A New and Efficient Total Synthesis of (±)-Laurencenone C

Kuo-Ching Chu,[a] Hsing-Jang Liu,*[a] Jia-Liang Zhu*[b]

[a] Department of Chemistry, National Tsing Hua University, Hsinchu 30043, Taiwan, Republic of China
Fax +886(3)35665; E-mail: hjliu@mx.nthu.edu.tw

[b] Department of Chemistry, National Dong-Hwa University, Hualien 974, Taiwan, Republic of China
Fax +886(3)8633570; E-mail: jlzhu@mail.ndhu.edu.tw

Received 14 September 2010

Abstract: A novel total synthesis of laurencenone C, a chamigrene sesquitepenoid natural product, has been accomplished in 11 steps. In the synthetic sequence, the B-ring of the spirocyclic core was constructed by a one-pot operation involving a Knoevenagel condensation between ethyl cyanoacetate and paraformaldehyde combined with a Diels–Alder reaction of the resulting ethyl 2-cyanoacrylate with isoprene. Moreover, a lithium naphthalenide-induced reductive alkylation of the Diels–Alder adduct was employed to create the C-6 quaternary center and to set the stage for assembling the A-ring.

Key words: chamigrene sesquitepene, laurencenone C, Diels–Alder reaction, natural product, total synthesis

Laurencenone C (**1**) belongs to an abundant family of sesquitepenoids known as the chamigrenes, which includes more than one hundred members[1] and is characterized by a spiro[5.5]undecane core bearing two vicinal quaternary carbon centers at C-5 and C-6 positions. It was first isolated from the alga of the genus *Laurencia obtuse*,[1] along with three other structurally related chamigrenes, namely laurencenones A, B, and D (Figure 1).[2] These natural products contain the same A-ring bearing an enone moiety, and differ from each other by the functionalities on the B-ring. Like many other chamigrenes,[3] laurencenone C has attracted attention from the synthetic community with five total syntheses so far having been documented in the literature.[4–8] The first total synthesis was reported by Takeshita and co-workers.[4] In their synthetic sequence, a photo-cycloaddition of terpinolene with methyl 2,4-dioxopentanoate followed by a base-promoted *retro*-benzilic acid rearrangement of the resulting hydroxy spiro[3.5]nonene ester was employed to prepare the key precursor for assembling the spiro framework. Following this, Chen's group described the synthesis of **1** by utilizing a crucial intramolecular radical cyclization of an α-allenic ketone to access the spiro ring fusion.[5] However, both syntheses provided **1** in relatively low overall yields (2.9 and 6.4%, respectively) due to the formation of other regio- and stereoisomers as side products in the key synthetic steps. In similar approaches, Srikrishna and co-workers twice described the total synthesis of **1** through the use of an Ireland ester Claisen rearrangement combined with a RCM reaction[6] or an intramolecular type II carbonyl ene reaction[7] as the key operations. Besides these approaches, the RCM strategy was also employed in an enantioselective synthesis of **1** recently reported by Stoltz and Grubbs et al.[8] As can be seen, the syntheses of **1**, as well as other chamigrenes,[3] are critically dependent on the efficient creation of the quaternary spirocenter with the necessary functionalities for building the spiro[5.5]undecane core.

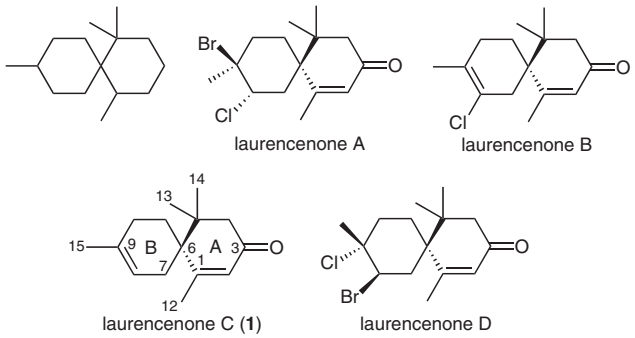
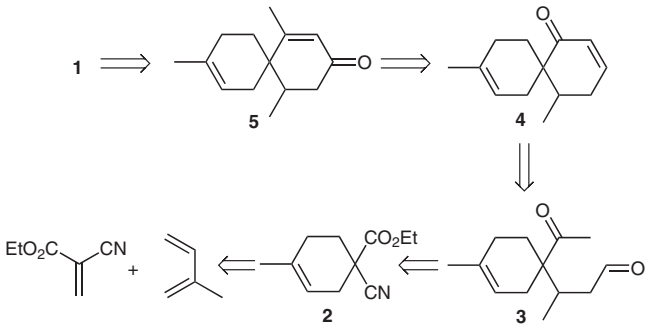


