

TOTAL SYNTHESSES OF ZALUZANIN C, ZALUZANIN D, AND 3-EPIZALUZANIN C¹⁾

Masayoshi ANDO,* Hiroaki YAMAOKA, and Kahei TAKASE

Department of Chemistry, Faculty of Science, Tohoku University
Aramaki-aza-Aoba, Sendai 980

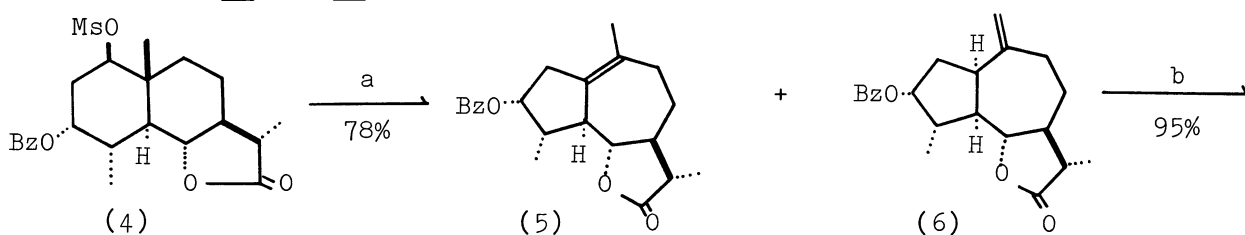
The biologically active guaianolides, zaluzanin C and zaluzanin D, and the stereoisomeric guaianolide, 3-epizaluzanin C, have been synthesized by two different procedures. The stereochemistry at C₃ of zaluzanin C has been established to be S configuration by this synthesis.

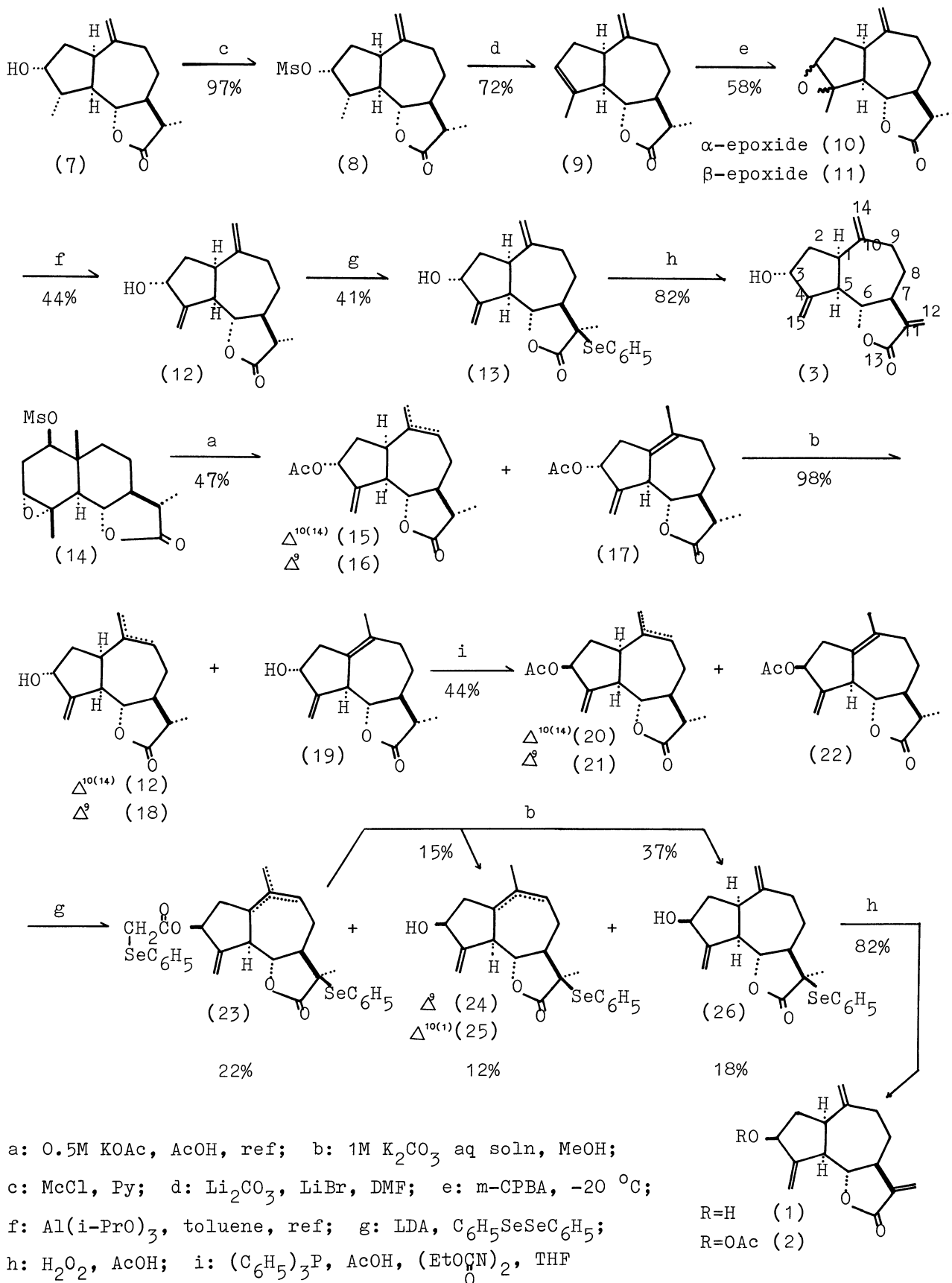
Zaluzanin C (1) and zaluzanin D (2) were originally isolated from Zaluzania augusta and Zaluzania triloba and their structures were proposed by Romo de Vivar et al. as shown in structures (1) and (2) except the stereochemistry at C₃.²⁾ The stereochemistry at C₃ of 1 was later deduced to be S configuration by Nagumo et al. on the basis of Horeau's method.³⁾ Recently 3-epizaluzanin C (3) was also isolated from Vernonia anisochaetoides by Bohlmann et al.⁴⁾ It is interesting that 1 and 2 show high biological activities. Thus 1 shows tumor inhibitory activity⁵⁾ and 1 and 2 show the inhibitory activity toward germination and root elongation of rice in the husk.⁶⁾ In this paper we want to report the syntheses of 1, 2, and 3.

