Total Synthesis of (+)-Cladantholide and (−)-Estafiatin: 5-*Exo*,7-*Endo* Radical Cyclization Strategy for the Construction of Guaianolide Skeleton

Eun Lee,* Jong Won Lim, Cheol Hwan Yoon, Yong-suk Sung, and Young Kwon Kim

Department of Chemistry, College of Natural Sciences Seoul National University, Seoul 151-742 Korea

Mikyung Yun and Sangsoo Kim

Biotech Research Institute, LG Chemical Ltd. Yu-Seong P.O. Box 61, Dae-jeon 305-600, Korea

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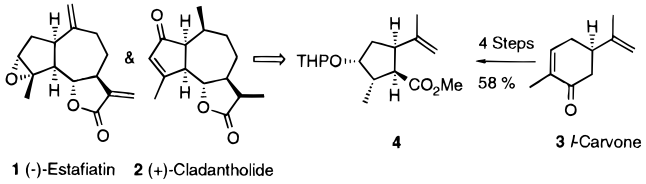
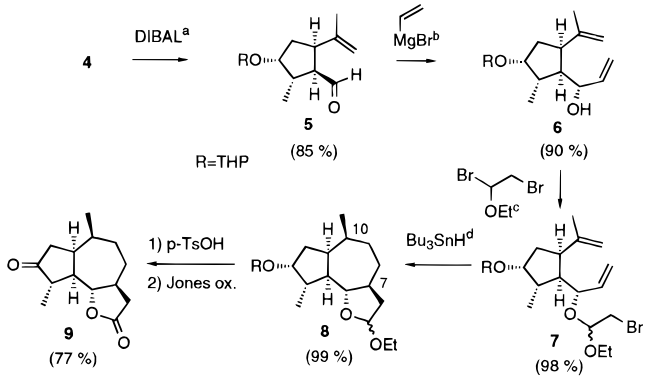
Guaianolides represent one of the largest groups of naturally occurring sesquiterpene lactones.[1] Apart from relay syntheses[2] involving eudesmane and germacrane sesquiterpenes as starting points, total syntheses of only a handful of natural guaianolides are reported. (±)-Compressanolide and (±)-estafiatin (**1**) were synthesized by Vandewalle and co-workers[3] starting from 2-cyclopentenone via a hydroazulenic diketone. Rigby and co-workers[4] utilized *cis*-fused hydroazulenic intermediates derived from tropone for the preparation of (±)-**1**, (±)-dehydrocostus lactone, and (±)-grosshemin. In view of the known tumor inhibitory, schistosomicidal, anthelmintic, contraceptive, and plant growth regulatory activities[5] for members of the guaianolide family, this paucity of synthetic successes is surprising[6] and in contrast to the prodigious synthetic output registered for the closely related pseudoguaianolides.[7]

We reported recently that the chlorohydrin derivative of (−)-carvone (**3**) was stereoselectively converted into the cyclopentanecarboxylate **4** via Favorskii rearrangement.[8] In the product **4**, the isopropenyl substituent and the methoxycarbonyl group were *cis* to each other. This particular arrangement is reminiscent of the *cis*-fused hydroazulenic ring system in many guaianolides, and it was realized that effective synthesis of guaianolides might be possible, provided reasonably efficient ways of seven-membered ring formation are devised (Scheme 1). Herein, we report that 5-*exo*,7-*endo* tandem radical cyclizations can be employed successfully for the formation of *cis*-fused hydroazulenic lactone systems culminating in stereoselective total syntheses of (−)-estafiatin (**1**)[9] and (+)-cladantholide (**2**).[10]

Scheme 1



Scheme 2



[a] THF, −90 to −80 °C. [b] THF, 0 °C. [c] 3.0 equiv; 3.0 equiv TEA, cat. DMAP, DCM, 0 °C to rt, 12 h. [d] 1.5 equiv; 0.2 equiv of AIBN, benzene (0.025 M), reflux, 6 h (syringe pump, 5 h). TEA = triethylamine, DMAP = 4-(dimethylamino)pyridine, DCM = dichloromethane.

