes containing vicinal quaternary carbon atoms. The versatility of the sequence has been demonstrated by the efficient total synthesis of sesquiterpenes tochuinyl acetates and herbertene-1,14-diol.

Keywords: Terpene synthesis, vicinal quaternary carbons, Claisen rearrangement, ring-closing metathesis, herbertanes, cuparanes

The herbertane group[1] is a small group of aromatic sesquiterpenes, isomeric to cuparanes, containing a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework incorporating two vicinal quaternary carbon atoms on a cyclopentane ring. Even though cuparene **1**, isomeric to herbertane, was known[2] since 1958, herbertane family of sesquiterpenes was reported only in nineteen eighties. Isolation of the first member of the family, herbertene **2** was reported in 1981 by Matsuo and co-workers from the ethyl acetate extract of the liverwort *Herberta adunca* (Dicks) S. Gray belonging to the family herbertaceae[3]. Subsequently few other phenolic herbertanes **3-9** were isolated from a variety of *Herbertus* sources[4]. In 2000, Asawaka and co-workers reported[5] the isolation of seven herbertenes herberteneacetal **10**, herbertene-1,14-diol **11**, herbertene-1,15-diol **12**, herbertene-1,13-diol **13**, herbertenones A and B **14** and **15** and 12-methoxyherbertenediol **16** from the ether and ethyl acetate extracts of the Japanese liverwort *Herbertus sakuraii*. Recently, Becker *et al.* reported[6] the isolation of two new herbertanes from a non-herbertus source, γ-herbertenol **17** and herbertene-1,12-diol **18** along with α-herbertenol **3** from the liverwort *Tylimanthus renifolius* (**Chart 1**).

The herbertane sesquiterpenes, mainly the phenolic herbertanes[1,5], have been shown to possess interesting biological properties such as growth inhibiting activity. Some of the phenolic herbertenes were found to be strong inhibitors of the plant pathogenic fungi, *Botrytis cinerea*, *Rhizoctonia solani* and *Pythium debaryanum*[4]. Presence of a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework, the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring and the significant biological properties associated with the phenolic herbertanes made herbertenoids interesting and challenging synthetic targets. Prior to 1999, there were only three reports cited in the literature on the synthesis of phenolic herbertanes. However, during the last seven years, nearly forty reports have appeared in the literature on the synthesis of phenolic herbertanes making it a topic of contemporary interest[7]. A combination of Claisen rearrangement and ring-closing metathesis (RCM) reactions based methodology has now been developed for the synthesis of phenolic herbertenes. Herein is described the details[7a] of the total synthesis of herbertene-1,14-diol **12** and 11-*epi*-herbertenolide **9a**.

It was conceived that a γ,γ-disubstituted allyl alcohol **19** could be conveniently transformed into a 2,2-disubstituted cyclopent-3-enecarboxylate **20** by a three step sequence (**Scheme I**), *viz* ortho ester Claisen rearrangement, allylation of the resultant γ,δ-unsaturated ester **21** followed by RCM reaction of the 1,6-heptadiene **22**.

To test the feasibility of the hypothesis (**Scheme II**), the allyl alcohol **23** was chosen as a starting material, which was prepared from cyclohexanone in two steps[8], Horner-Wadsworth-Emmons

†Respectfully dedicated to Professor G. S. Krishna Rao for his contributions to organic synthesis

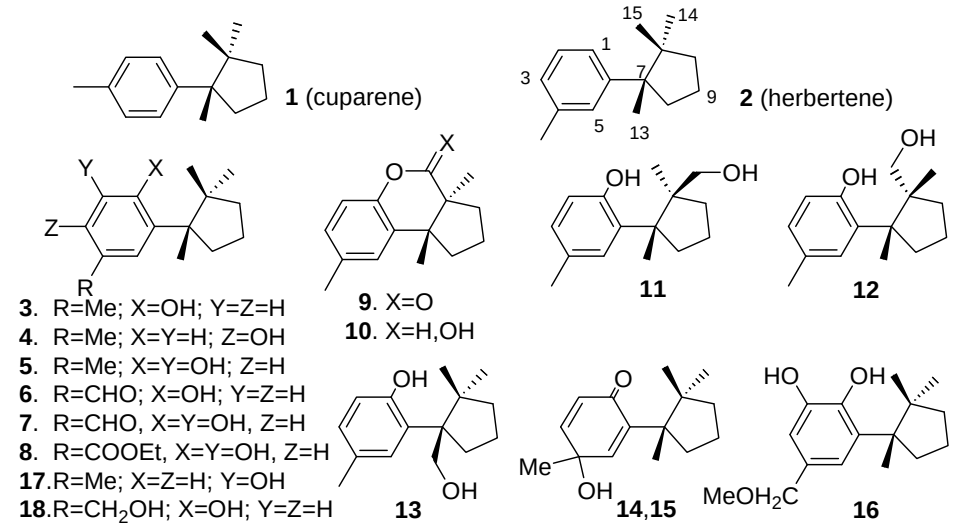
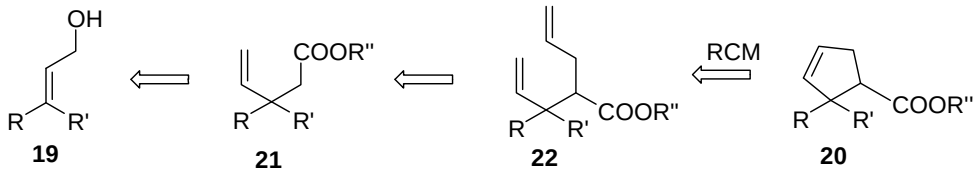
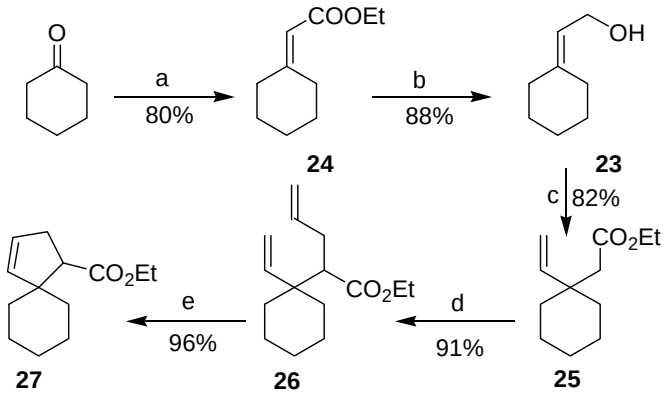


