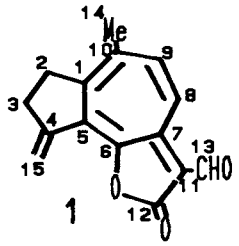
CHEMISTRY LETTERS, pp. 1283-1286, 1990. © 1990 The Chemical Society of Japan

Total Synthesis of Lettucenin A, a Guaianolid Phytoalexin from Lactuca sativa var. capitata[1)]

Kenji MONDE,* Mitsuo TAKASUGI, Nobukatsu KATSUI, and Tadashi MASAMUNE
Department of Chemistry, Faculty of Science,
Hokkaido University, Sapporo 060

Lettucenin A, a novel composite phytoalexin with 2H-cyclohepta[b]furan-2-one ring system was synthesized from an indanone. The unique ring system was constructed by reductive ring expansion of a dibromomethylcyclohexadienone.

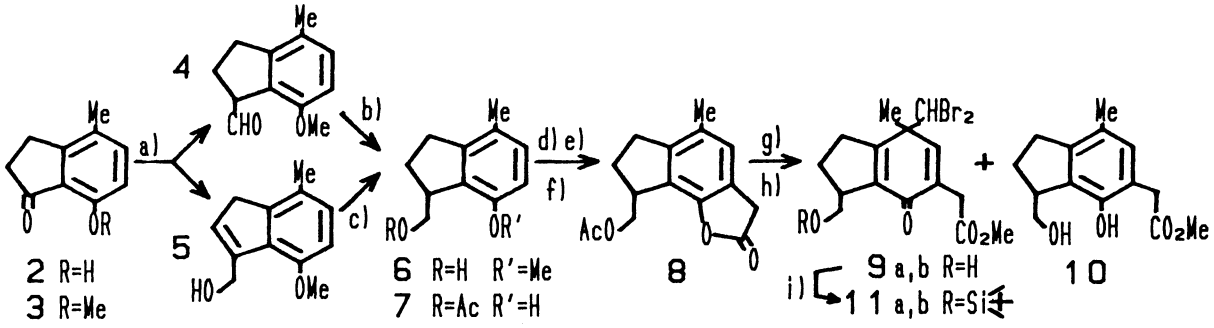
Recently, we reported the isolation of lettucenin A (**1**), a novel guaianolide phytoalexin with significant antifungal activity, from lettuce (Lactuca sativa var. capitata) inoculated with the bacterium Pseudomonas cichorii.[2)] Although the guaianolide family represents one of the largest groups of naturally occurring sesquiterpene lactones,[3)] lettucenin A is unique in having a 2H-cyclohepta[b]furan-2-one ring system and a formyl group at C11. To our knowledge, only two natural guaianolides with this ring system have been reported from an umbelliferous plant Ferula malacophylla[4)] and from a gorgonian Placogorgia sp.[5)] We wish to report herein the first total synthesis of **1** by a strategy which includes ring expansion as a key step of the synthesis.



1
Lettucenin A

We chose a known indanone **2**[6)] as a starting material, which was obtained from p-cresol by an improved procedure[7)] in 79% yield. Since the presence of both the exocyclic double bond and formyl groups in **1** makes the inherently stable ring system highly unstable we planned to introduce these groups at the later stages of the synthesis. To introduce an exocyclic methylene equivalent, the indanone **3** from **2** was treated with dimethyl sulfonium methylide to give an aldehyde **4** and an allyl alcohol **5**,[8)] which were reduced separately to give an alcohol **6** in a combined yield of 57% from **2**. Acetylation of the alcohol **6** followed by nucleophilic demethylation with ethanethiol in the presence of aluminum chloride[9)] gave a phenol **7** in 94% yield.

Next, a two-carbon unit (C11 and C12) of the γ-lactone moiety in **1** was introduced at the ortho position of the phenolic hydroxyl by treatment of **7** with glyoxal in the presence of a catalytic amount of hydrochloric acid[10] and a desired lactone **8** was obtained in 65% yield.[11]



a) $^{-}CH_2$-$^{+}SMe_2$, DMSO-THF, 22 h, rt. b) $NaBH_4$, 1.5 h, rt. c) H_2, 10%Pd-C, 3 h, rt. d) Ac_2O, Py, rt. e) $AlCl_3$, EtSH, CH_2Cl_2, 1 h, rt. f) 40% aq $(CHO)_2$, HCl, AcOH, 16 h, 65 °C → 110 °C g) $CHBr_3$, 10%NaOH-H_2O, γ-CD, 23 h, 80 °C h) CH_2N_2 i) t-Bu(Me)$_2$SiCl,imidazole

Scheme 1.