Reduction of **4** with diisobutylaluminum hydride afforded the corresponding aldehyde **5** in 85% yield. Addition of vinylmagnesium bromide to the aldehyde moiety in **5** was completely stereoselective: the Felkin type addition product **6** was isolated in high yield as the sole product. The allylic alcohol **6** was efficiently converted into the corresponding bromoacetal **7** upon exposure to 1,2-dibromo-1-ethoxyethane. When **7** was subjected to the standard high-dilution, radical generating conditions utilizing tributylstannane and 2,2′-azobisisobutyronitrile (AIBN), a 99% yield of the hydroazulenic acetal **8** was obtained. At this point, structural assignment of **8** was difficult, and the definite structural assignment had to wait until a suitable crystalline derivative was prepared for X-ray crystal diffraction studies. In the event, the ketolactone **9**, prepared from the radical cyclization product **8** via THP deprotection and Jones oxidation, was crystallized and and the structure was determined unambiguously[11] (Scheme 2).

The initial 5-*exo* radical cyclization was expected to give predominantly the *trans* cyclic acetal. It is well-known that radical cyclizations of 4-substituted 5-hexenyl radicals yield mainly *trans*-disubstituted cyclopentanoid products.[12] After 7-*endo* cyclization, hydrogen abstraction by the tertiary radical was also expected to occur from the sterically less encumbered α face to give the correct strereochemistry at C-10 (Scheme 3). The most noteworthy aspect of this transformation is the high efficiency of the 7-*endo* radical cyclization. Examples for the

(1) (a) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, 1991; Vol. 1, pp 476−541. (b) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, p 47.

(2) For introductory discussions in guaianolide synthesis, see: (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1983; Vol. 5, pp 341−343. For some of the more recent references, see: (b) Ando, M.; Ibayashi, K.; Minami, N.; Nakamura, T.; Isogai, K.; Yoshimura, H. *J. Nat. Prod.* **1994**, *57*, 433. (c) Ando, M.; Yoshimura, H. *J. Org. Chem.* **1993**, *58*, 4127. (d) Greene, A. E.; Edgar, M. T. *J. Org. Chem.* **1989**, *54*, 1468. (e) González, A. G.; Galindo, A.; Mar Afonso, M.; Mansilla, H.; Palenzuela, J. A.; Gómez Rodriguez, M. A.; Martinez-Ripoll, M. *Tetrahedron* **1988**, *44*, 4575.

(3) (a) Devreese, A. A.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron Lett.* **1980**, *21*, 4767. (b) Demuynck, M.; Devreese, A. A.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron Lett.* **1982**, *23*, 2501. (c) Devreese, A. A.; Demuynck, M.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3049.

(4) (a) Rigby, J. H.; Wilson, J. Z. *J. Am. Chem. Soc.* **1984**, *106*, 8217. (b) Rigby, J. H.; Wilson, J. Z. *J. Org. Chem.* **1987**, *52*, 34. (c) Rigby, J. H.; Senanayake, C. *J. Am. Chem. Soc.* **1987**, *109*, 3147.

(5) For discussions on the biological activities of guaianolides, refer to the references cited in ref 2b.

(6) There are a few additional reports dealing with synthesis of related compounds: (a) Posner, G. H.; Babiak, K. A.; Loomis, G. L.; Frazee, W. J.; Mittal, R. D.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 7498. (b) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041. (c) Monde, K.; Takasugi, M.; Katsui, N.; Masamune, T. *Chem. Lett.* **1990**, 1283.

(7) For example, see pp 347−377 in ref 2a.

(8) Lee, E.; Yoon, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 479.

(9) (a) Sanchez-Viesca, F.; Romo, J. *Tetrahedron* **1963**, *19*, 1285. (b) Bohlman, F.; Bornowski, H.; Arndt, C. *Chem. Ber.* **1966**, *99*, 2828.

(10) Daniewski, W. M.; Danikiewicz, W.; Gumulka, M.; Pankowska, E.; Krajewski, J.; Grabarczyk, H.; Wichlacz, M. *Phytochemistry* **1993**, *34*, 1639.

(11) For **9**: $C_{14}H_{20}O_3$, fw = 236.31, orthorhombic $P2_12_12_1$; a = 6.608(1), b = 8.310(3), and c = 22.780(6) Å; V = 1251.0 Å^3, Z = 4, ρ_{calcd} = 1.25 g/cm^3, μ = 0.8 cm^{-1}, $R(R_w)$ = 0.038(0.046) for 1186 observed data [$F_o \geq \sigma(F_o)$]. The diffraction data were collected on an Enraf-Nonius CAD4 diffractometer at 23 °C in the $\omega - 2\theta$ scan mode using Mo Kα radiation (λ = 0.710 73 Å) to a maximum 2θ value of 50°. The structure was solved by direct methods and refined by full-matrix least-squares procedures using the MolEN software package (Enraf-Nonius). For full X-ray data tables, see the Supporting Information.