Figure 1 Skeleton of chamigrenes and structures of laurencenones A–D

Presented here is our total synthesis of **1** based on a new approach. As outlined in our retrosynthetic analysis (Scheme 1), we envisioned that a Diels–Alder reaction between ethyl cyanoacrylate and isoprene could be used to deliver the spirocyclic core and provide intermediate **2**. The cyano moiety of **2** was intended to be elaborated into a 1-methyl-3-oxopropyl group via a lithium naphthalenide (LN)-induced reductive alkylation operation developed by us,[9] while the ester group was to be converted into an acetyl functionality to give intermediate **3**. Aldol condensation of **3** would allow the establishment of the spiro skeleton and afford enone **4**, from which intermediate **5** was to be generated through a 1,2-addition of methyllithium and a subsequent oxidative rearrangement reaction. At the end, introduction of a methyl group to the β-position of the enone moiety of **5** followed by installation of the C1–C2 double bond would complete the total synthesis of **1**.

We initially tried to prepare ethyl cyanoacrylate by the Knoevenagel condensation of ethyl cyanoacetate with paraformaldehyde in pyridine according to the reported procedure.[10] However, it was found that the resulting acrylate was extremely unstable and polymerized easily upon usual work-up and purification. To circumvent this problem, we turned to a strategy of conducting the con-

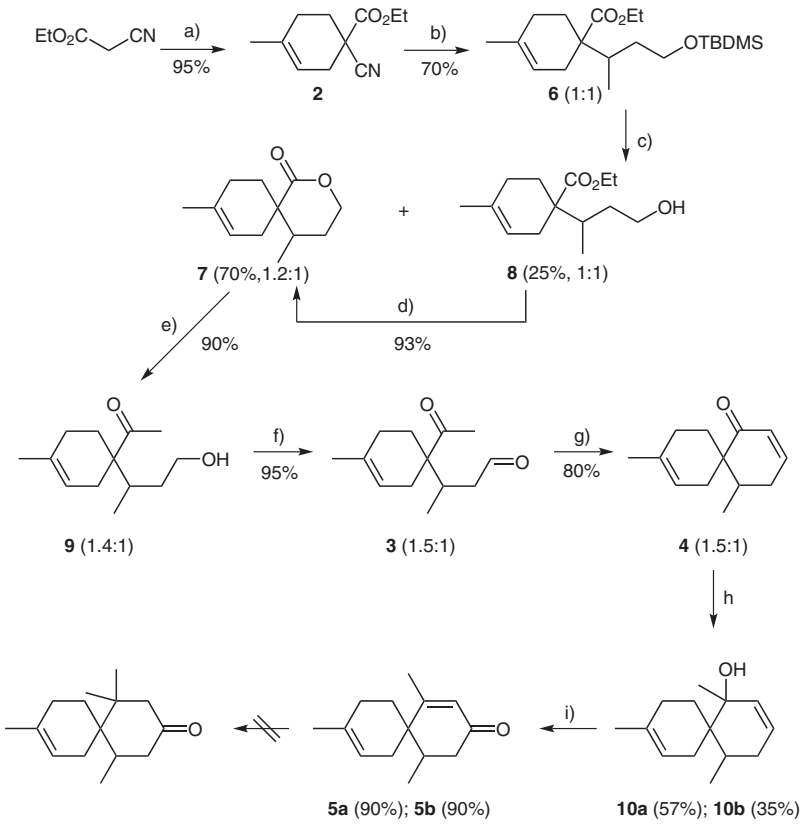
SYNLETT 2010, No. 20, pp 3061–3064
Advanced online publication: 17.11.2010
DOI: 10.1055/s-0030-1259052; Art ID: W14610ST



Scheme 1 Retrosynthetic analysis of **1**

densation and the subsequent Diels–Alder reaction with isoprene in one-pot. De Keyser et al. previously described a procedure in which anthracene was used to trap the methylidenemalonates generated in situ in a Diels–Alder process with the assistance of copper(II) acetate.[11] In light of this, we then applied similar reaction conditions to our system, and were pleased to find that the desired cycloadduct **2** could be formed in high yield (95%, Scheme 2).