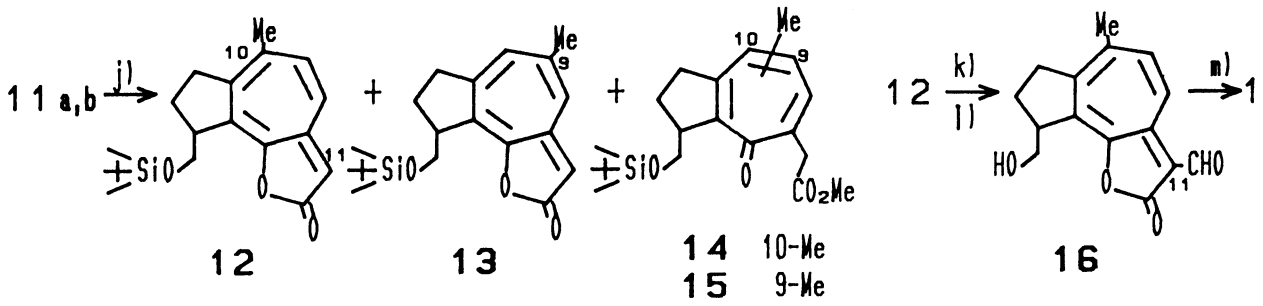
For construction of a tropone nucleus we utilized a ring expansion reaction developed recently by Barbier et al.[12] Treatment of the lactone **8** with dibromocarbene in the presence of γ-cyclodextrin,[13] followed by methylation with diazomethane gave diastereomeric dibromomethylcyclohexadienone methyl esters **9a** and **9b**,[14] together with a phenol **10**,[15] in 10, 9 and 47% yields,respectively. Silylation of **9a** gave a protected dienone **11a**.

Reaction of the dienone **11a** with tributyltin hydride in the presence of azobisisobutyronitrile as a radical initiator[12] resulted in expected ring expansion and gave regioisomeric 2H-cyclohepta[b]furan-2-ones **12** and **13**, and an inseparable mixture of tropones **14** and **15**[16] in 29, 9, and 28% yields, respectively. The isomeric dienone **11b** gave a similar result: Compounds **12**, **13**, and a mixture of **14** and **15** were obtained in 31, 10, and 21% yields, respectively. The ^{1}H-NMR spectrum of the major product **12** indicated that it has a methyl group at the desired C10 position in the system. Namely, it showed AB type signals at δ 6.94 and 7.16 (J = 11.5 Hz) while the minor product **13** showed two broad singlets at δ 6.72 and 7.08 (W_H = 4.3 Hz). Formation of **12** as major product would be explained by preferential attack of a radical intermediate at sterically less hindered position to form a less hindered bromocyclopropane intermediate, which would rearrange to the tropone **14** and then cyclize to **12**.

An unusually high proton chemical shift at δ 5.58 (11-H) of **12** indicated high electron density at the C11 carbon atom, suggesting ready electrophilic substitution at this position. Vilsmeir-Haack formylation

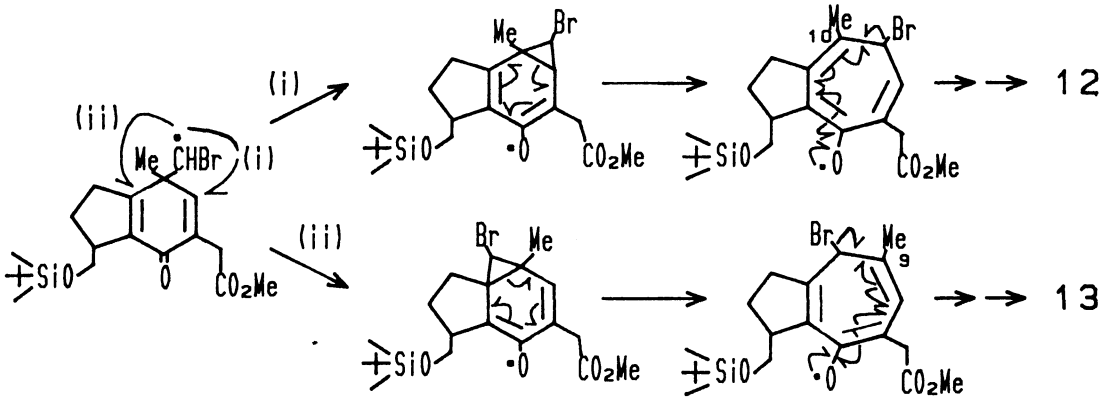
of **12** proceeded uneventfully with concomitant desilylation to give a formyl derivative **16** in 85% yield.

The final step of the synthesis was achieved by dehydration of the primary alcohol **16** using Mukaiyama's mild procedure:[17] Treatment of **16** with 2-fluoro-1-methylpyridinium p-toluenesulfonate and triethylamine in dichloromethane at room temperature afforded the desired dehydration product **1** in 70% yield, which was identical with natural lettucenin A (HPLC, UV, ^{1}H-NMR, and MS), confirming the proposed structure **1**.



j) n-Bu_3SnH, AIBN, PhH, 2 h, reflux k) $POCl_3$, DMF, 4 h, rt.
l) H_3O^+ m)  ·OTs^-, Et_3N, CH_2Cl_2, 9 h, rt.

