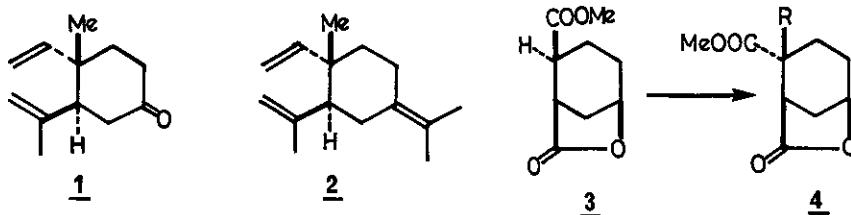


STERESELECTIVE ALKYLATION OF ESTER LACTONE.  
SYNTHESIS OF dl-GEIJERONE AND FORMAL SYNTHESIS OF dl- $\gamma$ -ELEMENE

Takeshi Wakamatsu,\* Hiromu Hara, and Keiko Taira (nee Abe)  
Faculty of Pharmaceutical Sciences, Hokkaido University,  
Sapporo 060, Japan  
Yoshio Ban  
School of Pharmaceutical Science, Toho University, Miyama 2-2-1,  
Funabashi, Chiba 274, Japan

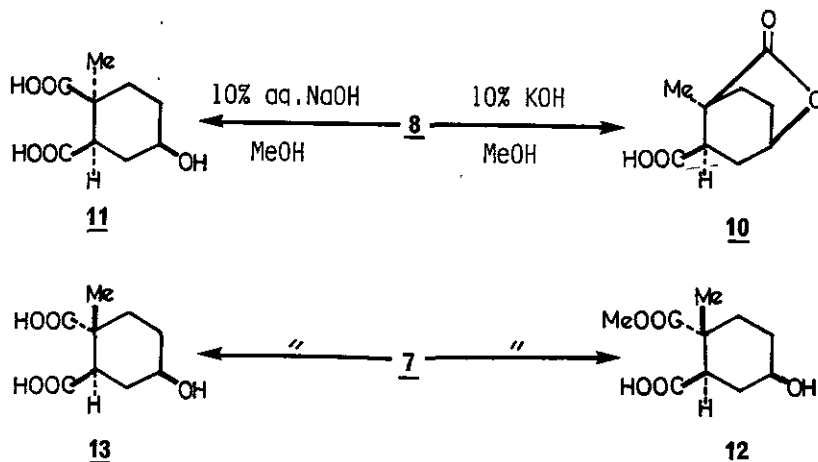
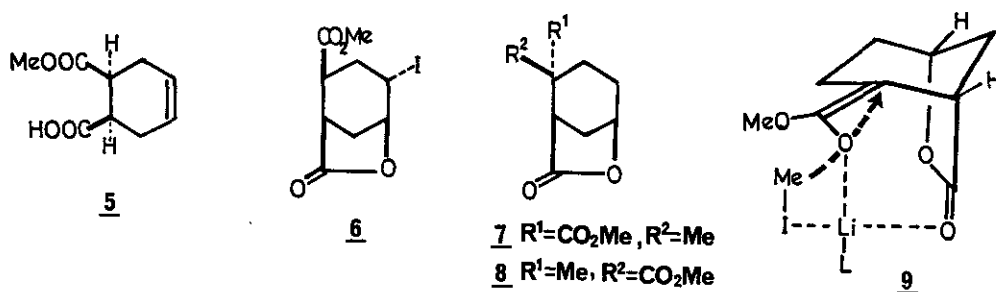
**Abstract** — Geijerone **1** was synthesized in racemic form via stereoselective alkylation of an ester lactone conformationally fixed with its bridged lactone ring. dl- $\gamma$ -Elemene **2** has already been obtained from **1**.