After the formation of the B-ring, we moved forward to create the spiro skeleton by utilizing a LN-induced reductive alkylation reaction of **2**. Thus, **2** was first treated with LN[12] in tetrahydrofuran (THF) at –40 °C for one hour, and the resulting enolate derived from the reductive decyanation was subsequently trapped in situ by *tert*-butyl-3-iodobutoxydimethylsilane[13] to produce the alkylated product **6** (70%) as a mixture of two diastereomers (1:1). Deprotection of **6** with tetrabutylammonium fluoride (TBAF) afforded 70% of spirolactone **7** (1.2:1) resulting from the spontaneous intramolecular lactonization, along with 25% of hydroxy ester **8**. Upon exposure to sodium hydride, compound **8** could be readily transformed into **7** in an almost quantitative yield (93%). Addition of methyllithium to **7** was subsequently conducted to yield ketoalcohol **9** (1.4:1, 90% yield), which was then converted into intermediate **3** (1.5:1) through oxidation with pyridinium chlorochromate (PCC). Aldol condensation of **3** under basic reaction conditions established the spirocyclic framework to give the key intermediate **4** (1.5:1) in 80% yield. Subsequent elaboration of **4** into intermediate **5** also proceeded smoothly via a two-step synthetic sequence in which **4** was first subjected to reaction with methyllithium to produce two separable diastereomeric alcohols **10a** and **10b**[14] in 57 and 35% yield, respectively, which were then individually treated with PCC [15] to produce **5a** and **5b**[14] in an equal yield (90%). With **5a** and **5b** in hand, we then attempted to introduce a methyl group to the β-position of the enone moiety through a nucleophilic conjugate addition reaction. However, treatment of **5a** or **5b** with lithium dimethylcuprate (Me_2CuLi) in diethyl ether from 0 °C to r.t. afforded only recovered starting materials. Additionally, application of Yamamoto's procedure (Me_2CuLi,



Scheme 2 *Reagents and conditions*: (a) Paraformaldehyde (2 equiv), isoprene (3 equiv), $Cu(OAc)_2$ (0.1 equiv), toluene–AcOH, 1:1, 80 °C, 24 h; (b) LN (3 equiv), THF, –40 °C, 1 h, then $(Me)CHICH_2CH_2OTBDMS$ (1.3 equiv), r.t., 2 h; (c) TBAF (3 equiv), THF, r.t., 20 h; (d) NaH (2 equiv), THF, 0 °C to r.t., 2 h; (e) MeLi (1.1 equiv), THF, –78 °C, 2 h; (f) PCC (2 equiv), CH_2Cl_2, r.t., 2 h; (g) KOH (2.8 equiv), THF–H_2O, 10:1, reflux, 24 h; (h) MeLi (1.4 equiv), THF, –78 °C to r.t., 2 h; (i) PCC (1.5 equiv), Celite, CH_2Cl_2, r.t., 3 h.

TMSCl, CH_2Cl_2, –78 °C to 0 °C)[16] to **5** also gave no trace of the desired addition products.

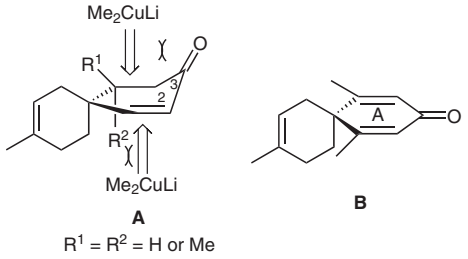
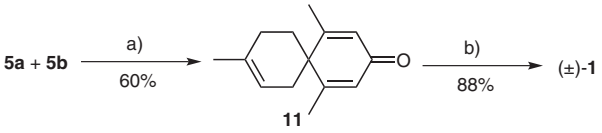


Figure 2 Proposed unfavorable steric interactions for 1,4-addition of **5** and favorable co-planar state of the A-ring

We envisioned that the failure of the addition reaction might be attributed to the unfavorable steric interactions between the nucleophile and the C2–C3 subunit of the A-ring (Figure 2, state **A**) and the C-1 axial methyl group (R^2 = Me). Nevertheless, it was possible that such interactions could be minimized when the A ring was forced to adopt a planar conformation by the introduction of an extra double bond (state **B**). In this regard, we then rerouted our original synthetic plan by transforming the mixture of **5a** and **5b** into dienone **11** using the well-established selenylation–oxidative elimination method (Scheme 3). To our delight, when **11** was allowed to react with Me_2CuLi in the presence of trimethylsilyl chloride,[16] the target molecule **1** could be produced in high yield (88%), indicating that a planar conformation of the A-ring was indeed favorable for the conjugate addition. The spectral data (^1H, ^{13}C NMR) of **1** were found to agree well with those reported for the natural product.[2,1,7]



Scheme 3 Reagents and conditions: (a) LDA (1.2 equiv), PhSeCl (1.2 equiv), THF, –78 °C, 30 min, then work-up, aq H_2O_2 (30%, 10 equiv), CH_2Cl_2, 10 min; (b) Me_2CuLi (3 equiv), TMSCl (3 equiv), CH_2Cl_2, –78 °C to r.t., 3 h.