One of the starting materials of our syntheses of zaluzanin C and its related compounds is an exocyclic olefin (6). As had been reported in our previous paper,⁷⁾ the solvolytic rearrangement of a mesylate (4) gave a mixture of an endocyclic olefin (5) and the exocyclic olefin (6). Since the direct separation of the mixture was difficult, 6 was isolated from the mixture in 40% yield by means of the selective epoxidation of 5. The hydrolysis of 6 and the successive mesylation of the resulting alcohol (7) gave a mesylate (8) in 92% yield. The treatment of 8 with LiBr and Li₂CO₃ in DMF gave a trisubstituted olefin (9) in 72% yield. The undesired disubstituted olefin was not formed. The regioelec-

tive epoxidation of 9 gave a 4:1 mixture of an α -epoxide (10) and a β -epoxide (11) in 58% yield. The stereochemical assignment is based on the consideration that the reagent attacks 9 preferentially from the less hindered convex face. The assignment was also supported from the analysis of the NMR spectrum (in CDCl_3) of the mixture of 10 and 11. The $\text{C}_6\text{-H}$ of 11 (δ 4.24) showed the signal at the 0.26 ppm lower field than the corresponding signal of 10 (δ 3.98) by the deshielding effect of the oxygen atom of the syn epoxide ring.^{7,8)} The treatment of the 4:1 mixture of 10 and 11 with $\text{Al}(\text{i-PrO})_3$ in refluxing toluene⁷⁾ for 23 h gave an α -allyl alcohol (12) in 44% yield and a 1:1 mixture of recovered 10 and 11 in 27% yield. The phenylselenenylation of 12 and the successive oxidation⁹⁾ of the resulting phenylseleno lactone (13) gave an α -methylene- γ -lactone (3) in 34% yield. The NMR spectrum (200 MHz, in C_6D_6) of 3 was in complete agreement with the NMR spectrum (270 MHz, in C_6D_6) of 3-epizaluzanin C.⁴⁾ The stereochemistry at C_3 of 3-epizaluzanin C was established to be R configuration from this synthesis.