Scheme 2.



Scheme 3.

References

1) Part 11 in the series "Studies on Stress Metabolites;" Part 10, K.Monde, T.Oya, A.Shirata, and M.Takasugi, Phytochemistry, in press.

2) M.Takasugi, S.Okinaka, N.Katsui, T.Masamune, A.Shirata, and M.Ohuchi, J.Chem.Soc., Chem.Commun.,1985, 621. This compound was also isolated from dandelion leaves treated with cupric chloride. S.Tahara, F.Hanawa, Y.Harada, J.Mizutani, Agric. Biol. Chem.,52, 2947 (1988).

3) N. H. Fischer, E. Olivier, and H. D. Fischer, Fortschr. Chem. Org. Naturst., 38, 47 (1979).

4) V. Yu. Bagirov, V.I.Sheichenko, R.Yu.Gasanova, and M.G.Pimenov,

Khim. Prirod. Soedin., 1978, 811.

5) M.K.W.Li and P.J.Scheuer, Tetrahedron Lett., 25, 2109, (1984).

6) B.R.Davis and I.R.N.McCormick, J. Chem. Soc., Perkin Trans. 1, 1979, 3001.

7) cf. S.Wagatsuma, S.Higuchi, H.Ito, T.Nakano, Y.Naoi, K.Sakai T.Matsui, Y.Takahashi, A.Nishi, and S.Sano, Org. Prep. Proced. Int.5, 65 (1973).

8) The compounds **4** and **5** could be formed through the opening of an initially formed epoxide by participation of the methoxyl group on the benzene ring.

9) M.Node, K.Nishide, K.Fuji, and E.Fujita, J. Org. Chem.,45, 427(1980).

10) R. W. Layer, J. Heterocycl. Chem., 12, 1067 (1975).

11) The spectral data for new compounds were in accord with the structure assigned. **8:** mp 61-62 °C, IR ($CHCl_3$) 1800 and 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=2.07 (3H, s), 2.24 (3H, s), 2.85 (2H, m), 3.66 (2H, s), 4.26 (2H, dd, J = 3 and 7 Hz), and 6.30 (1H, s); $C_{15}H_{16}O_4$ (m/z 260.1038). **11a:** viscous oil, IR ($CHCl_3$) 1735, 1662, and 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=1.47 (3H, s), 3.40 (2H, AB q), 3.70 (3H, s), 3.90 (1H, dd, J = 4 and 10 Hz), 5.69 (1H, s),and 6.96 (1H, s); $C_{17}H_{23}O_4Br_2Si$ (m/z 476.9703, M^+ - t-Bu). **12:** mp 137-138 °C, UV (MeOH) 238 (ε, 19100), 263 (19600), 381 (sh, 16000),and 394 nm (19200); IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=-0.16 (3H,s), 0.04 (3H ,s), 0.78 (9H, s), 2.10-2.18 (2H), 2.25 (3H,s), 2.89-3.06 (2H, m), 3.67-3.87(3H, m), 5.58 (1H, s), 6.94, and 7.16 (each 1H, AB type, J = 11.5 Hz); $C_{20}H_{28}O_3Si$ (m/z 344.1807). **13:** amorphous solid, UV (MeOH) 234 (ε, 15100), 267 (19200), 377 (sh, 12200), and 393 nm (15200); IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=-0.10 (3H,s), -0.01 (3H,s), 0.81 (9H,s), 2.00-2.23 (2H,m) 2.33 (3H,s) 2.83-3.10 (2H,m) 3.68-3.91 (3H, m), 5.52 (1H, s), 6.72 (1H, brs, W_H = 4.3 Hz),and 7.08 (1H, brs, W_H = 4.3 Hz);. $C_{20}H_{28}O_3Si$ (m/z 344.1814). **16:** amorphous solid, UV (MeOH) 240 (ε, 16000), 285 (111600), and 423 nm (16500); IR($CHCl_3$) 3350, 1755, 1723, and 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=2.51 (3H, s), 3.98 (3H, brs, W_H = 5.1Hz), 7.64 (1H, d, J = 11.4 Hz) 8.85(1H, d, J = 11.4 Hz), and 9.96 (1H, s).

12) M.Barbier, D.H.R.Barton, M.Devys, and R.S.Topgi, J. Chem. Soc., Chem. Commun., 1984, 743.

13) M. Komiyama and H. Hirai, Bull. Chem. Soc. Jpn., 54, 2053 (1981).

14) The relative configuation of **9a** or **9b** has not been determined.

15) Hydrolysis of **10** with potassium hydroxide/methanol gave the corresponding acid which was converted directly into **8** by treatment with a catalytic amount of sulfuric acid in refluxing acetic acid. (81% from **10**)

16) Treatment of the mixture with p-toluenesulfonic acid in refluxing benzene gave a separable mixture of desilylated **12** and **13**.

17) T. Mukaiyama, Angew. Chem., In. Ed. Engl., 18, 707 (1979).

(Received May 7, 1990)