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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2103–2106

Construction of spiro[5.5]undecanes containing a quaternary carbon atom adjacent to a spirocentre via an Ireland ester Claisen rearrangement and RCM reaction sequence. Total syntheses of (±)-α-chamigrene, (±)-β-chamigrene and (±)-laurencenone C

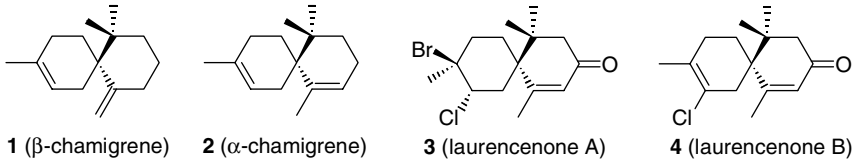
A. Srikrishna,* B. Vasantha Lakshmi and Manoj Mathews

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

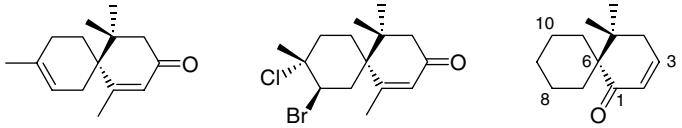
Received 13 December 2005; revised 18 January 2006; accepted 26 January 2006

Abstract—Starting from cyclohexanecarboxylic acid, a combination of an Ireland ester Claisen rearrangement and RCM reactions was exploited for an efficient construction of spiro[5.5]undecanes containing a quaternary carbon atom adjacent to the spirocentre and the methodology was extended to complete total syntheses of three chamigrenes.

Chamigrenes, which contain a spiro[5.5]undecane carbon framework incorporating two vicinal quaternary carbon atoms, are interesting sesquiterpene natural products isolated from plant and liverwort as well as marine sources. Chamigrenes appear to be metabolites from algae of the genus *Laurencia*, and most of these are characterised by the incorporation of chlorine and bromine atoms.[1] The isolation of β-chamigrene **1** was first reported by Ito et al.[2] in 1967 from the leaf oil of *Chamaecyparis taiwanensis*, whereas the isolation of α-chamigrene **2** was reported by Ohta and Hirose[3] from the oil of the fruits of *Schisandra chinensis* almost at the same time. Subsequently, a variety of chlorine and bromine-containing chamigrenes were isolated from marine sources. Over 120 chamigrenes were isolated from *Laurencia* species and from sea hares grazing on them. Thomson and co-workers reported[4] the isolation of laurencenones A–D **3**–**6** from *Laurencia obtusa*, which contain an enone functionality in the A-ring of chamigrenes. Several halogenated chamigrenes were shown to exhibit cytostatic activity and remarkable antimicrobial activity on both Gram-positive and Gram-negative bacteria.[5] Recently, Cueto and co-workers reported the isolation of several halogenated chamigrenes



1 (β-chamigrene) **2** (α-chamigrene) **3** (laurencenone A) **4** (laurencenone B)



5 (laurencenone C) **6** (laurencenone D) **7**

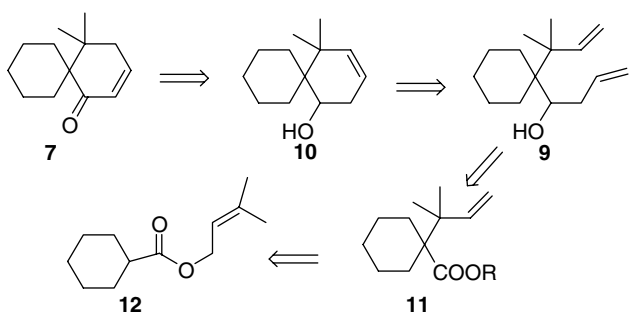
* Corresponding author. Tel.: +91 80 22932215; fax: +91 80 23600529; e-mail: ask@orgchem.iisc.ernet.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.131

from *Aplysia dactylomela* from the Canary Islands, some of which were shown to exhibit cytotoxic activity against HeLa and Hep-2 cancer cell lines.[6] Synthesis of chamigrenes is challenging owing to the presence of a quaternary carbon adjacent to the spirocentre.[5,7,8] Herein, we report an efficient methodology for the construction of spiro[5.5]undecanes containing a quaternary carbon atom adjacent to the spirocentre, and its application to syntheses of (±)-laurencenone C **5**, (±)-α-chamigrene **2** and (±)-β-chamigrene **1**.

