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A simple, ring-closing metathesis reaction based approach to (±)-1,14-herbertenediol and (±)-11-*epi*-herbertenolide

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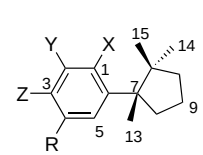
Abstract—A total synthesis of 1,14-herbertenediol via 11-*epi*-herbertenolide, and a formal total synthesis of tochuinyl acetate and dihydrotochuinyl acetate, employing a ring-closing metathesis reaction based methodology, are described.

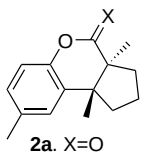
The herbertane group of sesquiterpenes are considered as chemical markers for the liverworts belonging to the genus *Herbertus*.[1] Isolation of the first members of the herbertane group **1a**–**e** and **2a** from *Herberta adunca* was reported earlier by Matsuo and co-workers.[2] Recently,[1] Asakawa et al. reported the isolation of seven new herbertanes **2b** and **3**–**7** along with the dimeric herbertanes, mastigophorenes, from the Japanese liverwort *Herbertus sakuraii*. The phenolic herbertanes, e.g. **1b**–**d**, are shown to possess interesting biological activity such as growth inhibiting activity[2] and antilipid peroxidation activity.[3] Despite their interesting biological properties, until recently the phenolic herbertanes have received relatively little attention from synthetic chemists.[4] Since its isolation, there has been only one report[5] on the synthesis of herbertenolide **2a**. Recently, Fukuyama and co-workers[4g] reported the synthesis of 11-*epi*-herbertenolide **8** and 1,14-herbertenediol **4**, employing an intramolecular Heck reaction, during their synthesis of herbertenediol **1d** en route to the dimeric herbertanes, mastigophorenes. Herein, we wish to report a very simple, ring-closing metathesis (RCM)[6] based approach to 1,14-herbertenediol **4** via 11-*epi*-herbertenolide **8** along with a formal total synthesis of the marine sesquiterpenes tochuinyl acetate and dihydrotochuinyl acetate **9** and **10**.

It was conceived that a γ,γ-disubstituted allyl alcohol **11** could be conveniently transformed into the 2,2-disubstituted cyclopent-3-enecarboxylate **12** employing a three-step strategy; namely a Claisen rearrangement, allylation and RCM, as depicted in Scheme 1. To test the feasibility of this protocol, the readily available allyl alcohol **13** was chosen as the starting material. Thus, orthoester Claisen rearrangement of the allyl alcohol **13** with triethyl orthoacetate and propionic acid furnished the γ,δ-unsaturated ester **14**.[7] Alkylation of the ester **14** with lithium diisopropylamide (LDA) and allyl bromide generated the RCM precursor, diene ester **15**. RCM reaction of the diene ester **15** with 6 mol% of Grubbs' catalyst in methylene chloride at room temperature

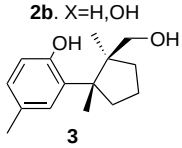


1a-e

a.R=Me; X=Y=Z=H
b.R=Me; X=OH; Y=Z=H
c.R=Me; X=Y=H; Z=OH
d.R=Me; X=Y=OH; Z=H
e.R=CHO; X=OH; Y=Z=H



2a. X=O
2b. X=H,OH



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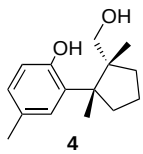

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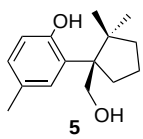

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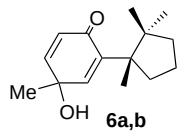
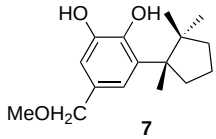


6a,b



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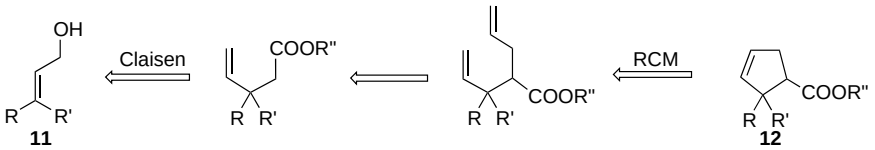
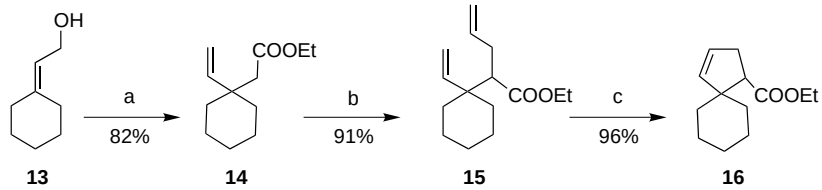