In summary, a concise total synthesis of (±)-laurencenone C (**1**) has been accomplished in 11 steps. This new one-pot approach, involved a Knoevenagel condensation combined with a Diels–Alder reaction, and a reductive alkylation reaction of the resulting Diels–Alder adduct, as efficient key steps in the creation of the B-ring as well as the spiro quaternary center. Compared with other precedents, our synthesis has the advantage of offering straightforward access to **1** in relatively high overall yield (17.4%), at low cost and without the formation of side products or isomers. The synthetic strategies employed for the synthesis of **1** are being applied to the syntheses of other chamigrenes, and the results will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We are grateful to the National Science Council of Republic of China (Taiwan), National Tsing Hua University for financial support.

References and Notes

(1) For examples of isolations of chemigrenes, see: (a) Erickson, K. L. In *Marine Natural Products: Chemical and Biological Perspectives*, Vol. 5; Scheuer, P. J., Ed.; Academic Press: New York, **1990**, 131–257. (b) Attaway, D. H.; Zaborsky, O. R. In *Marine Biotechnology: Pharmaceutical and Bioactive Natural Products*; Plenum Press: London, **1993**, 333–334. (c) Sim, J. J.; Lin, G. H.; Wing, R. M. *Tetrahedron Lett.* **1974**, *15*, 3487. (d) Kikuchi, H.; Suzuki, T.; Suzuki, M.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2473. (e) Elsworth, J. F. *J. Nat. Prod.* **1989**, *52*, 893. (f) Rashid, M. A.; Gustafson, K. R.; Gardellina, J. H.; Boyd, M. R. *Nat. Prod. Lett.* **1995**, *6*, 255. (g) Francisco, M. E. Y.; Erickson, K. L. *J. Nat. Prod.* **2001**, *64*, 790. (h) Dorta, E.; Díaz-Marrero, A. R.; Cueto, M.; D'Croz, L.; Maté, J. L.; Darias, J. *Tetrahedron Lett.* **2004**, *45*, 7065; and references cited therein.

(2) (a) Kennedy, D. J.; Selby, I. A.; Thomson, R. H. *Phytochemistry* **1988**, *27*, 1761. (b) For the isolation of laurencenone C from the other natural source, see: Asakawa, Y.; Tori, M.; Masuya, T.; Frahm, J.-P. *Phytochemistry* **1990**, *29*, 1577.

(3) For examples on total syntheses of chamigrenes, see: (a) Wolinsky, L. E.; Faulkner, D. J. *J. Org. Chem.* **1976**, *41*, 597. (b) Martin, J. D.; Pérez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 7801. (c) Niwa, H.; Yoshida, Y.; Hasegawa, T.; Yamada, K. *Tetrahedron* **1991**, *47*, 2155. (d) White, D. E.; Stewart, I. C.; Crubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810. (e) Cui, Q.; Kang, L.; Yang, H. S.; Xu, X. H. *Chin. Chem. Lett.* **2009**, 554; and references cited therein.

(4) Hatsui, T.; Wang, J.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2507.

(5) Chen, Y. J.; Wang, C. Y.; Lin, W. Y. *Tetrahedron* **1996**, *52*, 13181.

(6) Srikrishna, A.; Lakshmi, B. V.; Mathews, M. *Tetrahedron Lett.* **2006**, *47*, 2103.

(7) Srikrishna, A.; Babu, R. R. *Tetrahedron* **2008**, *64*, 10501.

(8) White, D. E.; Stewart, I. C.; Seashore-Ludlow, B. A.; Grubbs, R. H.; Stoltz, B. M. *Tetrahedron* **2010**, *66*, 4668.

(9) Shia, K. S.; Chang, N. Y.; Yip, J.; Liu, H. J. *Tetrahedron Lett.* **1998**, *39*, 7713.

(10) Khalafallah, A. K.; Elal, R. M. A.; Kanzi, N. A. A. *Heterocycl. Commun.* **2002**, 397.

(11) De Keyser, J.-L.; De Cock, C. J. C.; Poupaert, J. H.; Dumont, P. *J. Org. Chem.* **1998**, *53*, 4859.

(12) For preparing a stock solution of LN, see: Liu, H. J.; Yip, J.; Shia, K. S. *Tetrahedron Lett.* **1997**, *38*, 2253.

(13) Yefidoff, R.; Albeck, A. *Tetrahedron* **2004**, *60*, 8093.

(14) The relative stereochemistry of two diastereoisomers remains to be determined.