First, as a model study, the synthesis of spiroenone **7**, containing two vicinal quaternary carbon atoms was investigated starting from cyclohexanecarboxylic acid **8**. It was conceived (Scheme 1) that a ring-closing metathesis (RCM) reaction[9] of diene **9** would generate the spiro system **10**, and that diene **9** could be generated from ester **11**. An Ireland ester Claisen rearrangement[10] of the dimethylallyl ester **12** was chosen for generation of ester **11** containing two vicinal quaternary carbon atoms.

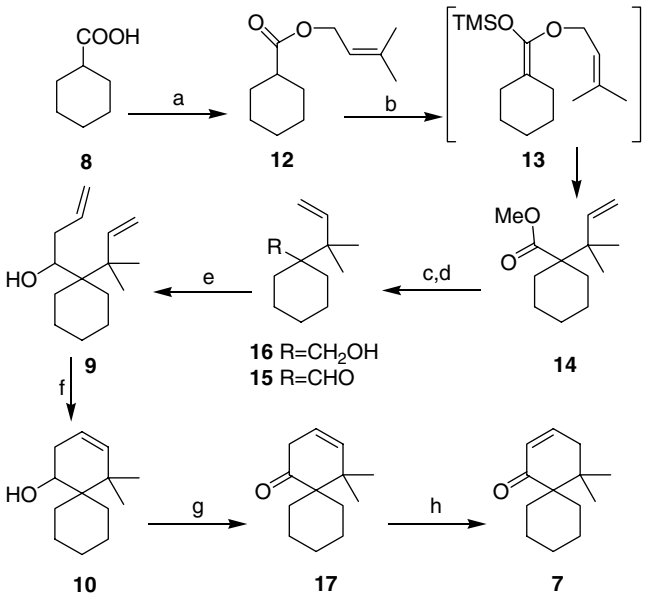
The synthetic sequence is depicted in Scheme 2. Coupling of the acid **8** with dimethylallyl alcohol in methylene chloride in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) produced the dimethylallyl ester **12**. Ireland–Claisen rearrangement of ester **12** was explored via the corresponding trimethylsilyl (TMS) enol ether **13**. Thus, generation of the TMS enol ether **13** of ester **12** with LDA, trimethylsilyl chloride and triethylamine in THF at −70 °C followed by refluxing the reaction mixture for 3 h resulted in the Ireland ester Claisen rearrangement. Hydrolysis of the reaction mixture with dilute hydrochloric acid followed by esterification with ethereal diazomethane furnished ester **14**. Ester **14** was then converted into aldehyde **15** by a two-step protocol, involving reduction with lithium aluminium hydride (LAH) in refluxing THF, followed by oxidation of the resultant primary alcohol **16** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride. Coupling of aldehyde **15** with allyl bromide under Barbier conditions generated the hydroxydiene **9**. RCM reaction of the dienol **9** with Grubbs' first generation catalyst furnished the spiro system **10** in an efficient manner. Oxidation of the alcohol **10** with PCC followed by isomerisation of the resultant β,γ-unsaturated enone **17** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnished spiroenone **7**, whose structure was established from its spectral data.[†]



Scheme 1.