Chart I



Scheme I



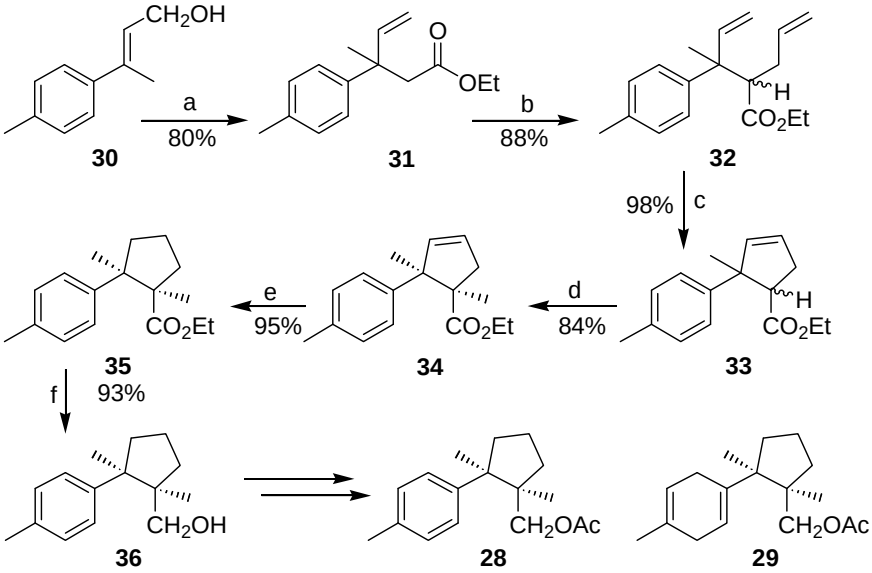
Scheme II — (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (b) LAH, Et_2O; (c) $MeC(OEt)_3$, $EtCO_2H$, Δ; (d) LDA, THF; $CH_2{=}CHCH_2Br$; (e) $PhCH{=}Ru(PCy_3)_2Cl_2$, CH_2Cl_2.

reaction followed by reduction of the ester **24** with LAH. Johnson's ortho ester Claisen rearrangement[9] of the allyl alcohol **23** with triethyl orthoacetate and a catalytic amount of propionic acid at 180°C in a sealed tube furnished the γ,δ-unsaturated ester **25** in 82% yield. Generation of the lithium enolate of the ester **25** with LDA in THF at –70°C followed by alkylation with allyl bromide, generated the diene ester **26** in 91% yield. The diene ester **26** was then subjected to the RCM reaction[10] with first generation Grubbs' catalyst. Reaction of the diene ester **26** with 6 mol% of Grubbs' catalyst in anhydrous methylene chloride at RT for 4 hr, furnished the spiro compound **27** in 96% yield, whose structure was established from its spectral data.

As an application of this methodology, attention was initially focused on the formal total synthesis of tochuinyl acetate **28** and dihydrotochuinyl acetate **29**. In 1987, Andersen and Williams have reported the isolation and structure elucidation of the cuparenoid marine sesquiterpene natural products tochuinyl acetate **28** and dihydrotochuinyl acetate **29** from the skin extracts of dendronotid nudibranch *Tochuina tetraquetra*, collected from the Port Hardy, British Columbia and also from its feed, the soft coral *Gersemia rubiformis*[11]. The tochuinyl acetate **28** and dihydrotochuinyl acetate **29** were the first examples of cuparenes to be isolated from a soft coral. Presence of two vicinal stereogenic quaternary carbons in a cyclopentane ring made tochuinyl acetates interesting synthetic targets[12,7f]. Based on the methodology described for the spiro ester **27**, a formal synthesis of these marine sesquiterpenes was investigated starting from the dimethylcinnamyl alcohol **30**, **Scheme III**.

Reaction of the allyl alcohol **30** with triethyl orthoacetate and a catalytic amount of propionic acid at 180°C in a sealed tube for 48 hr furnished the pentenoate **31** in 80% yield[12d]. Generation of the lithium enolate of the ester **31** with LDA in THF at –70°C followed by alkylation with allyl bromide, generated a 5:1 epimeric mixture of the RCM precursor, the diene ester **32** in 88% yield, whose structure as well as the epimeric nature was established from its spectral data. RCM reaction of the diene ester **32** with 6 mol% of Grubbs' catalyst in anhydrous methylene chloride at RT for 4 hr generated a 5:1 diastereomeric mixture of the cyclopentenecarboxylate **33** in near quantitative yield. Generation of the lithium enolate of the ester **33** with LDA in THF and HMPA at 0°C followed by treatment with methyl iodide furnished the alkylated product **34** in 84% yield, creating the second quaternary carbon in a highly stereoselective manner. Presence of only one set of signals in the ^{1}H and ^{13}C NMR spectra established the high stereoselectivity of the alkylation reaction, which is a consequence of the approach of the electrophile from the less hindered face (opposite to aryl group) of the enolate. Hydrogenation of the cyclopentene moiety in **34** using 10% Pd-C as the catalyst at 1.0 atm pressure (balloon) of hydrogen in ethanol for 1 hr furnished the hydrogenated compound **35** in 95% yield, whose structure was established from its spectral data. Reduction of the ester moiety in **35** to the primary alcohol using LAH in ether at –20°C furnished the tochuinyl alcohol **36** in 93% yield. Structure of the primary alcohol **36** was confirmed by comparison of the spectral data, in particular ^{1}H and ^{13}C NMR, with those of the authentic sample prepared earlier[12d]. Since the primary alcohol **36** has already been converted[12d] into the natural products tochuinyl acetate **28** and dihydrotochuinyl acetate **29**, the present sequence constitutes a formal total synthesis of these marine sesquiterpenes.

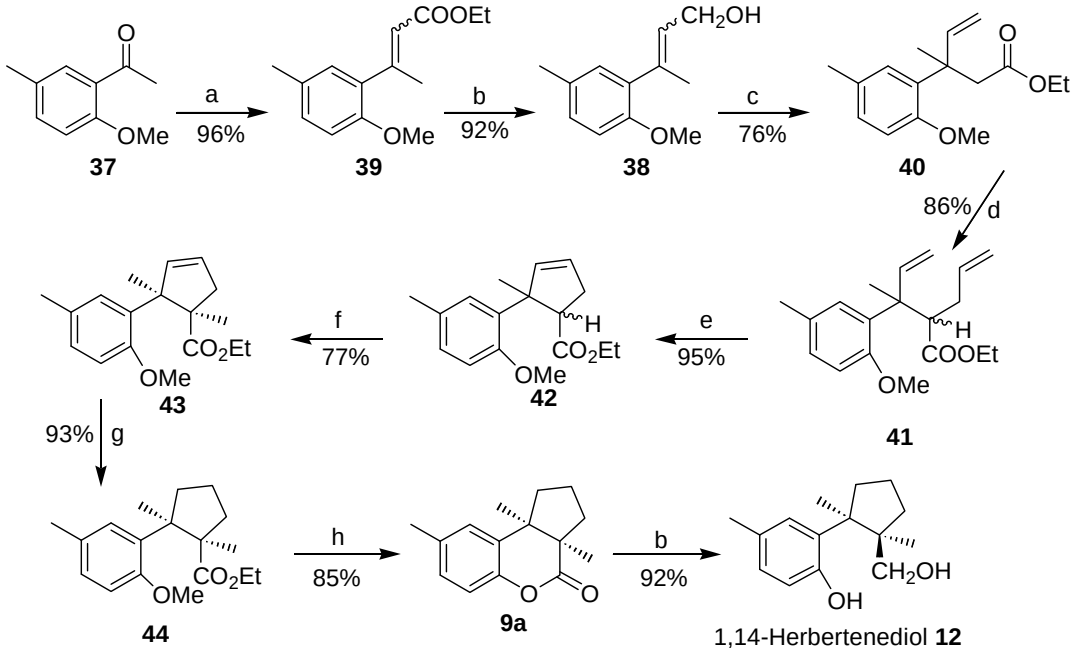
After successfully accomplishing the synthesis of tochuinyl acetates, attention was turned towards the synthesis of herbertenolide **9**. It was very clear, since



Scheme III — (a) $MeC(OEt)_3$, $EtCO_2H$, Δ; (b) LDA, THF; $CH_2{=}CHCH_2Br$; (c) $PhCH{=}Ru(PCy_3)_2Cl_2$, CH_2Cl_2; (d) LDA, THF, HMPA; MeI; (e) H_2, 10% Pd/C, EtOH; (f) LAH, Et_2O.

the second alkylation introduces methyl opposite to aryl group, the sequence was only suitable for 11-*epi*-herbertenolide **9a** and 1,14-herbertenediol **12**, **Scheme IV**. The acetophenone **37** was identified as the suitable starting material.

