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TOTAL SYNTHESES OF ZALUZANIN C, ZALUZANIN D, AND 3-EPIZALUZANIN C[1)]

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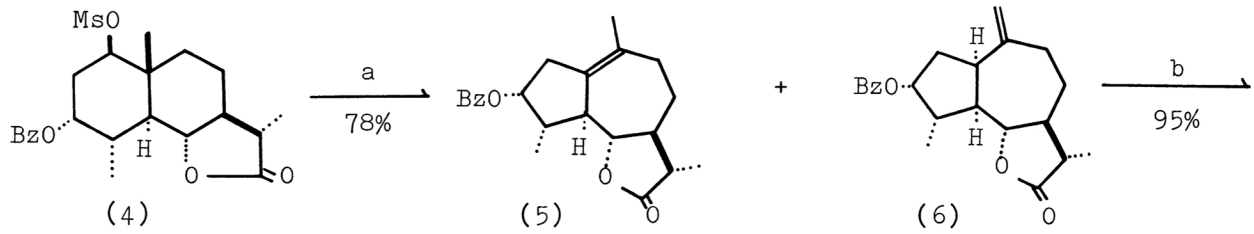
The biologically active guaianolides, zaluzanin C and zaluzanin D, and the stereoisomeric guaianolide, 3-epizaluzanin C, have been synthesized by two different procedures. The stereochemistry at C_3 of zaluzanin C has been established to be S configuration by this synthesis.

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 C_3.[2)] The stereochemistry at C_3 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 activity[5)] 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.

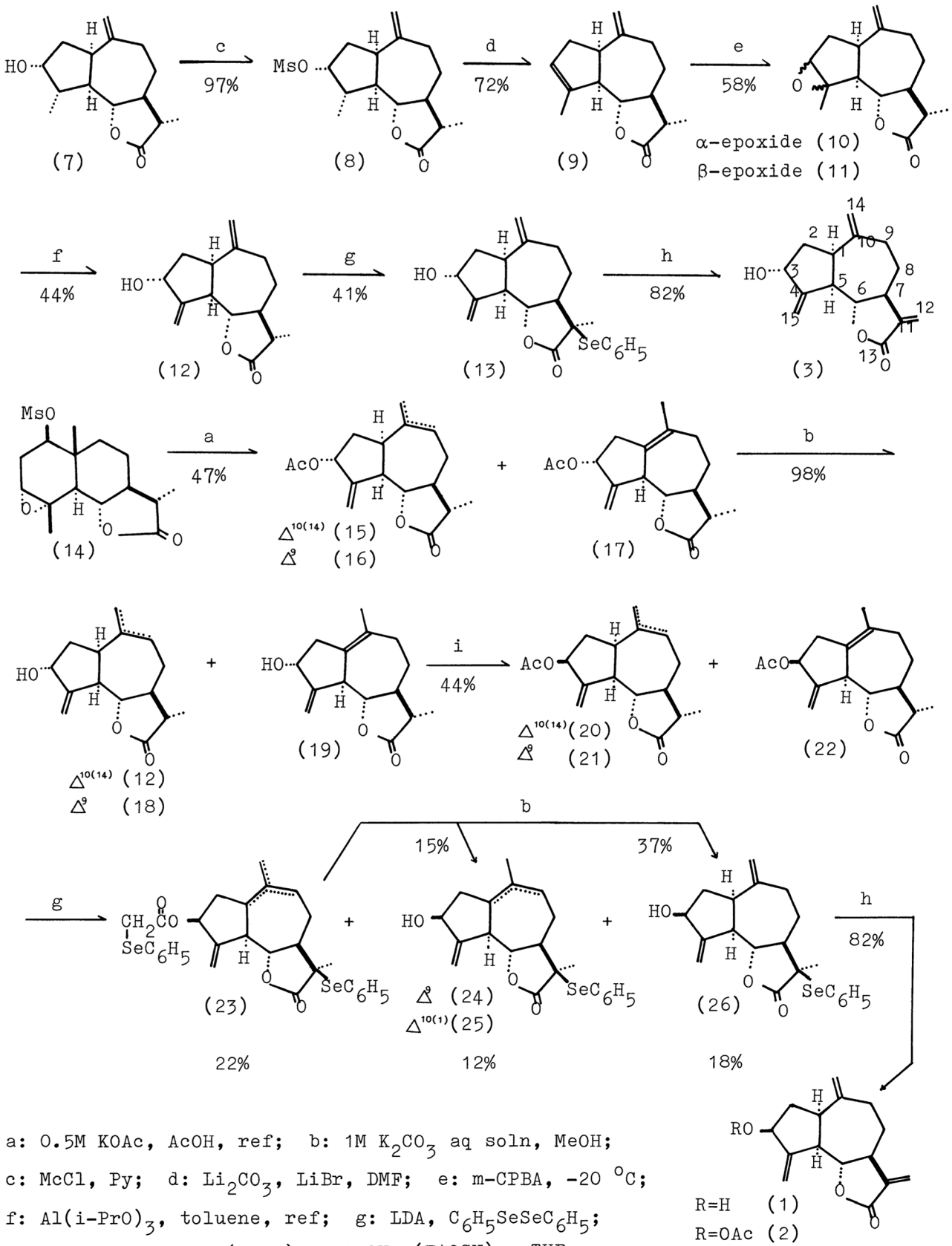
One of the starting materials of our syntheses of zaluzanin C and its related compounds is an exocyclic olefin (6). As had been reported in our previous paper,[7)] the solvolytic rearrangement of a mesylate (4) gave a mixture of an endocyclic olefin (5) and the exocyclic olefin (6). Since the direct 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 Li_2CO_3 in DMF gave a trisubstituted olefin (9) in 72% yield. The undesired disubstituted olefin was not formed. The regioselec-

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 C_6-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 $Al(i\text{-}PrO)_3$ in refluxing toluene[7] 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 oxidation[9] 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 azodicarboxylate[12] gave a mixture of acetates (20, 21, and 22).[11] The phenylselenenylation[9] 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



(4) (5) (6)



a: 0.5M KOAc, AcOH, ref; b: 1M K_2CO_3 aq soln, MeOH;
c: McCl, Py; d: Li_2CO_3, LiBr, DMF; e: m-CPBA, -20 °C;
f: $Al(i\text{-}PrO)_3$, toluene, ref; g: LDA, $C_6H_5SeSeC_6H_5$;
h: H_2O_2, AcOH; i: $(C_6H_5)_3P$, AcOH, $(EtO\overset{O}{\overset{\|}{C}}N)_2$, THF

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.

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