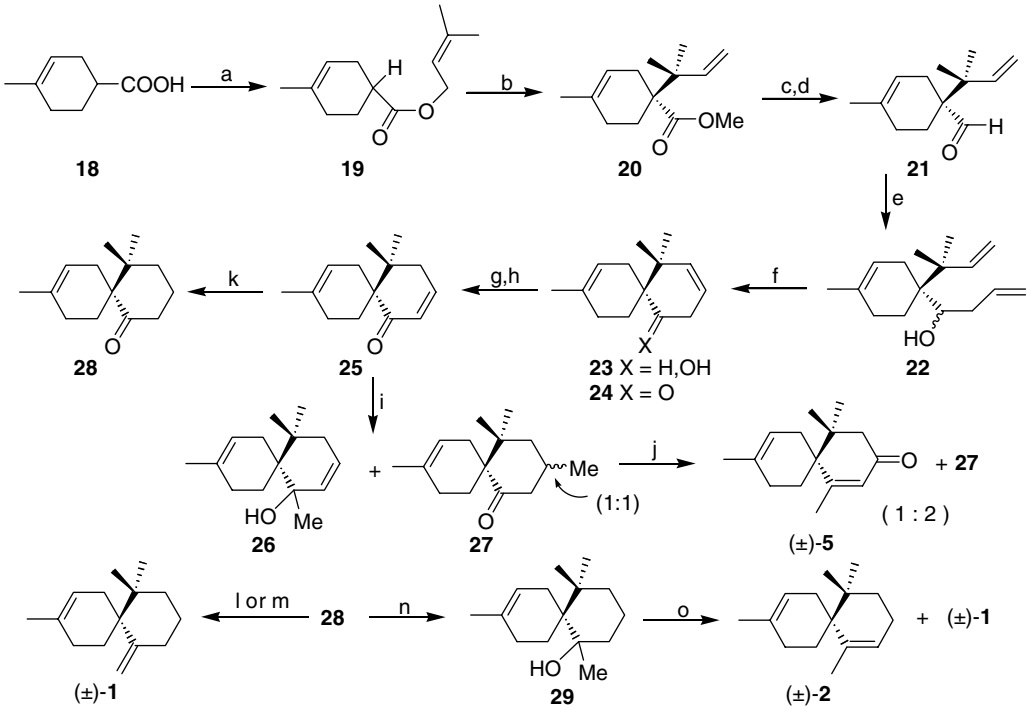
After demonstrating the feasibility of the strategy, it was extended to chamigrenes starting from the readily available[11] isoprene–acrylic acid Diels–Alder adduct **18** (Scheme 3). Accordingly, reaction of the acid **18** with dimethylallyl alcohol and DCC in the presence of a catalytic amount of DMAP furnished the dimethyl allyl ester **19** in 95% yield.[†] Generation of the TMS enol ether of ester **19** with LDA, trimethylsilyl chloride and triethylamine in THF at −70 °C followed by refluxing the reaction mixture for 3 h resulted in the Ireland ester Claisen rearrangement. Hydrolysis of the reaction mixture with dilute hydrochloric acid followed by esterification with ethereal diazomethane furnished ester **20** in 92% yield, whose structure was deduced from its spectral data.[†] Reduction of ester **20** with LAH followed by oxidation of the resultant primary alcohol with PCC and silica gel generated aldehyde **21** in 80% yield. A sonochemically accelerated Barbier reaction of aldehyde **21** with lithium and allyl bromide furnished the secondary alcohol **22** in 86% yield. Treatment of the hydroxydiene **22** with 10 mol % of Grubbs' first generation catalyst [$Cl_2Ru(PCy_3)_2$=CHPh] in methylene chloride for 5 h at room temperature cleanly furnished the spiro compound **23** in 90% yield. Oxidation of the secondary alcohol **23** with PCC and silica gel followed by isomerisation