(15) Mehta, G.; Nandakumar, J. *Tetrahedron Lett.* **2001**, *42*, 7667.

(16) Asao, N.; Lee, S.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 4265.

(17) The spectral data of **1** are as follows. IR (neat): 3023, 2960, 2932, 1668, 1610, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz):

δ = 5.77 (s, 1 H), 5.41 (s, 1 H), 2.53 (d, *J* = 18.2 Hz, 1 H), 2.15 (d, *J* = 18.2 Hz, 1 H), 1.88 (s, 3 H), 1.98–1.91 (m, 2 H), 1.82–1.78 (m, 2 H), 1.68–1.64 (m, 2 H), 1.59 (s, 3 H), 0.94 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.5 (C), 170.3 (C), 133.9 (C), 126.8 (CH), 121.4 (CH), 48.8 (CH_2), 43.2 (C), 40.2 (C), 30.5 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 24.7 (CH_3), 24.1 (CH_3), 23.7 (CH_3), 23.2 (CH_3); HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{22}O$: 218.1671; found: 218.1669.

The spectral data of the key intermediate **4** are as follows. IR (neat): 3035, 2960, 2912, 1674, 1447 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.67–6.64 (m, 1 H, major), 6.63–6.61 (m, 1 H, minor), 5.87–5.82 (m, 2 H), 5.31 (d, *J* = 1.3 Hz, 1 H, minor), 5.26 (d, *J* = 1.5 Hz, 1 H, major), 2.69 (ddt, *J* = 17.7, 5.4, 2.7 Hz, 1 H, minor), 2.55 (ddt, *J* = 20, 5.5, 2.8 Hz, 1 H, major), 2.46–2.43 (m, 1 H, minor), 2.19–2.17 (m, 2 H), 2.13–2.04 (m, 4 H), 1.92–1.64 (m, 9 H), 1.59–1.57 (m, 6 H), 0.91–0.86 (m, 6 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (major) = 204.6 (C), 145.8 (CH), 133.5 (C), 128.3 (CH), 118.2 (CH), 46.7 (C), 35.8 (CH), 37.5 (CH_2), 31.2 (CH_2), 26.5 (CH_2), 24.3 (CH_2), 23.2 (CH_3), 15.5 (CH_3). ^{13}C NMR δ (minor) = 203.9 (C), 145.0 (CH), 132.1 (C), 127.9 (CH), 119.0 (CH), 47.5 (C), 32.4 (CH), 31.5 (CH_2), 29.6 (CH_2), 28.9 (CH_2), 27.9 (CH_2), 23.2 (CH_3), 15.5 (CH_3); HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}O$: 190.1358; found: 190.1362.

The spectral data of the key intermediate **6** are as follows. IR (neat): 2957, 2929, 2857, 1726, 1447 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.28 (br s, 2 H), 4.06–4.03 (m, 4 H), 3.61–3.59 (m, 2 H), 3.51–3.48 (m, 2 H), 2.44–2.36 (m, 2 H), 1.96–1.72 (m, 14 H), 1.60 (s, 6 H), 1.17–1.15 (m, 6 H), 1.10–1.02 (m, 2 H), 0.84–0.81 (m, 24 H), –0.02 to –0.03 (m, 12 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 175.8 (C), 175.7 (C), 133.0 (C), 132.9 (C), 119.8 (CH), 119.6 (CH), 61.6 (CH_2), 61.5 (CH_2), 59.8 (CH_2), 48.3 (C), 36.3 (CH), 36.1 (CH), 29.6 (CH_2), 29.4 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 25.8 (CH_3), 23.1 (CH_3), 18.2 (C), 14.7 (CH_3), 14.1 (CH_3), 13.9 (CH_3), –5.35 (CH_3), –5.43 (CH_3); HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{38}O_3Si$: 354.2590; found: 354.2593.

The spectral data of the key intermediate **11** are as follows. IR (neat): 2920, 1651, 1614 cm^{-1}; mp 106.3–107.6 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.96 (s, 2 H), 5.46 (t, *J* = 1.6 Hz, 1 H), 2.13–2.11 (m, 2 H), 2.03–2.01 (m, 2 H), 1.95 (s, 6 H), 1.67–1.65 (m, 5 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 185.9 (C), 166.5 (C), 133.5 (C), 126.8 (2CH), 119.5 (CH), 44.1 (C), 31.9 (CH_2), 29.5 (CH_2), 27.3 (CH_2), 23.4 (CH_3), 21.4 (CH_3), 21.3 (CH_3); HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{18}O$: 202.1358; found: 202.1358[cc].