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 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, isomeric to herbertane, was known since 1958, herbertane family of sesquiterpenes was reported only in nineteen eighties. Isolation of the first member of the family, herbertene, 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 herbacetaceae. Subsequently few other phenolic herbertanes were isolated from a variety of Herbertus sources. In 2000, Asawaka and co-workers reported the isolation of seven herbertenes herberteneacetal, herbertene-1,14-diol, herbertene-1,15-diol, herbertene-1,13-diol, herbenenones A and B and 12-methoxyherbertenediol from the ether and ethyl acetate extracts of the Japanese liverwort Herbertus sakuraii. Recently, Becker et al. reported the isolation of two new herbertanes from a non-herbertus source, γ-herbertenol and herbertene-1,12-diol along with α-herbertenol from the liverwort Tylimanthus renifolius (Chart 1).

The herbertane sesquiterpenes, mainly the phenolic herbertanes, have been shown to possess interesting biological properties such as growth inhibiting activity. Some of the phenolic herbertanes were found to be strong inhibitors of the plant pathogenic fungi, Botrytis cinerea, Rhizoctonia solani and Pythium debaryanum. 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. A combination of Claisen rearrangement and ring-closing metathesis (RCM) reactions based methodology has now been developed for the synthesis of phenolic herbertanes. Herein is described the details of the total synthesis of herbertene-1,14-diol and 11-epi-herbertenolide.

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

To test the feasibility of the hypothesis (Scheme II), the allyl alcohol was chosen as a starting material, which was prepared from cyclohexanone in two steps, Horner-Wadsworth-Emmons
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 \(\gamma,\delta\)-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\(^\text{10}\) 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*.

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. 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. 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 cyclopentene carboxylate 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 1H and 13C 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 1H and 13C NMR, with those of the authentic sample prepared earlier.

Since the primary alcohol 36 has already been converted 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](image-url)

**Scheme III** — (a) MeC(OEt)3, EtCO2H, Δ; (b) LDA, THF; CH2=CHCH2Br; (c) PhCH=RPcy3Cl2, CH2Cl2; (d) LDA, THF, HMPA; Mel; (e) H2, 10% Pd/C, EtOH; (f) LAH, Et2O.
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 CH₂Cl₂ 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 cyclopentene-carboxylate 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 BBr₃ 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 96% 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 ¹³C 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 with that of the natural

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**Scheme IV** — (a) (EtO)₂P(O)CH₂CO₂Et, NaH, THF; (b) LAH, Et₂O; (c) MeC(OEt)₃, EtCO₂H, Δ; (d) LDA, THF; CH₂=CHCH₂Br; (e) PhCH=Ru(PCy₃)₂Cl₂, CH₂Cl₂; (f) LDA, THF, HMPA; MeI; (g) H₂, 10% Pd/C, EtOH; (h) BBr₃, CH₂Cl₂.
product and $^{13}$C NMR spectral data$^7$ 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. $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were recorded on JNM $\lambda$-300 spectrometer. The chemical shifts ($\delta$ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for $^1$H) 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 ($7.5 \times 2.5$ and $7.5 \times 5.0$ 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$_2$O$_5$.

**Ethyl 2-(1-vinylcyclohexyl)pent-4-enoate 26**. To a cold (–70°C), magnetically stirred solution of diisopropylamine (0.33 mL, 2.30 mmol) in anhydrous THF (2 mL) was slowly added a solution of “BuLi (2.5 M, 0.84 mL, 2.1 mmol) and stirred for 10 min. To LDA thus formed was added dropwise a solution of the ester$^7$ 25 (180 mg, 0.92 mmol) 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 mmol) 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$_2$SO$_4$). 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, 1733, 1617, 1450, 1371, 1345, 1228, 1176, 1156, 1000, 915, 855 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 5.70-5.55 (2 H, m, 2 × CH=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, OCH$_2$CH$_2$), 2.40-2.10 (3 H, m), 1.85-1.30 (10 H, m), 1.24 (3 H, t, $J = 6.9$ Hz, OCH$_2$CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 173.6 (C, OC=O), 142.6 (CH, C-1’), 136.2 (CH, C-4), 116.4 (CH$_2$), 115.4 (CH$_3$), 59.6 (CH$_2$, OCH$_2$CH$_2$), 55.1 (CH, C-2), 42.0 (C, C-1’), 33.6 (CH$_3$), 33.1 (CH$_2$), 31.6 (CH$_3$), 26.3 (CH$_2$), 22.1 (2 C, CH$_2$), 14.5 (CH$_3$, OCH$_2$CH$_2$); 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$_2$Na (M+Na): 259.1674; Found: 259.1681.