We tried another approach employing an epoxymesylate (14) as the starting material.¹⁰⁾ The treatment of 14 with 0.5 M KOAc in refluxing acetic acid for 24 h gave an inseparable mixture of a disubstituted olefin (15), a trisubstituted olefin (16), and a tetrasubstituted olefin (17) in 47% yield.¹¹⁾ The hydrolysis of this mixture gave a corresponding mixture of allyl alcohols. The analysis of the NMR spectrum of this mixture showed that the major product was identical with 12 and the two minor products were the corresponding tri- and tetrasubstituted olefins (18 and 19).¹¹⁾ For the practical purpose, we employed this mixture in the next step. For the syntheses of zaluzanin C and zaluzanin D, the inversion of the 3α -hydroxyl group of 12 is necessary in this stage. The treatment of the mixture of 12, 18, and 19 with acetic acid in the presence of triphenylphosphine and diethyl azodicarboxylate¹²⁾ gave a mixture of acetates (20, 21, and 22).¹¹⁾ The phenylselenenylation⁹⁾ of this mixture and the successive separation by TLC gave diselenides as a mixture of the three possible regioisomers of double bond (23, 22%), a 1:1 mixture of seleno lactones possessing tri- and tetrasubstituted double bonds (24 and 25, 12%), and a seleno lactone possessing a disubstituted





double bond (26, 18%). The hydrolysis of 23 gave the 1:1 mixture of 24 and 25, and 26 in 15% and 37% yields, respectively. The structure of 26 was supported by the analysis of the NMR spectrum (in CDCl_3)¹³⁾ as well as the consideration of the reaction path. The oxidative syn-elimination of 26 gave an α -methylene- γ -lactone (1), which was identical with zaluzanin C in the comparison of the NMR spectra. The conversion of zaluzanin C to zaluzanin D has already been reported.²⁾ The stereochemistries at C_3 of zaluzanin C and zaluzanin D were established to be S configuration from this synthesis.

The authors wish to express their thanks to Professor Ferdinand Bohlmann of Technical University Berlin, for the generous gift of the NMR spectrum of 3-epi-zaluzanin C. We also would like to thank Professor Yoshinori Asakawa of Tokushima-Bunri University for the NMR and IR spectra of zaluzanin C and its related compounds. The present work was partially supported by a Grant-in-Aid for Scientific Research from Ministry of Education (No 554155). The authors are indebted to Nippon Shinyaku Co., LTD., for the generous donation of santonin.

References

- 1) Studies on the Syntheses of Sesquiterpene Lactones VI. Part V in this series: see reference 7).
- 2) A. Romo de Vivar, A. Cabrera, A. Ortega, and J. Romo, *Tetrahedron*, 23, 3903 (1967); J. Romo, C. L. Vanegas, *Bol. Inst. Quim. Univ. Nac. Aunto. Mex.*, 21, 82 (1969)[*Chem. Abstr.*, 73, 35540k (1970)].
- 3) S. Nagumo, K. Izawa, K. Higashiyama, and M. Nagai, *Yakugaku Zasshi*, 100, 427 (1980).
- 4) F. Bohlmann, G. Brindöpke, and R. C. Rastogi, *Phytochemistry*, 17, 475 (1978).
- 5) S. D. Jolad, R. M. Wiedhopf, and J. R. Cole, *J. Pharm. Sci.*, 63, 1321 (1974).
- 6) Y. Asakawa and T. Takemoto, *Phytochemistry*, 18, 285 (1979).
- 7) M. Ando, A. Akahane, and K. Takase, *Chem. Lett.*, 1978, 727.
- 8) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-day Inc., San Fransisco (1964), p 99; L. A. Paquette, W. E. Fristad, C. A. Schuman, M. A. Beno, and G. G. Christoph, *J. Am. Chem. Soc.*, 101, 4645 (1979); L. A. Maçaira, F. W. L. Machado, M. Garcia, and J. A. Rabi, *Tetrahedron Lett.*, 21, 773 (1980).
- 9) P. A. Grieco and M. Miyashita, *J. Org. Chem.*, 39, 120 (1974).
- 10) M. Ando, K. Tajima, and K. Takase, *Chem. Lett.*, 1978, 617.
- 11) The attempted separations of these mixtures by HPLC or TLC of silica gel in various conditions were unsuccessful in any case. The ratio of exo olefin/endo olefins (tri- and tetrasubstituted olefins) in these mixtures was determined to be ca. 2 by the analyses of their NMR spectra.
- 12) O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Jpn.*, 44, 3427 (1971).
- 13) The C_6 -H of 26 appeared at the 0.16 ppm lower field than the C_6 -H of 13 by the deshielding effect of the 3β -hydroxyl group of 26 (δ 4.16 and δ 4.00).

(Received January 28, 1982)