The acetophenone **37** was converted into the cinnamyl alcohol **38** in two steps. Thus, Horner-Wadsworth-Emmons reaction of the acetophenone **37** with triethyl phosphonoacetate and sodium hydride in THF at RT furnished the *E*-crotonate **39** in a highly stereoselective manner, which on reduction with LAH at low temperature (–70°C) in dry ether gave the allyl alcohol **38** in a highly regioselective and efficient manner. Thermal activation of the allyl alcohol **38** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid in a sealed tube at 180°C generated the γ,δ-unsaturated ester **40**. Generation of the lithium enolate of the ester **40** with LDA in THF at –70°C followed by alkylation with allyl bromide furnished a 1:1 epimeric mixture of the diene ester **41** in 86% yield. RCM reaction of the diene ester **41** with 6 mol% of the first generation Grubbs' catalyst in anhydrous CH_2Cl_2 for 4 hr at RT, as expected, generated a 1:1 diastereomeric mixture of the cyclopentenecarboxylate **42** in 95% yield, whose structure and the epimeric nature was established from its spectral data. Generation of the lithium enolate of the ester **42** with LDA in THF and HMPA at 0°C followed by treatment with methyl iodide furnished the alkylated ester **43** in 77% yield, creating the second quaternary carbon atom in a highly stereoselective manner. Hydrogenation of the cyclopentenecarboxylate **43** using 10% Pd-C as the catalyst at 1.0 atm pressure (balloon) of hydrogen in ethanol for 1 hr generated the cyclopentanecarboxylate **44** in 93% yield. Treatment of the ester **44** with BBr_3 in anhydrous methylene chloride at 0°C for 2 hr furnished 11-*epi*-herbertenolide **9a** in 85% yield *via* simultaneous hydrolysis of the methyl ether and lactonization. Presence of the molecular ion peak at *m/z* 230 in the mass spectrum and in the IR spectrum, shift in the carbonyl absorption band to 1755 cm^{-1} due to the lactone revealed the formation of *epi*-herbertenolide **9a**. In the ^1H NMR spectrum, absence of resonances due to the ethoxy group and presence of those at δ 2.37-1.41 (6 H, m) due to the cyclopentane methylene protons and two singlets at 1.25 and 1.20 ppm due to the tertiary methyl protons, established the structure of *epi*-herbertenolide **9a**. It was further confirmed by the 15 lines ^{13}C NMR spectrum. Reduction of *epi*-herbertenolide **9a** with LAH in ether at –20°C furnished 1,14-herbertenediol **12** in 92% yield. The structure was confirmed by comparison of the ^1H NMR spectral data[2] with that of the natural



Scheme IV — (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (b) LAH, Et_2O; (c) $MeC(OEt)_3$, $EtCO_2H$, Δ; (d) LDA, THF; $CH_2=CHCH_2Br$; (e) $PhCH=Ru(PCy_3)_2Cl_2$, CH_2Cl_2; (f) LDA, THF, HMPA; MeI; (g) H_2, 10% Pd/C, EtOH; (f) BBr_3, CH_2Cl_2.

product and ^{13}C NMR spectral data[7e] with that of the racemic compound reported by Fukuyama and co-workers.

In conclusion, a short approach for the construction of cyclopentanes containing vicinal quaternary carbon atoms employing a combination of Claisen rearrangement, alkylation and RCM reactions has been developed. The versatility of the methodology was demonstrated by the synthesis of tochuinyl acetates and herbertene-1,14-diol.

Experimental Section

IR spectra were recorded on Perkin-Elmer 781 spectrometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JNM λ-300 spectrometer. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. Low-resolution mass spectra were recorded using Jeol JMS-DX 303 and Shimadzu QP-5050A GCMS instruments using direct inlet mode. Relative intensities are given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer using electrospray ionization. Hydrogenation reaction at 1.0 atm pressure was carried out using a balloon filled with hydrogen. Analytical thin-layer chromatographies (TLC) were performed on glass plates (7.5 × 2.5 and 7.5 × 5.0 cm) coated with Acme's silica gel G containing 13% calcium sulphate as binder and ethyl acetate and hexane mixtures in various ratios were used as eluent. Visualization of spots was accomplished by exposure to iodine vapour. Acme's silica gel (100-200 mesh) was used for column chromatography (approximately 15-20 g per 1 g of the crude product). All small-scale dry reactions were carried out using standard syringe-septum technique. Dry THF was obtained by distillation over sodium-benzophenone ketyl. Dry ether was obtained by distillation over sodium and stored over sodium wire. Dry methylene chloride was prepared by distillation over P_2O_5.

Ethyl 2-(1-vinylcyclohexyl)pent-4-enoate 26. To a cold (–70°C), magnetically stirred solution of diisopropylamine (0.33 mL, 2.30 mmoles) in anhydrous THF (2 mL) was slowly added a solution of ^{n}BuLi (2.5 *M*, 0.84 mL, 2.1 mmoles) and stirred for 10 min. To LDA thus formed was added dropwise a solution of the ester[8] **25** (180 mg, 0.92 mmoles) in anhydrous THF (2 mL) and stirred for 40 min at the same temperature. The enolate was then treated with allyl bromide (0.23 mL, 2.76 mmoles) and stirred for 3 hr at RT. The reaction mixture was diluted with water and extracted with ether (3×4 mL). The combined ether extract was washed with 3 *N* aqueous HCl, saturated aqueous $NaHCO_3$ solution and brine, and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the ester **26** (197 mg, 91%) as oil. IR (neat) 3079, 2979, 2931, 2857, 1730, 1640, 1449, 1413, 1371, 1345, 1228, 1176, 1156, 1000, 915, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.70-5.55 (2 H, m, 2 × C*H*=CH_2), 5.22 (1 H, d, *J* = 10.8 Hz) and 5.05-4.85 (3 H, m) [2 × CH=CH_2], 4.09 (2 H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 2.40-2.10 (3 H, m), 1.85-1.30 (10 H, m), 1.24 (3 H, t, *J* = 6.9 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 173.6 (C, OC=O), 142.6 (CH, C-1''), 136.2 (CH, C-4), 116.4 (CH_2), 115.4 (CH_2), 59.6 (CH_2, OCH_2CH_3), 55.1 (CH, C-2), 42.0 (C, C-1'), 33.6 (CH_2), 33.1 (CH_2), 31.6 (CH_2), 26.3 (CH_2), 22.1 (2 C, CH_2), 14.5 (CH_3, OCH_2CH_3); MS: *m/z* (%) 163 (M–COOEt, 8), 162 (12), 149 (9), 148 (12), 135 (7), 128 (19), 109 (100), 108 (25); HRMS: *m/z* Calcd. for $C_{15}H_{24}O_2Na$ (M+Na): 259.1674; Found: 259.1681.