**Ethyl spiro[4.5]decap-3-ene-1-carboxylate 27**. To a magnetically stirred solution of the ester 26 (30 mg, 0.13 mmol) in anhydrous CH$_2$Cl$_2$ (8 mL) was added a solution of Grubbs’ first generation catalyst (6.4 mg, 6 mol%) in anhydrous CH$_2$Cl$_2$ (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 (1:20) 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$^{-1}$; $^1$H NMR (CDCl$_3$ + CCl$_4$): $\delta$ 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, OCH$_2$CH$_2$), 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$_2$CH$_2$); $^{13}$C NMR (CDCl$_3$ + CCl$_4$): $\delta$ 173.7 (C, OC=O), 135.7 (CH, C-4), 127.7 (CH, C-3), 59.9 (CH$_3$, OCH$_2$CH$_2$), 54.5 (CH, C-1), 52.3 (C, C-5), 38.2...
(CH₂), 34.0 (CH₂), 33.5 (CH₂), 26.3 (CH₂), 24.1
(CH₂), 23.1 (CH₂), 14.6 (CH₃, OCH₂CH₃). 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 C₁₃H₂₀O₂Na (M+Na):
231.1361; Found: 231.1357.

**Ethyl 3-methyl-3-(4-methylphenyl)pent-4-enoate 31.** A solution of the allyl alcohol⁴⁵ 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 3 hr. The reaction mixture
was cooled, diluted with ether (3 × 4 mL), washed
with 0.5 N aqueous NaHCO₃ solution and brine, and dried
(anhyd. Na₂SO₄). Evaporation of the solvent and
purification on a silica gel column using ethyl acetate-
hexane (1:10) as eluent furnished the pentenoate
(1.14 g, 80%) as oil. IR (neat): 3076, 2976, 2926, 1734,
1637, 1511, 1454, 1412, 1369, 1322, 1227, 1159,
1116, 1070, 1034, 916, 814, 724 cm⁻¹; ¹H NMR
(CDC₁₃ + CCl₄): 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, H₄), 5.10 (1 H, d, J = 10.8 Hz) and
5.03 (1 H, d, J = 17.1 Hz) [H⁻⁵]; 13C NMR
(CDC₁₃ + CCL₄): δ 170.9 (C, OC=O), 145.9 (CH, C=
C₄), 143.1 (C, C=1’), 135.5 (C, C=4’), 128.8 (2 C, CH),
126.3 (2 C, CH), 112.2 (CH₃, C-5), 59.9 (CH₃,
OCH₂CH₃), 45.8 (CH₂, C-2), 43.2 (C, C-3), 25.7
(CH₃, tert-CH₃), 21.0 (CH₃, ArCH₃), 14.3 (CH₃,
OCH₂CH₃).

**Ethyl 2-allyl-3-methyl-3-(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 CH₂Cl₂ (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, 871, 761, 721, 699 cm⁻¹; ¹H NMR
(CDC₁₃ + CCl₄, 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, OCH₂CH₃), 3.03 (1
H, j, J = 7.8 Hz), 3.00-2.85 (1 H, m), 2.62-2.40 (1 H,
m), 2.28 (3 H, s, ArCH₃), 1.69 (3 H, s, tert-CH₃), 0.92
(3 H, t, J = 7.2 Hz, OCH₂CH₃); ¹³C NMR (CDC₁₃ +
CCl₄, 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 (CH₂, OCH₂CH₃), 56.0 (CH, C=1’), 55.7 (C,
C=3), 34.7 (CH₂, C=5), 28.0 (CH₃, tert-CH₃), 21.0
(CH₃, ArCH₃), 14.0 (CH₃, OCH₂CH₃); 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 C₁₅H₂₀O₂Na (M+Na): 267.1361;
Found: 267.1373.