[†] Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^{1}H and ^{13}C NMR and mass) consistent with their structures. Selected spectral data for spiroenone **7**: IR (neat): ν_{max}/cm^{-1}: 1676; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.54 (1H, td, *J* 10.2 and 4.2 Hz), 5.82 (1H, dt, *J* 10.2 and 3.9 Hz), 2.30–1.17 (12H, m), 0.96 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 206.1 (C), 143.4 (CH), 128.5 (CH), 52.0 (C), 39.8 (C), 39.5 (CH_2), 26.1 (2C, CH_2), 23.8 (2C, CH_3), 23.1 (3C, CH_2); HRMS: *m*/*z* calcd for $C_{13}H_{20}ONa$ (M+Na): 215.1412. Found: 215.1420. 3-Methylbut-2-enyl 4-methylcyclohex-3-ene-1-carboxylate **19**: IR (neat): ν_{max}/cm^{-1} 1735; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.40–5.25 (2H, m), 4.53 (2H, d, *J* 6.9 Hz), 2.50–2.37 (1H, m), 2.25–2.15 (2H, m), 2.05–1.90 (3H, m), 1.76 (3H, s), 1.71 (3H, s), 1.64 (3H, s), 1.75–1.60 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 175.3 (C), 138.1 (C), 133.4 (C), 119.6 (CH), 119.3 (CH), 61.0 (CH_2), 39.2 (CH), 29.4 (CH_2), 27.7 (CH_2), 25.8 (CH_3), 25.6 (CH_2), 23.6 (CH_3), 18.1 (CH_3); HRMS: *m*/*z* Calcd for $C_{13}H_{20}O_2Na$ (M+Na): 231.1361. Found: 231.1361. Methyl 1-(1,1-dimethylallyl)-4-methylcyclohex-3-ene-1-carboxylate **20**: IR (neat): ν_{max}/cm^{-1} 1727, 914; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.88 (1H, dd, *J* 17.4 and 10.8 Hz), 5.32–5.26 (1H, m), 4.98 (1H, dd, *J* 10.8 and 1.5 Hz), 4.94 (1H, dd, *J* 17.4 and 1.5 Hz), 3.63 (3H, s), 2.56–2.45 (1H, m), 2.32–1.80 (4H, m), 1.58 (3H, s), 1.52–1.41 (1H, m), 1.02 (3H, s), 1.017 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 175.2 (C), 144.7 (CH), 133.2 (C), 120.2 (CH), 112.3 (CH_2), 51.3 (C), 51.0 (CH_3), 41.1 (C), 29.0 (CH_2), 28.6 (CH_2), 25.9 (CH_2), 23.3 (CH_3), 23.1 (CH_3), 23.08 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{22}O_2Na$ (M+Na): 245.1517. Found: 245.1518. 5,5,9-Trimethylspiro[5.5]undec-8-en-1-one **28**: IR (neat): ν_{max}/cm^{-1} 1706; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.27 (1H, br s), 2.53 (1H, td, *J* 12.3 and 6.9 Hz), 2.30–2.00 (3H, m), 1.92 (1H, td, *J* 13.2 and 4.8 Hz), 1.86–1.60 (6H, m), 1.51 (3H, s), 1.31–1.23 (1H, m), 0.89 (3H, s), 0.75 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 213.5 (C), 131.4 (C), 120.7 (CH), 54.8 (C), 40.8 (C), 36.9 (CH_2), 35.7 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 24.9 (CH_3), 23.4 (CH_3), 23.3 (CH_3), 23.1 (CH_2); HRMS: *m*/*z* calcd for $C_{14}H_{23}O$ (M+H): 207.1749. Found: 207.1709.



Scheme 2. Reagents, conditions and yields: (a) DCC, DMAP (catalytic), $Me_2C{=}CHCH_2OH$, CH_2Cl_2, rt, 5 h, 88%; (b) (i) LDA, THF, TMSCl, NEt_3, −70 °C, 30 min, rt, 6 h; reflux, 3 h; (ii) dil HCl, 40 min; (iii) CH_2N_2, Et_2O, 0 °C, 30 min, 70%; (c) LAH, THF, reflux, 3 h, 75%; (d) PCC, silica gel, CH_2Cl_2, rt, 0.25 h, 86%; (e) Li, $CH_2{=}CHCH_2Br$,))), 0 °C→rt, 1 h, 75%; (f) $Cl_2(PCy_3)_2Ru{=}CHPh$ (5 mol %), CH_2Cl_2, rt, 5 h, 86%; (g) PCC, silica gel, CH_2Cl_2, rt, 2 h, 86%; (h) DBU, CH_2Cl_2, rt, 12 h, 79%.