Ethyl spiro[4.5]dec-3-ene-1-carboxylate 27. To a magnetically stirred solution of the ester **26** (30 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (8 mL) was added a solution of Grubbs' first generation catalyst (6.4 mg, 6 mol%) in anhydrous CH_2Cl_2 (3 mL) and the reaction mixture was stirred at RT for 4 hr. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the spiro compound **27** (25 mg, 96%) as oil. IR (neat): 3055, 2929, 2857, 1733, 1617, 1450, 1371, 1343, 1270, 1250, 1199, 1048, 951, 717 cm^{-1}; ^1H NMR ($CDCl_3 + CCl_4$): δ 5.91 (1 H, d, *J* = 5.4 Hz, H-4), 5.70-5.62 (1 H, m, H-3), 4.21-4.09 (2 H, m, OC$H_2$$CH_3$), 2.80 (1 H, t of dd, *J* = 16.2, 8.4 and 2.2 Hz, H-2A), 2.66 (1 H, t, *J* = 8.4 Hz, H-1), 2.42 (1 H, t of dd, *J* = 16.2, 8.4 and 1.5 Hz, H-2B), 1.80-1.12 (10 H, m), 1.30 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3 + CCl_4$): δ 173.7 (C, OC=O), 135.7 (CH, C-4), 127.7 (CH, C-3), 59.9 (CH_2, OCH_2CH_3), 54.5 (CH, C-1), 52.3 (C, C-5), 38.2

(CH_2), 34.0 (CH_2), 33.5 (CH_2), 26.3 (CH_2), 24.1 (CH_2), 23.1 (CH_2), 14.6 (CH_3, OCH_2CH_3). MS: *m/z* (%) 208 (M^+), 199 (21), 159 (16), 149 (34), 135 (60), 134 (60), 133 (100), 132 (70), 117 (55), 109 (40), 105 (45); HRMS: *m/z* Calcd. for $C_{13}H_{20}O_2Na$ (M+Na): 231.1361; Found: 231.1357.

Ethyl 3-methyl-3-(4-methylphenyl)pent-4-enoate 31. A solution of the allyl alcohol[12d] **30** (1.0 g, 6.17 mmol), triethyl orthoacetate (3.4 mL, 18.5 mmol) and a catalytic amount (*ca* 5 μL) of propionic acid was placed in a Carius tube under nitrogen atmosphere and heated to 180°C for 48 hr. The reaction mixture was cooled, diluted with ether (3 × 4 mL), washed with 0.5 *N* aqueous HCl followed by saturated aqueous $NaHCO_3$ solution and brine, and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the pentenoate **31** (1.14 g, 80%) as oil. IR (neat): 2976, 2926, 1734, 1637, 1511, 1454, 1412, 1369, 1322, 1227, 1159, 1116, 1070, 1034, 916, 814, 724 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 7.16 (2 H, d, *J* = 8.1 Hz) and 7.06 (2 H, d, *J* = 8.1 Hz) [Ar-H], 6.11 (1 H, dd, *J* = 17.1 and 10.8 Hz, H-4), 5.10 (1 H, d, *J* = 10.8 Hz) and 5.03 (1 H, d, *J* = 17.1 Hz) [H-5], 3.97 (2 H, q, *J* = 6.9 Hz, OCH_2CH_3), 2.74 and 2.65 (2 H, AB q, *J* = 14.1 Hz, H-2), 2.30 (3 H, s, $ArCH_3$), 1.53 (3 H, s, *tert*-CH_3), 1.11 (3 H, t, *J* = 6.9 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 170.9 (C, OC=O), 145.9 (CH, C-4), 143.1 (C, C-1'), 135.5 (C, C-4'), 128.8 (2 C, CH), 126.3 (2 C, CH), 112.2 (CH_2, C-5), 59.9 (CH_2, OCH_2CH_3), 45.8 (CH_2, C-2), 43.2 (C, C-3), 25.7 (CH_3, *tert*-CH_3), 21.0 (CH_3, $ArCH_3$), 14.3 (CH_3, OCH_2CH_3).

Ethyl 2-allyl-3-methyl-3-(4-methylphenyl)pent-4-enoate 32. To a cold (–70°C), magnetically stirred solution of diisopropylamine (0.5 mL, 3.44 mmol) in anhydrous THF (2 mL) was slowly added a solution of ^{n}BuLi (2.5 *M* in hexane, 1.24 mL, 3.10 mmol) and stirred for 10 min. To LDA thus formed was added dropwise a solution of the ester **31** (400 mg, 1.72 mmoles) in anhydrous THF (3 mL) and stirred for 40 min at the same temperature. Allyl bromide (0.43 mL, 5.16 mmoles) was added to the reaction mixture and stirred for 3 hr. Work-up as described for the ester **26**, followed by purification on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished a 5:1 diastereomeric mixture of the diene ester **32** (412 mg, 88%) as oil. IR (neat): 3081, 2979, 2925, 1731, 1641, 1512, 1444, 1371, 1345, 1230, 1182, 1019, 995, 916, 856 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4, peaks due to the major isomer): δ 7.20 (2 H, d, *J* = 7.5 Hz) and 7.07 (2 H, d, *J* = 7.5 Hz) [Ar-H], 6.35 (1 H, dd, *J* = 17.1 and 10.5 Hz, H-4), 5.70-5.55 (1 H, m, H-2''), 5.30-4.85 (4 H, m), 3.96 (2 H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.00-2.85 (1 H, m), 2.30 (2 H, s, $ArCH_3$), 2.40-1.95 (2 H, m), 2.05-1.90 (1 H, m), 1.48 (3 H, s, *tert*-CH_3), 1.10 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4, peaks due to the major isomer): δ 173.4 (C, OC=O), 144.3 (CH, C-4), 142.7 (C), 136.0 (CH, C-2"), 135.6 (C), 128.8 (2 C, CH), 126.6 (2 C, CH), 116.4 (CH_2), 113.0 (CH_2), 59.7 (CH_2, OCH_2CH_3), 54.9 (CH, C-2), 46.1 (C, C-3), 32.7 (CH_2, C-1''), 21.0 (2 C, CH_3), 14.3 (CH_3, OCH_2CH_3); MS: *m/z* (%) 272 (M^+, 1), 159 (11), 145 (100), 130 (11), 129 (11), 128 (10), 115 (9), 105 (12), 91 (8); HRMS: *m/z* Calcd. for $C_{18}H_{24}O_2Na$ (M+Na): 295.1674; Found: 295.1688.