**Ethyl cis-1, 2-dimethyl-2-(4-methylphenyl)cyclo-
pent-3-ene-carboxylate 34.** To a cold (0°C), magnetically
stirred solution of disopropylamine (0.07 mL,
0.5 mmoles) in anhydrous THF (2 mL) was slowly
added a solution of "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 mmole) 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 mmole) 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; ¹H NMR (CDCl₃ + CCl₄): 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 = 7.2 Hz, OCH₂), 0.90 (3 H, t, J = 7.2 Hz, CH₃), 0.86 (3 H, t, J = 7.2 Hz, OCH₂CH₃), 0.32 (3 H, s) and 1.32 (3 H, s) [2 × tert-CH₃]; ¹³C NMR (CDCl₃ + CCl₄): 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), 59.7 (CH₂, OCH₂CH₃), 57.0 (C), 56.8 (C), 43.2 (CH₂, C-5), 22.7 (CH₃), 21.7 (CH₃, ArCH₃), 13.8 (CH₃, OCH₂CH₃); 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 C₁₇H₂₂O₂Na (M+Na): 281.1517; Found: 281.1534.

Ethyl cis-1,2-dimethyl-2-(4-methylphenyl)cyclopentanecarboxylate 35. To a solution of the cyclopentanecarboxylate 34 (25 mg, 0.1 mmole) in ethanol (3 mL) was added 10% Pd-C (5 mg) and the reaction mixture was stirred for 30 min at RT. A solution of the acetophenone (2.56 mL, 12.8 mmoles) was added dropwise and the reaction mixture was stirred for 30 min at the same temperature. The reaction was then quenched by careful addition of 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. Na₂SO₄). 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; ¹H NMR (CDCl₃ + CCl₄): 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, CH₂), 2.60-2.40 (1 H, m), 2.31 (3 H, s, OCH₂CH₃), 1.90-1.40 (6 H, m), 1.30 (3 H, s) and 1.11 (3 H, s) [2 × tert-CH₃]; ¹³C NMR (CDCl₃ + CCl₄): δ 143.4 (C, C-1'), 135.3 (C, C-4'), 128.9 (2 C, CH), 126.7 (2 C, CH), 69.4 (CH₂, CH₂OH), 49.6 (C) and 49.3 (C) [C-1 and C-2], 37.6 (CH₂) and 35.1 (CH₂) [C-3 and C-5], 25.3 (CH₃), 20.9 (CH₃), 20.4 (CH₃, C-4), 19.6 (CH₃); 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 C₁₅H₂₂ONa (M+Na): 241.1568; Found: 241.1580.

Ethyl E-3-(2-methoxy-5-methylphenyl)but-2-enolate 39. A suspension of sodium hydride (440 mg, 60% dispersion in oil, 11.0 mmole, 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 NH₄Cl solution and extracted with ether (3 × 4 mL). The combined ether extract was washed with brine and dried (anhyd. Na₂SO₄),
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 (CDCl₃ + CCl₄): δ 7.02 (1 H, d, J = 8.1 Hz, H-4'), 6.90 (1 H, d, J = 1.8 Hz, 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, OCH₂CH₃), 3.78 (3 H, s, ArOCH₃), 2.45 (3 H, s, OCH₂CH₃), 2.28 (3 H, s, ArCH₃), 1.30 (3 H, t, J = 6.9 Hz, OCH₂CH₃); ¹³C NMR (CDCl₃ + CCl₄): δ 159 (C, C-2'), 154.5 (C, C-2'), 138.3 and 138.2 (CH, C-2''), 133.5 and 133.4 (C), 126.5 (CH₂, C-2), 126.9 (CH₂, C-2'), 119.2 (CH, C-2), 111.0 (CH, C-3'), 59.5 (CH₂, OCH₂CH₃), 55.5 (CH₃, OCH₃), 45.9 (CH₃, ArCH₃), 19.9 (CH₃, C-4), 14.5 (CH₃, OCH₂CH₃); MS: m/z 380 (M+, 10), 262 (M⁺Na): 378.1467; Found: 378.1465.