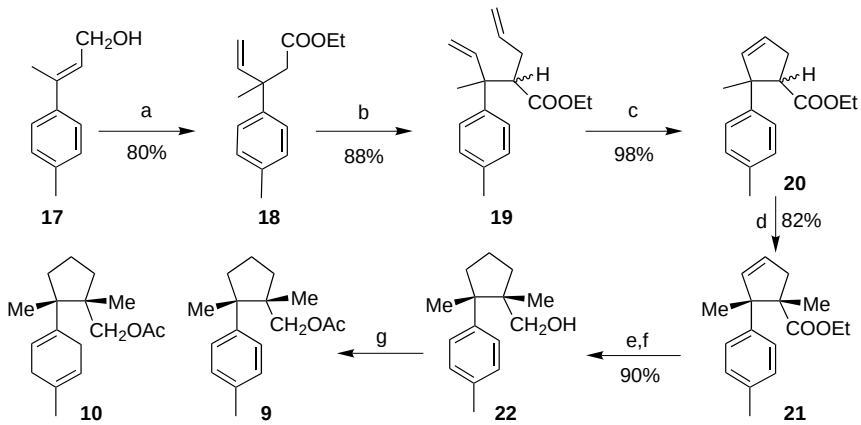
Scheme 1.

cleanly furnished the spiro compound **16**[†] in almost quantitative yield, highlighting the potential of the strategy (Scheme 2).

To demonstrate the applicability of the present strategy in natural product synthesis, attention was initially focused on the formal total synthesis of tochuinyl acetate and dihydrotochuinyl acetate, **9** and **10**, starting from the readily available[8] dimethylcinnamyl alcohol **17** (Scheme 3). The cuparane based marine sesquiterpenes **9** and **10** were isolated from the dendronotid nudibranch *Tochuina tetraquetra* and also from its feed the

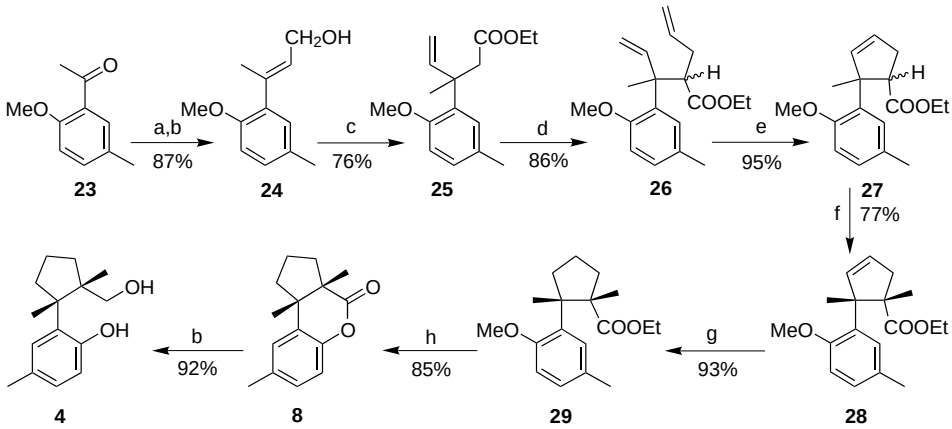


Scheme 2. *Reagents and conditions*: (a) $MeC(OEt)_3$, EtCOOH, 180°C, 48 h; (b) LDA, THF, −70°C→rt, allyl bromide, 4 h; (c) 6 mol% Grubbs' catalyst, CH_2Cl_2, rt, 5 h.



Scheme 3. *Reagents and conditions*: (a) $MeC(OEt)_3$, EtCOOH, 180°C, 48 h; (b) LDA, THF, −70°C→rt, allyl bromide, 4 h; (c) 6 mol% Grubbs' catalyst, CH_2Cl_2, rt, 4 h; (d) LDA, THF–HMPA, 0°C→rt, MeI, 8 h; (e) 10% Pd/C, H_2 (1 atm), EtOH, rt, 1 h; (f) $LiAlH_4$, Et_2O, rt, 2 h; (g) Ref. 8.