Ethyl 2-methyl-2-(4-methylphenyl)cyclopent-3-enecarboxylate 33. RCM reaction of a 5:1 diastereomeric mixture of the diene ester 190 (60 mg, 0.22 mmoles) in anhydrous CH_2Cl_2 (8 mL) using Grubbs' catalyst (11 mg, 6 mol%) for 4 hr at RT, followed by purification on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished a 5:1 diastereomeric mixture of the cyclised compound **33** (53 mg, 98%) as oil. IR (neat): 3053, 2974, 2932, 2870, 1734, 1512, 1450, 1371, 1342, 1277, 1188, 1051, 1018, 817, 761, 721, 699 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4, peaks due to the major isomer): δ 7.12 (2 H, d, *J* = 8.1 Hz) and 7.01 (2 H, d, *J* = 8.1 Hz) [Ar-H], 5.89-5.80 (1 H, m) and 5.75-5.55 (1 H, m) [*olefinic*-H], 3.75-3.50 (2 H, m, OCH_2CH_3), 3.03 (1 H, t, *J* = 7.8 Hz), 3.00-2.85 (1 H, m), 2.62-2.40 (1 H, m), 2.28 (3 H, s, $ArCH_3$), 1.69 (3 H, s, *tert*-CH_3), 0.92 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4, peaks due to the major isomer): δ 172.6 (C, OC=O), 139.7 (C, C-1'), 138.9 (CH, C-3), 135.8 (C, C-4'), 128.5 (2 C, CH), 128.3 (CH, C-4), 127.0 (2 C, CH), 59.8 (CH_2, OCH_2CH_3), 56.0 (CH, C-1), 55.7 (C, C-2), 34.7 (CH_2, C-5), 28.0 (CH_3, *tert*-CH_3), 21.0 (CH_3, $ArCH_3$), 14.0 (CH_3, OCH_2CH_3); MS: *m/z* (%) 244 (M^+, 26), 229 (36), 183 (50), 171 (45), 170 (63), 169 (40), 156 (80), 155 (100), 143 (54), 141 (50), 129 (50), 128 (60), 119 (46), 115 (55), 105 (30); HRMS: *m/z* Calcd. for $C_{16}H_{20}O_2Na$ (M+Na): 267.1361; Found: 267.1373.

Ethyl *cis*-1, 2-dimethyl-2-(4-methylphenyl)cyclopent-3-enecarboxylate 34. To a cold (0°C), magnetically stirred solution of diisopropylamine (0.07 mL, 0.5 mmoles) in anhydrous THF (2 mL) was slowly

added a solution of ^{n}BuLi (2.5 *M* in hexane, 0.18 mL, 0.46 mmole) and stirred for 10 min. To LDA thus formed was added dropwise a solution of the ester **33** (50 mg, 0.20 mmoles) in anhydrous THF (1 mL) and HMPA (2 mL) and stirred for 40 min at the same temperature. Methyl iodide (0.04 mL, 0.6 mmoles) was added to the reaction mixture and stirred for 7 hr. Work-up as described for the ester **26**, followed by purification on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the ester **34** (44 mg, 84%) as oil. IR (neat): 3030, 2977, 2933, 1725, 1512, 1447, 1377, 1301, 1265, 1197, 1167, 1141, 1112, 1025, 814, 761, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 7.13 (2 H, d, *J* = 8.1 Hz) and 7.00 (2 H, d, *J* = 8.1 Hz) [Ar-H], 5.90 (1 H, t of d, *J* = 6.0 and 3.0 Hz, H-4), 5.51 (1 H, d, *J* = 6.0 Hz, H-3), 3.51 (2 H, q of AB q, *J* = 10.5 and 7.2 Hz, OC*H*$_2$CH$_3$), 3.20 (1 H, d, *J* = 16.5 Hz, H-5A), 2.23 (3 H, s, ArCH$_3$), 2.10 (1 H, d, *J* = 16.5 Hz, H-5B), 1.52 (3 H, s) and 1.34 (3 H, s) [2 × *tert*-CH$_3$], 0.90 (3 H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 175.2 (C, OC=O), 140.6 (C, C-1'), 137.8 (CH, C-3), 135.6 (C, C-1), 128.5 (CH, C-4), 128.4 (2 C, CH), 127.1 (2 C, CH), 59.9 (CH$_2$, OCH$_2$CH$_3$), 57.0 (C), 56.8 (C), 43.2 (CH$_2$, C-5), 22.7 (CH$_3$), 21.7 (CH$_3$), 21.0 (CH$_3$, ArCH$_3$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); MS: *m/z* (%) 258 (M$^+$, 12), 197 (10), 185 (43), 184 (22), 170 (20), 169 (22), 157 (45), 156 (43), 145 (100), 144 (35), 143 (40), 129 (35), 128 (37), 119 (45), 115 (40), 105 (42); HRMS: *m/z* Calcd. for $C_{17}H_{22}O_2Na$ (M+Na): 281.1517; Found: 281.1534.

Ethyl *cis*-1,2-dimethyl-2-(4-methylphenyl)cyclopentanecarboxylate 35. To a solution of the cyclopentenecarboxylate **34** (25 mg, 0.1 mmole) in ethanol (3 mL) was added 10% Pd-C (5 mg) and the reaction mixture was stirred at RT in an atmosphere of hydrogen created by evacuative displacement of air (balloon) for 1 hr. The reaction mixture was filtered through a short silica gel column. Evaporation of the solvent furnished the ester **35** (24 mg, 95%) as oil. IR (neat): 2972, 2878, 1718, 1515, 1464, 1380, 1282, 1224, 1164, 1141, 1108, 1022, 814 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 7.16 (2 H, d, *J* = 8.4 Hz) and 7.01 (2 H, d, *J* = 8.4 Hz) [Ar-H], 3.70-3.55 (2 H, m, OC*H*$_2$CH$_3$), 2.60-2.20 (2 H, m), 2.29 (3 H, s, ArCH$_3$), 2.00-1.40 (4 H, m), 1.38 (3 H, s) and 1.32 (3 H, s) [2 × *tert*-CH$_3$], 0.86 (3 H, t, *J* = 6.9 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 176.2 (C, OC=O), 143.6 (C, C-1'), 135.1 (C, C-4'), 128.3 (2 C, CH), 126.4 (2 C, CH), 59.7 (CH$_2$, OCH$_2$CH$_3$), 56.5 (C), 51.5 (C), 38.1 (CH$_2$), 36.1 (CH$_2$), 24.7 (CH$_3$), 21.3 (CH$_2$, C-4), 21.0 (CH$_3$), 20.7 (CH$_3$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); MS: *m/z* (%) 260 (M$^+$, 12), 186 (46), 159 (20), 158 (30), 147 (40), 146 (53), 143 (30), 131 (55), 115 (100), 105 (51); HRMS: *m/z* Calcd. for $C_{17}H_{24}O_2Na$ (M+Na): 283.1674; Found: 283.1693.