**E-3-(2-Methoxy-5-methylphenyl)but-2-en-1-ol 38.** Reduction of the cinnamate 39 (800 mg, 3.42 mmol) in dry ether (8 mL) with LAH (65 mg, 1.71 mmol) 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 allylated ester 40 (600 mg, 2.30 mmol) 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 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 (CDCl₃ + CCl₄): 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) and 4.95 (1 H, d, J = 17.7 Hz) [CD=CH₂]; 3.91 (2 H, q, J = 6.9 Hz, OCH₂CH₃), 3.78 (3 H, s, OCH₃), 3.06 and 2.84 (2 H, 2 × d, J = 13.8 Hz, H-2), 2.26 (3 H, s, ArCH₃), 1.55 (3 H, s, tert-CH₃), 1.03 (3 H, t, J = 6.9 Hz, OCH₂CH₃); ¹³C NMR (CDCl₃ + CCl₄): 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 (CH₂, C-5), 111.3 (CH, C-3'), 59.5 (CH₂, OCH₂CH₃), 55.2 (CH₃, OCH₃), 43.8 (CH₂, C-2'), 42.8 (C, C-3), 24.8 (CH₃, tert-CH₃), 20.9 (CH₃, ArCH₃), 14.2 (CH₃, OCH₂CH₃); 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 C₁₆H₂₂O₃Na (M+Na): 285.1467; Found: 285.1465.
Ethyl 2-methyl-2-(2-methoxy-5-methylphenyl)cyclopent-3-ene-carboxylate 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 CH2Cl2 (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, 1253, 1182, 1155, 1070, 1053, 806, 732 cm⁻¹; 1H NMR (CDCl3 + CCl4, 400 MHz): 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]; 13C NMR (CDCl3 + CCl4): δ 174.4 and 174.1 (C, OC=O), 155.6 (C, C-2'), 136.2 (C), 128.6 (C), 128.3 (C), 128.4 (C), 127.8 (CH), 126.8 (CH), 111.1 (CH, C-3'), 59.5 (CH2, OCH2CH3), 58.9 (C), 55.5 (C), 54.9 (CH3, OCH3), 46.4 (CH2, C-5), 23.4 (CH3), 21.5 (CH3), 20.7 (CH3), 13.7 (CH3, OCH2CH3); 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 C18H22O3Na (M+Na): 313.1623; Found: 313.1646.

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, 1030, 805 cm⁻¹; 1H NMR (CDCl3 + CCl4, 400 MHz): δ 6.69 (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), 5.80 (1 H, d, J = 5.8 Hz) and 5.72 (1 H, d, J = 5.8 Hz) [olefinic-H]; 13C NMR (CDCl3 + CCl4): 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 (CH2, OCH2CH3), 58.9 (C), 55.5 (C), 54.9 (CH3, OCH3), 46.4 (CH2, C-5), 23.4 (CH3), 21.5 (CH3), 20.7 (CH3), 13.7 (CH3, OCH2CH3); 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 C18H22O3Na (M+Na): 311.1623; Found: 311.1646.
CH₂Cl₂ (3 mL) at 0°C and the reaction mixture was stirred for 2 hr at RT. It was then quenched with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂ (3×3 mL). The combined CH₂Cl₂ extract was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished 1,14-herbertenediol (25 mg, 85%) as oil. IR (neat): 2968, 2875, 1755, 1494, 1221, 1136, 1118, 1080, 1048, 817 cm⁻¹; ¹H NMR (CDCl₃ + CCl₄): 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, Ar-CH₃), 2.37-1.41 (6 H, m), 1.25 (3 H, s, Ar-CH₂), 1.13 (3 H, s). MS: m/z 257.1517; Found: 257.1517.

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References