[†] All the compounds exhibited spectral data consistent with their structures. Selected spectral data for the spiroester **16**: IR (neat): ν_{max}/cm^{-1} 1733; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.91 (1H, m of d, J=5.4 Hz), 5.65 (1H, d of t, J=5.4 and 2 Hz), 4.15–4.05 (2H, m), 2.78 (1H, m of dd, J=15.6 and 8.1 Hz), 2.66 (1H, t, J=8.1 Hz), 2.42 (1H, m of dd, J=15.6 and 8.1 Hz), 1.80–1.05 (10H, m), 1.30 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 173.7 (C), 135.8 (CH), 127.8 (CH), 59.9 (CH_2), 54.6 (CH), 52.3 (C), 38.2 (CH_2), 34.0 (CH_2), 33.5 (CH_2), 26.3 (CH_2), 24.1 (CH_2), 23.2 (CH_2), 14.6 (CH_3). For the alcohol **22**: IR (neat): ν_{max}/cm^{-1} 3385; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.25 (2H, d, J=8.4 Hz), 7.07 (2H, d, J=8.4 Hz), 3.07 and 3.02 (2H, AB quartet, J=11.4 Hz), 2.55–2.40 (1H, m), 2.31 (3H, s), 1.90–1.40 (5H, m), 1.30 (3H, s), 1.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 143.4 (C), 135.3 (C), 128.9 (2 C, CH), 126.7 (2 C, CH), 69.4 (CH_2), 49.6 (C), 49.3 (C), 37.6 (CH_2), 35.1 (CH_2), 25.3 (CH_3), 21.0 (CH_3), 20.4 (CH_2), 19.6 (CH_3). For the ester **28**: IR (neat): ν_{max}/cm^{-1} 1724, 1500, 1250; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 (1H, s), 6.87 (1H, d, J=8.1 Hz), 6.63 (1H, d, J=8.1 Hz), 5.79 (1H, d, J=6 Hz), 5.73 (1H, d, J=6 Hz), 3.74 (3H, s), 3.40–3.25 (2H, m), 3.01 (1H, d, J=16.5 Hz), 2.25 (1H, d, J=16.5 Hz), 2.21 (3H, s), 1.49 (3H, s), 1.47 (3H, s), 0.77 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 176.2 (C), 156.8 (C), 139.4 (CH), 133.6 (C), 129.8 (CH), 128.4 (C), 127.8 (CH), 126.8 (CH), 111.1 (CH), 59.5 (CH_2), 58.9 (C), 55.5 (C), 54.9 (CH_3), 46.4 (CH_2), 23.4 (CH_3), 21.5 (CH_3), 20.7 (CH_3), 13.7 (CH_3). For *epi*-herbertenolide **8**:[4g] IR (neat): ν_{max}/cm^{-1} 1755; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.05 (1H, s), 6.97 (1H, d, J=8.5 Hz), 6.85 (1H, d, J=8.5 Hz), 2.32 (3H, s), 2.45–2.30 (1H, m), 2.15–1.60 (5H, s), 1.25 (3H, s), 1.20 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 172.8 (C), 147.8 (C), 133.7 (C), 128.7 (CH), 128.5 (C), 126.8 (CH), 116.6 (CH), 51.0 (C), 47.7 (C), 39.0 (CH_2), 35.7 (CH_2), 21.8 (CH_3), 21.2 (CH_3), 20.1 (CH_2), 18.1 (CH_3). For 1,14-herbertenediol **4**:[1,4g] IR (neat): ν_{max}/cm^{-1} 3350; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.90 (1H, s), 6.84 (1H, d, J=7.8 Hz), 6.67 (1H, d, J=7.8 Hz), 3.26 (2H, s), 2.55–2.25 (1H, m), 2.25 (3H, s), 2.00–1.70 (3H, m), 1.55 (3H, s), 1.50–1.15 (4H, m), 1.23 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 153.1 (C), 132.7 (C), 129.9 (CH), 128.9 (C), 128.1 (CH), 117.4 (CH), 70.5 (CH_2), 51.1 (C), 49.1 (C), 42.5 (CH_2), 36.2 (CH_2), 24.2 (CH_3), 21.3 (CH_2), 21.2 (CH_3), 20.8 (CH_3).