***cis*-1, 2-Dimethyl-2-(4-methylphenyl)cyclopentanemethanol 36**. To a solution of the ester **35** (15 mg, 0.06 mmole) in dry ether (4 mL) was added LAH (5 mg, 0.12 mmole) at –20°C and stirred the reaction mixture for 2 hr at the same temperature. Ethyl acetate (2 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice-cold water (5 mL). The solution was filtered through a sintered funnel and the residue thoroughly washed with ether (3×5 mL). The ether layer was separated, washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished tochuinyl alcohol **36** (11 mg, 93%) as oil. IR (neat): 3385 (OH), 2963, 2877, 1513, 1455, 1377, 1024, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 7.25 (2 H, d, *J* = 8.4 Hz) and 7.07 (2 H, d, *J* = 8.4 Hz) [Ar-H], 3.07 and 3.01 (2 H, AB q, *J* = 11.4 Hz, C*H*$_2$OH), 2.55-2.40 (1 H, m), 2.31 (3 H, s, Ar-CH$_3$), 1.90-1.40 (6 H, m), 1.30 (3 H, s) and 1.11 (3 H, s) [2 × *tert*-CH$_3$]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 143.4 (C, C-1'), 135.3 (C, C-4'), 128.9 (2 C, CH), 126.7 (2 C, CH), 69.4 (CH$_2$, CH$_2$OH), 49.6 (C) and 49.3 (C) [C-1 and C-2], 37.6 (CH$_2$) and 35.1 (CH$_2$) [C-3 and C-5], 25.3 (CH$_3$), 20.9 (CH$_3$), 20.4 (CH$_2$, C-4), 19.6 (CH$_3$); MS: *m/z* (%) 218 (M$^+$, 21), 157 (12), 145 (45), 132 (76), 131 (40), 119 (100), 105 (38), 91 (30); HRMS: *m/z* Calcd. for $C_{15}H_{22}ONa$ (M+Na): 241.1568; Found: 241.1580.

Ethyl *E*-3-(2-methoxy-5-methylphenyl)but-2-enoate 39. A suspension of sodium hydride (440 mg, 60% dispersion in oil, 11.0 mmoles, washed with dry hexanes) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free NaH was then suspended in dry THF (5 mL) and cooled in an ice bath. Triethyl phosphonoacetate (2.56 mL, 12.8 mmoles) was added dropwise and the reaction mixture was stirred for 30 min at RT. A solution of the acetophenone **37** (1.0 g, 6.10 mmoles) in dry THF (1 mL) was added dropwise to the reaction mixture and stirred for 12 hr at RT. The reaction was then quenched by careful addition of saturated aqueous NH_4Cl solution and extracted with ether (3 × 4 mL). The combined ether extract was washed with brine and dried (anhyd. Na_2SO_4).

Evaporation of the solvent followed by purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the *E*-cinnamate **39** (1.37 g, 96%), containing a small amount of *Z*-isomer, as oil. IR (neat): 3031, 2929, 1713, 1633, 1499, 1450, 1267, 1200, 1159, 1030, 888, 666 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 7.02 (1 H, d, *J* = 8.1 Hz, H-4'), 6.92 (1 H, s, H-6'), 6.73 (1 H, d, *J* = 8.1 Hz, H-3'), 5.83 (1 H, s, H-2), 4.18 (2 H, q, *J* = 6.9 Hz, OCH_2CH_3), 3.78 (3 H, s, $ArOCH_3$), 2.45 (3 H, s, H-4), 2.28 (3 H, s, $ArCH_3$), 1.30 (3 H, t, *J* = 6.9 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 166.4 (C, OC=O), 156.7 (C, C-3), 154.3 (C, C-2'), 133.1 (C), 129.65 (CH), 129.6 (C), 129.5 (CH), 119.2 (CH, C-2), 111.0 (CH, C-3'), 59.5 (CH_2, OCH_2CH_3), 55.5 (CH_3, OCH_3), 20.5 (CH_3, $ArCH_3$), 19.9 (CH_3, C-4), 14.5 (CH_3, OCH_2CH_3); MS: *m/z* (%) 234 (M^+, 17), 203 (74), 189 (22), 175 (76), 145 (36), 111 (32), 97 (49), 95 (44), 57 (100).

***E*-3-(2-Methoxy-5-methylphenyl)but-2-en-1-ol 38**. Reduction of the cinnamate **39** (800 mg, 3.42 mmoles) in dry ether (8 mL) with LAH (65 mg, 1.71 mmole) at –20°C, as described for tochuinyl alcohol **36**, followed by purification on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the allyl alcohol **38** (603 mg, 92%) as oil. IR (neat): 3366, 2922, 2830, 1656, 1609, 1497, 1462, 1237, 1176, 1146, 1029, 1010, 807, 630 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 6.96 (1 H, dd, *J* = 8.1 and 1.8 Hz, H-4'), 6.90 (1 H, d, *J* = 1.8 Hz, H-6'), 6.70 (1 H, d, *J* = 8.1 Hz, H-3'), 5.61 (1 H, t, *J* = 7.2 Hz, H-2), 4.27 (2 H, d, *J* = 7.2 Hz, H-1), 3.77 (3 H, s, OCH_3), 2.26 (3 H, s, $ArCH_3$), 1.98 (3 H, s, H-4), 1.82 (1 H, br s, OH); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 154.5 (C, C-2'), 138.3 (C), 133.7 (C, C-5'), 130.2 (CH), 129.6 (C, C-1'), 128.5 (CH), 128.2 (CH), 110.7 (CH, C-3'), 59.5 (CH_2, C-1), 55.4 (CH_3, OCH_3), 20.5 (CH_3, $ArCH_3$), 17.4 (CH_3, C-4); MS: *m/z* (%) 192 (M^+, 55), 177 (40), 175 (87), 159 (46), 149 (95), 121 (48), 115 (43), 105 (40), 91 (100); HRMS: *m/z* Calcd. for $C_{12}H_{15}O$ (M–OH): 175.1123; Found: 175.1122.

Ethyl 3-methyl-3-(2-methoxy-5-methylphenyl)-pent-4-enoate 40. Reaction of the allyl alcohol **38** (200 mg, 1.04 mmole) with triethyl orthoacetate (0.95 mL, 5.20 mmoles) and a catalytic amount of propionic acid at 180°C for 48 hr and work-up as described for the ester **31**, followed by purification on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the pentenoate **40** (207 mg, 76%) as oil. IR (neat): 3082, 2976, 2930, 1730, 1636, 1607, 1410, 1368, 1289, 1240, 1118, 1032, 914, 807, 738 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 7.00 (1 H, s, H-6'), 6.95 (1 H, d, *J* = 8.1 Hz, H-4'), 6.71 (1 H, d, *J* = 8.1 Hz, H-3'), 6.30 (1 H, dd, *J* = 17.7 and 10.8 Hz, H-4), 5.01 (1 H, d, *J* = 10.8 Hz) and 4.95 (1 H, d, *J* = 17.7 Hz) [$CH=CH_2$], 3.91 (2 H, q, *J* = 6.9 Hz, OCH_2CH_3), 3.78 (3 H, s, OCH_3), 3.06 and 2.84 (2 H, 2 × d, *J* = 13.8 Hz, H-2), 2.26 (3 H, s, $ArCH_3$), 1.55 (3 H, s, *tert*-CH_3), 1.03 (3 H, t, *J* = 6.9 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 171.6 (C, OC=O), 155.9 (C, C-2'), 145.9 (CH, C-4), 133.6 (C, C-5'), 129.2 (CH), 128.7 (C, C-1'), 128.0 (CH), 111.6 (CH_2, C-5), 111.3 (CH, C-3'), 59.5 (CH_2, OCH_2CH_3), 55.2 (CH_3, OCH_3), 43.8 (CH_2, C-2), 42.8 (C, C-3), 24.8 (CH_3, *tert*-CH_3), 20.9 (CH_3, $ArCH_3$), 14.2 (CH_3, OCH_2CH_3); MS: *m/z* (%) 262 (M^+, 8), 203 (17), 189 (20), 175 (100), 173 (38), 159 (36), 149 (56), 145 (27), 135 (24), 115 (23), 105 (32), 91 (40); HRMS: *m/z* Calcd. for $C_{16}H_{22}O_3Na$ (M+Na): 285.1467; Found: 285.1465.