of the resultant β,γ-enone **24** with DBU furnished the key precursor to the chamigrenes, the spirodienone **25**, in 93% yield. An alkylative 1,3-enone transposition[12] was considered highly suitable for the conversion of the enone **25** into laurencenone C **5**. After exploring various conditions, it was found that reaction of the enone **25** with anhydrous cerium chloride and methyllithium[13] generated a 1:2 mixture of the 1,2- and 1,4-addition products **26** and **27**, in quantitative yield. Oxidation of the mixture of **26** and **27** with PCC in methylene chloride followed by purification on a silica gel column furnished the spiroketone **27** and (±)-laurencenone C **5**. Laurencenone C **5** exhibited spectral data identical to those reported in the literature.[4] In another direction, treatment of the enone **25** with zinc and potassium hydroxide[14] in refluxing ethanol regioselectively reduced the enone to generate norchamigrenone **28** in excellent yield.[†] Reaction of the norketone **28** with methylenetriphenylphosphorane (generated from triphenylphosphonium bromide and tertiary amyl oxide in benzene and tertiary amyl alcohol)[15,16] or with the Lombardo reagent (prepared from methylene bromide, zinc and titanium tetrachloride)[17] quantitatively furnished (±)-β-chamigrene **1**. Even though reaction of norchamigrenone **28** with either methyllithium or methylmagnesium iodide was unsuccessful (contrary to that reported by Plamondon and Canonne),[8] reaction with a combination of anhydrous cerium chloride and methylmagnesium



Scheme 3. Reagents, conditions and yields: (a) DCC, DMAP (catalytic), $Me_2C{=}CHCH_2OH$, CH_2Cl_2, rt, 5 h, 95%; (b) (i) LDA, THF, TMSCl, NEt_3, −70 °C, 30 min, rt, 6 h, reflux, 3 h; (ii) dil HCl, 40 min; (iii) CH_2N_2, Et_2O, 0 °C, 30 min, 92%; (c) LAH, Et_2O, 0 °C→rt, 2 h, 90%; (d) PCC, silica gel, CH_2Cl_2, rt, 0.5 h, 89%; (e) Li, $CH_2{=}CHCH_2Br$,))), 0 °C→rt, 1 h, 86%; (f) $Cl_2(PCy_3)_2Ru{=}CHPh$ (10 mol %), CH_2Cl_2, rt, 5 h, 90%; (g) PCC, silica gel, CH_2Cl_2, rt, 2 h, 96%; (h) DBU, CH_2Cl_2, rt, 6 h, 98%; (i) CH_3Li, $CeCl_3$, THF, 0 °C→rt, 2 h; (j) PCC, silica gel, CH_2Cl_2, 1 h; 100% (from **25**) (**5**:**27** 1:2); (k) Zn, KOH, EtOH, H_2O (4:1), reflux, 10 h, 95%; (l) Ph_3PCH_3Br, $^tAmO^-K^+$, C_6H_6, ^{t}AmOH, reflux, 10 h, 100%; (m) Zn, $TiCl_4$, CH_2Br_2, CH_2Cl_2, 0 °C→rt, 3 h, 100%; (n) CH_3MgCl, $CeCl_3$, THF, 0 °C→rt, 3 h 88%; (o) $POCl_3$, py, CH_2Cl_2, 0 °C→rt, 3 h, 92%.

chloride furnished the tertiary alcohol **29** in 88% yield. Dehydration of the alcohol **29** with phosphorus oxychloride and pyridine furnished a 5:1 mixture of α- and β-chamigrenes **2** and **1** in 92% yield, which were separated by column chromatography on silica gel impregnated with silver nitrate. Both α-chamigrene **2** and β-chamigrene **1** exhibited spectral data identical to those of the authentic compounds reported[5,7] in the literature.

In summary, we have accomplished efficient total syntheses of (±)-laurencenone C **5**, (±)-α-chamigrene **2** and (±)-β-chamigrene **1**. Starting from the acid **18**, (±)-laurencenone C **5** was obtained in an overall yield of 17% in 10 steps, (±)-α-chamigrene **2** in 32% in 11 steps and (±)-β-chamigrene **1** in 48% in 10 steps. A combination of an Ireland ester Claisen rearrangement and RCM reactions was employed for the efficient construction of the requisite two vicinal quaternary carbon atoms. Extension of the methodology for the enantioselective generation of these and related spiro sesquiterpenes is currently in progress.

Acknowledgements

We thank the Council of Scientific and Industrial Research, New Delhi, for the financial support and award of a research fellowship to B.V.L.

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