(12) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

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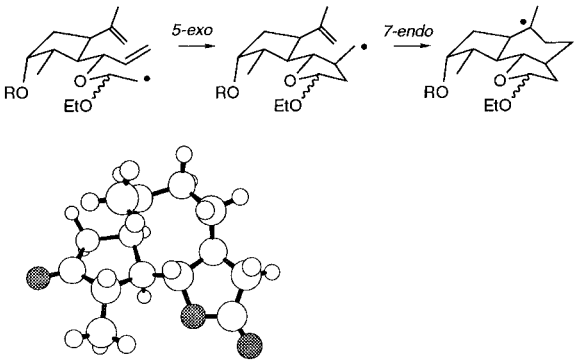
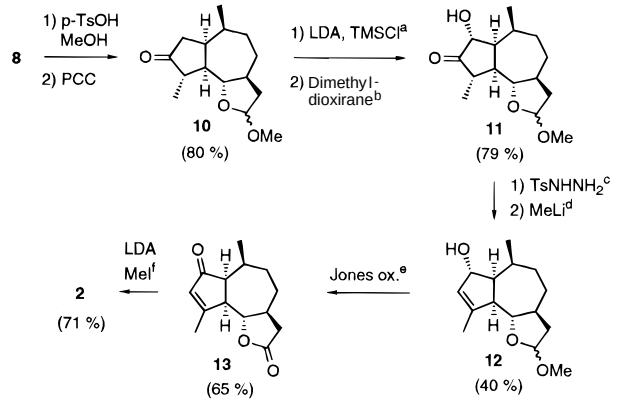
Scheme 3



Scheme 4



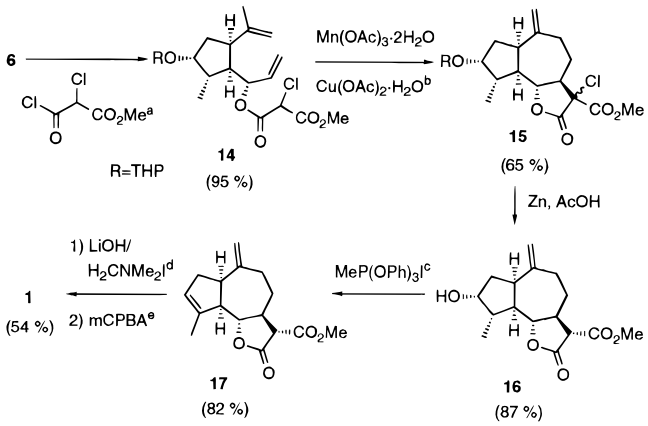
[a] 1.1 equiv; 2.0 equiv; THF, −78 °C. [b] 1.2 equiv; DCM, −78 °C, 30 min. [c] 1.2 equiv; MeOH, 3 Å MS, reflux, 4 h. [d] 7.0 equiv; THF, rt, 30 min. [e] Acetone, 0 to 10 °C, 8 h. [f] 2.2 equiv; 1.0 equiv; THF, −78 °C.

preferential 7-*endo* radical cyclization over the 6-*exo* mode alternative are known,[13] but an almost quantitative yield of **8** from **7** is truly remarkable. Thus, radical cyclization appears to be a viable alternative in the preparation of compounds containing seven-membered rings.

Deprotection and pyridinium chlorochromate (PCC) oxidation of **8** yielded the keto acetal **10** in 80% yield, which was converted into the hydroxy ketone **11** in good yield via trimethylsilyl enol ether formation and oxidation with dimethyldioxirane. Under standard Shapiro reaction conditions using excess methyllithium, **11** was transformed into the allylic alcohol **12** in 40% yield. The yield did not improve despite considerable amount of efforts made.[14] It is worth mentioning that the double bond was formed away from the resident hydroxyl group. Presumably, the reaction proceeded through an intermediate in which the alkoxylithium is coordinated with the first nitrogen atom of the hydrazone moiety.[15] Jones oxidation of **12** afforded the enone **13** in 65% yield, and lithium diisopropylamide (LDA)-mediated enolate formation and subsequent methylation proceeded stereoselectively to give (+)-cladantholide (**2**)[16] in 71% yield (Scheme 4).