Ethyl 2-allyl-3-(2-methoxy-5-methylphenyl)-3-methylpent-4-enoate 41. To a cold (–70°C), magnetically stirred solution of diisopropylamine (0.66 mL, 4.60 mmoles) in anhydrous THF (3 mL) was slowly added a solution of ^{n}BuLi (2.5 *M* in hexane, 1.6 mL, 4.0 mmoles) and stirred for 10 min. To LDA thus formed was added dropwise a solution of the ester **40** (600 mg, 2.30 mmoles) in anhydrous THF (3 mL) and stirred for 40 min at the same temperature. Allyl bromide (0.58 mL, 6.90 mmoles) was added to the reaction mixture and stirred for 3 hr. Work-up as described for the ester **26**, followed by purification on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished a 1:1 diastereomeric mixture of the allylated ester **41** (595 mg, 86%) as oil. IR (neat): 3079, 2978, 2950, 2833, 1728, 1640, 1607, 1498, 1463, 1441, 1373, 1288, 1240, 1183, 1152, 1031, 915, 808 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4, 1:1 mixture of epimers): δ 6.93 (1 H, d, *J* = 8.1 Hz, H-4'), 6.92 (1 H, s, H-6'), 6.72 (1 H, d, *J* = 8.1 Hz, H-3'), 6.65 and 6.49 (1 H, dd, *J* = 17.4 and 10.5 Hz, H-4), 5.75-5.55 (1 H, m, H-2"), 5.15-4.80 (4 H, m), 3.95-3.60 (3 H, m, H-2 and OCH_2CH_3), 3.82 (3 H, s, OCH_3), 2.23 (3 H, s, $ArCH_3$), 2.50-1.85 (2 H, m), 1.53 and 1.50 (3 H, s, *tert*-CH_3), 1.00 and 0.88 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4, 1:1 mixture of epimers): δ 174.0 and 173.6 (C, OC=O), 156.2 and 156.1 (C, C-2'), 144.0 and 143.8 (CH, C-4), 136.8 and 136.7 (CH, C-2"), 133.5 and 133.4 (C), 129.1 (C), 128.5 (CH), 128.0 (CH), 116.0 (CH_2), 113.0 and 112.9 (CH_2), 111.7 (CH, C-3'), 59.5 and

59.4 (CH_2, O*C*H_2CH_3), 55.2 and 55.1 (CH_3, OCH_3), 50.8 and 50.7 (CH, C-2), 46.4 (C, C-3), 32.8 and 32.4 (CH_2, C-1"), 20.9 (CH_3), 20.0 and 19.9 (CH_3), 14.2 and 14.0 (CH_3, OCH_2CH_3); MS: *m/z* (%) 302 (M^+, 2), 175 (100), 160 (13), 149 (22), 145 (14), 135 (14), 115 (11), 105 (21), 91 (16); HRMS: *m/z* Calcd. for $C_{19}H_{26}O_3Na$ (M+Na): 325.1780; Found: 325.1805.

Ethyl 2-methyl-2-(2-methoxy-5-methylphenyl) cyclopent-3-enecarboxylate 42. RCM reaction of a 1:1 diastereomeric mixture of the diene ester **42** (230 mg, 0.76 mmole) with Grubbs' catalyst (37 mg, 6 mol%) in anhydrous CH_2Cl_2 (12 mL) for 4 hr at RT followed by purification on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished a 1:1 diastereomeric mixture of the cyclised compound **42** (197 mg, 95%) as oil. IR (neat): 3072, 2929, 2820, 1728, 1499, 1461, 1369, 1340, 1253, 1182, 1155, 1070, 1035, 806, 732 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4, for the syn isomer): δ 7.02 (1 H, s, H-6'), 6.90 (1 H, d, *J* = 8.1 Hz, H-4'), 6.65 (1 H, d, *J* = 8.1 Hz, H-3'), 5.98-5.93 (1 H, m) and 5.75-5.70 (1 H, m) [*olefinic*-H], 3.74 (3 H, s, OCH_3), 3.75-3.50 (2 H, m, OC*H*$_2CH_3$), 3.31 (1 H, dd, *J* = 7.8 and 3.9 Hz, H-1), 2.75-2.60 (2 H, m, H-5), 2.25 (3 H, s, $ArCH_3$), 1.52 (3 H, s, *tert*-CH_3), 0.80 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4, 1:1 diastereomeric mixture): δ 174.4 and 174.1 (C, OC=O), 155.6 (C, C-2'), 139.0 and 138.0 (CH, C-3), 135.6 and 133.0 (C), 128.9 and 128.7 (C), 128.6 and 128.1 (CH), 127.7 and 127.6 (CH), 126.8 and 126.5 (CH), 111.4 and 110.7 (CH, C-3'), 59.7 and 59.3 (CH_2, O*C*H_2CH_3), 55.9 (C, C-2), 54.9 and 54.8 (CH_3, OCH_3), 53.7 and 51.9 (CH, C-1), 36.5 and 35.5 (CH_2, C-5), 28.3 (CH_3), 22.2 and 20.8 (CH_3), 14.5 and 13.8 (CH_3, OCH_2CH_3); MS: *m/z* (%) 274 (M^+, 38), 259 (23), 213 (100), 201 (17), 186 (20), 185 (56), 149 (35), 128 (25), 122 (30), 115 (25), 91 (25); HRMS: *m/z* Calcd. for $C_{17}H_{22}O_3Na$ (M+Na): 297.1467; Found: 297.1465.