Scheme 4. *Reagents and conditions*: (a) NaH, $(EtO)_2P(O)CH_2COOEt$, THF, rt, 16 h; (b) $LiAlH_4$, Et_2O, −70°C→rt, 2 h; (c) $MeC(OEt)_3$, EtCOOH, 180°C, 48 h; (d) LDA, THF, −70°C→rt, allyl bromide, 4 h; (e) 6 mol% Grubbs' catalyst, CH_2Cl_2, rt, 4 h; (f) LDA, THF–HMPA, 0°C→rt, MeI, 8 h; (g) 10% Pd/C, H_2 (1 atm), EtOH, rt, 1 h; (h) BBr_3, CH_2Cl_2, 0°C→rt, 2 h.

soft coral *Gersemia rubiformis*.[9] The presence of a cyclopentane ring with two stereogenic vicinal quaternary carbon atoms makes the acetates **9** and **10** interesting synthetic targets.[8] Thus, orthoester Claisen rearrangement of the cinnamyl alcohol **17** with triethyl orthoacetate and propionic acid furnished the pentenoate **18**, which on alkylation with LDA and allyl bromide furnished a 1:1 mixture of the diene **19**. Treatment of the diene **19** with 6 mol% of Grubbs' catalyst in methylene chloride at room temperature furnished a 1:1 diastereomeric mixture of the cyclopentenecarboxylate **20** in near quantitative yield. Alkylation with LDA and methyl iodide created the second quaternary carbon atom and transformed the ester **20** into the ester **21** in a highly stereoselective manner. Hydrogenation of the cyclopentene moiety using 10% Pd/C as the catalyst followed by reduction of the ester with lithium aluminium hydride (LAH) transformed the cyclopentenecarboxylate **21** into the primary alcohol **22**,† which exhibited spectroscopic data identical to those reported earlier.[8] Since the alcohol **22** has already been transformed[8] into tochuinyl acetate and dihydrotochuinyl acetate **9** and **10**, the present sequence constitutes a formal total synthesis of these marine sesquiterpenes.

After successfully accomplishing the formal total synthesis of the acetates **9** and **10**, attention was turned to the synthesis of 11-*epi*-herbertenolide **8** and 1,14-herbertenediol **4** (Scheme 4). To begin with 2-methoxy-5-methylacetophenone **23**, obtained in two steps from 4-methylphenyl acetate, was transformed into the cinnamyl alcohol **24** employing a Horner–Wadsworth–Emmons reaction, followed by regioselective reduction of the resultant cinnamate with LAH. The orthoester Claisen rearrangement of the alcohol **24** with triethyl orthoacetate and propionic acid in a sealed tube at 180°C furnished the ester **25** generating the first quaternary carbon atom. Alkylation of the ester **25** with LDA and allyl bromide generated a 1:1 epimeric mixture of the diene esters **26**. A RCM reaction with Grubbs' catalyst in methylene chloride at room temperature cleanly transformed the diene ester **26** into the cyclopentenecarboxylate **27**, in 95% yield. Alkylation of the cyclopentenecarboxylate **27** with LDA and methyl iodide, stereoselectively created the second quaternary center furnishing the ester **28**.† The stereostructure of the ester **28** was readily established from the upfield shift of the resonances [3.25–3.40 (2H, m) and 0.77 (3H, t)] due to the ethyl group of the ester in the ^1H NMR spectrum. The stereoselectivity of the alkylation reaction can be readily explained by the approach of the electrophile from the less hindered face (*anti* to the aryl group) of the intermediate enolate of ester **27**. Hydrogenation of the cyclopentene using 10% Pd/C as the catalyst transformed the ester **28** into the cyclopentanecarboxylate **29**. Treatment of the ester **29** with boron tribromide in methylene chloride furnished 11-*epi*-herbertenolide **8**,† via hydrolysis of the methyl ether and lactonization. Finally, reduction of the lactone **8** with LAH furnished (±)-1,14-herbertenediol **4**,† which exhibited ^1H and ^{13}C NMR spectroscopic data identical to those reported.[1,4g]

In conclusion, we have developed a very simple and efficient methodology based on the Claisen rearrangement and RCM reactions for the synthesis of herbertane sesquiterpenes 1,14-herbertenediol and 11-*epi*-herbertenolide, and the marine sesquiterpenes tochuinyl acetate and dihydrotochuinyl acetate.

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