The generality of 7-*endo* radical cyclization was then tested in the synthesis of (−)-estafiatin (**1**). The allylic alcohol **6** was

Scheme 5



[a] 1.3 equiv; cat. DMAP, DCM, pyridine, 0 °C to rt, 1 h. [b] 2.0 equiv; 1.0 equiv; EtOH, reflux, 3 h. [c] 1.1 equiv; HMPA, 80 °C, 1 h. [d] 1.1 equiv; $CH_3CN{\cdot}H_2O$ (10:1), rt, 10 h/3.0 equiv; reflux, 1 h. [e] 3.0 equiv; $CHCl_3$, −20 to 5 °C, 3 h.

esterified with chloromalonyl chloride to give the corresponding chloromalonate **14** in high yield. Under oxidative radical-generating conditions employing manganese(III) acetate and copper(II) acetate,[17] the substrate **14** underwent smooth 5-*exo*,7-*endo* tandem radical cyclizations affording a 3:1 mixture of the tricyclic chlorolactone **15** in 65% yield. Reductive dechlorination of **15** resulted in the simultaneous deprotection of the THP ether moiety, and a 10:1 epimeric mixture of the product **16** was obtained in 87% yield. Dehydration of **16** with methyltriphenoxyphosphonium iodide in hexamethylphosphoric triamide (HMPA)[18] proceeded uneventfully to give the diene **17** in 82% yield. Methylenation of the corresponding carboxylic acid with Eschenmoser's salt and subsequent epoxidation afforded (−)-estafiatin (**1**) (Scheme 5).[19]

In each of the present studies, a cyclopentanoid intermediate was utilized in the preparation of the guaianolide skeleton by fusing a seven-membered carbocycle and a lactone moiety. Remarkably, the 5-*exo*,7-*endo* tandem radical cyclizations were found to be highly efficient under reductive or oxidative radical-generating conditions solving at the same time the difficult stereochemical problems in forming functionalized seven-membered carbocycles.[20] The 7-*endo* radical cyclization strategy may lead to practical syntheses of many natural products containing seven-membered rings, and the progress in these areas of studies will be reported in due course.

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Supporting Information Available: Detailed synthetic procedures and spectroscopic data for compounds **8** and **15** and X-ray crystallographic details for **9** (13 pages). See any current masthead page for ordering and Internet access instructions.

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(13) For some of the references, see: (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (b) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427. (c) White, J. D.; Somers, T. C.; Yager, K. M. *Tetrahedron Lett.* **1990**, *31*, 59. (d) Snider, B. B.; Merritt, J. E. *Tetrahedron* **1991**, *47*, 8663. (e) Batty, D.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 875. (f) Rigby, J. H.; Qabar, M. N. *J. Org. Chem.* **1993**, *58*, 4473. (g) Ghosh, A. K.; Gosh, K.; Pal, S.; Chatak, U. R. *J. Chem. Soc., Chem. Commun.* **1993**, 809.

(14) Formation of the corresponding trisylhydrazone was sluggish.

(15) For discussions of Shapiro reaction, see: Chamberlin, A. R.; Sall, D. J. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 8, pp 923−953.

(16) The epimeric methylation product was not isolated. For (+)-**2**: $[\alpha]^{27}_D = +265°$ (*c* 0.9, $CHCl_3$); lit.[9] $[\alpha]^{20}_D = +309°$ (*c* 0.5, $CHCl_3$).

(17) Snider, B. B.; McCarthy, B. A. *Tetrahedron* **1993**, *49*, 9447.

(18) Hutchins, R. O.; Hutchins, M. G.; Milewski, C. A. *J. Org. Chem.* **1972**, *37*, 4190.

(19) The epoxide formation was reasonably stereoselective; a 10:1 mixture of (−)-**1** and the epimeric epoxide was obtained. For (−)-**1**: $[\alpha]^{22}_D = -11.2°$ (*c* 0.6, $CHCl_3$); lit.[10] $[\alpha]_D = -9.9°$.

(20) As far as we know, synthesis of (+)-**2** was never reported. In the present study, (+)-**2** was obtained in 5.0% overall yield in 16 steps from (−)-carvone. The same starting material was converted into (−)-**1** in 10.6% overall yield in 12 steps. For comparison, (±)-**1** was obtained in 0.92% overall yield in 13 steps from 2-cyclopentenone by Vandewalle and in 0.35% yield in 14 steps from tropone by Rigby. For synthesis of (−)-**1** or the triene precursor from α-santonin, see ref 2b and the following references: Edgar, M. T.; Greene, A. E.; Crabbé, P. *J. Org. Chem.* **1979**, *44*, 159. Ando, M.; Akahane, A.; Yamaoka, H.; Takase, K. *J. Org. Chem.* **1982**, *47*, 3909. Transformation of eremanthin into (−)-**1** was also reported: Maçaira, L. A.; Machado, W. L.; Garcia, M.; Rabi, J. A. *Tetrahedron Lett.* **1980**, *21*, 773.