Ethyl *cis*-1,2-dimethyl-2-(2-methoxy-5-methylphenyl)cyclopent-3-enecarboxylate 43. To a cold (0°C), magnetically stirred solution of diisopropylamine (0.20 mL, 1.37 mmole) in anhydrous THF (2 mL) was slowly added a solution of ^{n}BuLi (2.5 *M* in hexane, 0.5 mL, 1.26 mmole) and stirred for 10 min. To LDA thus formed was added dropwise a solution of a diastereomeric mixture of the ester **42** (150 mg, 0.55 mmole) in anhydrous THF (2 mL) and HMPA (2 mL) and stirred for 40 min at the same temperature. Methyl iodide (0.1 mL, 1.65 mmole) was added to the reaction mixture and stirred for 7 hr. Work-up followed by purification on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the ester **43** (121 mg, 77%) containing a small amount of other stereoisomer as oil. IR (neat): 2934, 1724, 1500, 1462, 1250, 1178, 1031, 807, 735 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 6.94 (1 H, s, H-6'), 6.87 (1 H, d, *J* = 8.1 Hz, H-4'), 6.65 (1 H, d, *J* = 8.1 Hz, H-3'), 5.80 (1 H, d, *J* = 5.8 Hz) and 5.72 (1 H, d, *J* = 5.8 Hz) [*olefinic*-H], 3.74 (3 H, s, OCH_3), 3.37-3.29 (2 H, m, OC*H*$_2CH_3$), 3.00 and 2.26 (2 H, d, *J* = 16.5 Hz, H-5), 2.21 (3 H, s, $ArCH_3$), 1.49 (3 H, s) and 1.47 (3 H, s) [2 × *tert*-CH_3], 0.77 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 176.2 (C, OC=O), 156.7 (C, C-2'), 139.4 (CH, C-3), 133.6 (C), 129.8 (CH), 128.4 (C), 127.8 (CH), 126.8 (CH), 111.1 (CH, C-3'), 59.5 (CH_2, O*C*H_2CH_3), 58.9 (C), 55.5 (C), 54.9 (CH_3, OCH_3), 46.4 (CH_2, C-5), 23.4 (CH_3), 21.5 (CH_3), 20.7 (CH_3), 13.7 (CH_3, OCH_2CH_3); MS: *m/z* (%) 288 (M^+, 31), 215 (44), 199 (19), 187 (45), 186 (58), 174 (48), 159 (37), 149 (100), 145 (35), 139 (70), 115 (39), 111 (39); HRMS: *m/z* Calcd. for $C_{18}H_{24}O_3Na$ (M+Na): 311.1623; Found: 311.1646.

Ethyl *cis*-1,2-dimethyl-2-(2-methoxy-5-methylphenyl)cyclopentanecarboxylate 44. Catalytic hydrogenation of the cyclopentenecarboxylate **43** (40 mg, 0.14 mmole) with 10% Pd-C (7 mg) in ethanol (4 mL) for 1 hr furnished the ester **44** (37 mg, 93%) as oil. IR (neat): 2964, 2875, 1722, 1499, 1461, 1380, 1280, 1248, 1173, 1137, 1103, 1030, 805 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 6.99 (1 H, s, H-6'), 6.86 (1 H, d, *J* = 8.1 Hz, H-4'), 6.63 (1 H, d, *J* = 8.1 Hz, H-3'), 3.70 (3 H, s, OCH_3), 3.65-3.50 (2 H, m, OC*H*$_2CH_3$), 2.59 (1 H, q, *J* = 9.9 Hz), 2.30-2.15 (1 H, m), 2.24 (3 H, s, $ArCH_3$), 1.90-1.60 (4 H, m), 1.44 (3 H, s) and 1.32 (3 H, s) [2 × *tert*-CH_3], 0.79 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 177.4 (C, OC=O), 155.9 (C, C-2'), 136.2 (C), 128.6 (C), 128.3 (CH), 127.0 (CH), 110.9 (CH, C-3'), 59.5 (CH_2, O*C*H_2CH_3), 55.5 (C), 54.6 (CH_3, OCH_3), 52.2 (C), 41.2 (CH_2), 40.6 (CH_2), 24.0 (CH_3), 22.1 (CH_2, C-4), 21.9 (CH_3), 20.9 (CH_3), 13.7 (CH_3, OCH_2CH_3); MS: *m/z* (%) 290 (M^+, 70), 216 (49), 201 (18), 188 (23), 176 (100), 173 (59), 161 (70), 147 (80), 135 (23), 119 (30), 115 (90), 105 (36); HRMS: *m/z* Calcd. for $C_{18}H_{26}O_3Na$ (M+Na): 313.1780; Found: 313.1793.

3a,8,9b-Trimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*c*]chromen-4-one (11-*epi*-herbertenolide 9a). A solution of BBr_3 (1 *M* in CH_2Cl_2, 0.52 mL, 0.52 mmole) was added dropwise to a magnetically stirred solution of the ester **44** (37 mg, 0.13 mmole) in

CH_2Cl_2 (3 mL) at 0°C and the reaction mixture was stirred for 2 hr at RT. It was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×3 mL). The combined CH_2Cl_2 extract was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished *epi*-herbertenolide **9a** (25 mg, 85%) as oil. IR (neat): 2968, 2875, 1755, 1494, 1221, 1136, 1118, 1080, 1048, 817 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 7.05 (1 H, s, H-9), 6.97 (1 H, d, *J* = 8.4 Hz, H-7), 6.85 (1 H, d, *J* = 8.4 Hz, H-6), 2.32 (3 H, s, $ArCH_3$), 2.37-1.41 (6 H, m), 1.25 (3 H, s) and 1.20 (3 H, s) [2 × *tert*-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 172.8 (C, OC=O), 147.8 (C, C-4a), 133.7 (C, C-8), 128.7 (CH), 128.5 (C, C-9a), 126.8 (CH), 116.6 (CH, C-5), 51.0 (C, C-3a), 47.7 (C, C-9b), 39.0 (CH_2), 35.7 (CH_2), 21.7 (CH_3), 21.1 (CH_3), 20.1 (CH_2, C-2), 18.1 (CH_3); MS: *m/z* (%) 230 (M^+, 93), 215 (20), 202 (16), 188 (37), 187 (100), 173 (20), 160 (50), 159 (89), 149 (28), 145 (40), 115 (33), 105 (26); HRMS: *m/z* Calcd. for $C_{15}H_{18}O_2Na$ (M+Na): 253.1204; Found: 253.1217.

2-(2-Hydroxymethyl-1, 2-dimethylcyclopentyl)-4-methylphenol (1,14-herbertenediol 12). Reduction of the 11-*epi*-herbertenolide **9a** (20 mg, 0.08 mmole) with LAH (6 mg, 0.16 mmole) in dry ether (4 mL) at –20°C for 2 hr and work-up as described for the alcohol **38**, followed by purification on a silica gel column using ethyl acetate-hexane (1:5) as eluent furnished 1,14-herbertenediol **12** (18.5 mg, 92%) as oil. IR (neat): 3352, 2960, 2878, 1464, 1231, 1026, 814 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 6.90 (1 H, s, H-3), 6.82 (1 H, d, *J* = 7.8 Hz, H-5), 6.67 (1 H, d, *J* = 7.8 Hz, H-6), 3.26 (2 H, s, C*H*$_2$OH), 2.43-2.19 (1 H, m), 2.25 (3 H, s, Ar-CH_3), 2.03-1.88 (3 H, m), 1.46-1.15 (4 H, m), 1.55 (3 H, s) and 1.23 (3 H, s) [2 × *tert*-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 153.0 (C, C-1), 132.7 (C), 129.9 (CH), 128.9 (C), 128.0 (CH), 117.4 (CH, C-6), 70.6 (CH_2, CH_2OH), 51.0 (C), 49.1 (C), 42.5 (CH_2), 36.2 (CH_2), 24.2 (CH_3), 21.3 (CH_2, C-4'), 21.2 (CH_3), 20.8 (CH_3); MS: *m/z* (%) 234 (M^+, 22), 201 (18), 173 (12), 161 (23), 159 (22), 135 (100), 121 (21), 105 (13); HRMS: *m/z* Calcd. for $C_{15}H_{22}O_2Na$ (M+Na): 257.1517; Found: 257.1517.

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