The generation of quaternary carbon atoms with stereochemical control is an important problem in organic synthesis. The occurrence of six-membered or its bicyclic system (i.e. sesquiterpenes such as elemenes<sup>1</sup>) in a number of biologically active natural products has prompted us to develop new methods for the elaboration of substituted cyclohexanes. We previously reported<sup>2</sup> a stereoselective alkylation of cyclohexanecarboxylate derivatives which provided a new process for the formation of cis-fused  $\delta$ -valerolactone. In this communication we describe the control of the stereochemistry of substituents necessary in the synthesis of geijerone **1**<sup>3</sup> and  $\gamma$ -elemene **2**<sup>4</sup> which we achieved by imposing a rigid conformation on the cyclohexanecarboxylate (**3**  $\rightarrow$  **4**).<sup>5</sup>

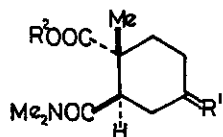


Treatment of *cis*-4-cyclohexene-1,2-dicarboxylic acid monomethyl ester **5** with iodine and potassium iodide in aqueous sodium carbonate afforded the iodolactone **6** [mp 83-86°C; IR max (nujol) 1765, 1720  $\text{cm}^{-1}$ ;  $^1\text{H NMR}(\text{CDCl}_3)\delta$  3.75(s,3H), 4.55(m,1H), 4.84(m,1H); MS  $m/z$  310( $\text{M}^+$ )] in 70% yield. Reduction of **6** with tri-*n*-butyltinhydride in ether over 1.5 h gave the bicyclic lactone **3** [bp 101°C(0.03mmHg); IR max (film) 1785, 1735  $\text{cm}^{-1}$ ;  $^1\text{H NMR}(\text{CDCl}_3)\delta$  2.78(m,1H), 3.75(s,3H), 4.85(m, w/2=15 Hz,1H); MS  $m/z$  184( $\text{M}^+$ )] in 97% yield after purification by chromatography on silica gel.

The crucial alkylation of **3** was carried out by methyl iodide using lithium diisopropylamide(LDA) as base in tetrahydrofuran(THF)-hexamethylphosphorous triamide(HMPT)(4:1) at room temperature for 20 h to give 74% of the desired lactone **7** [mp 79-80°C; IR max(nujol) 1765, 1720  $\text{cm}^{-1}$ ;  $^1\text{H NMR}(\text{CDCl}_3)\delta$  1.33(s,3H), 2.77(m,1H), 3.74(s,3H), 4.80(m,1H); MS  $m/z$  198( $\text{M}^+$ )] and 17% of the isomeric lactone **8** [mp 68.5-69.5°C; IR max (nujol) 1765, 1720  $\text{cm}^{-1}$ ;  $^1\text{H NMR}(\text{CDCl}_3)\delta$  1.35(s,3H), 2.95(m,1H), 3.74(s,3H), 4.76(m,1H); MS  $m/z$  198( $\text{M}^+$ )] in a ratio of 82:18, respectively. On the other hand, when this alkylation was performed in THF solution without the addition of HMPT, the ratio of the products of **7** and **8** was changed to 35:65.



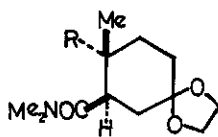
It is obviously of interest to note that alkylation of the anion obtained by deprotonation of 3 in the presence of HMPT occurred stereoselectively on the more hindered convex site. This degree of control should be proceeded with selective formation of the geometric enolate 9(E-enolate) rather than its isomeric enolate(Z-enolate), in which lithium cation is separated far from carbonyl oxygen, by the effects known as solvation of the coordinating HMPA.<sup>7,8</sup> The stereochemistry assigned to 7 and 8 obtained in this way was verified by the following chemical transformations. The minor lactone 8 was converted to the known derivatives 10 [mp 144-145°C (lit.<sup>9</sup> 144-145°C)] and 11 [mp 181-182°C (lit.<sup>9</sup> 181-182°C)] under basic conditions, as depicted. Similarly, exposure of the major lactone 7 to basic solution gave the corresponding compounds 12 [mp 128-129°C; IR max (nujol) 3430, 1710  $\text{cm}^{-1}$ ;  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.24(s,3H), 3.02(dd, J=13 and 4 Hz,1H), 3.66(s,3H); MS m/z 216( $\text{M}^+$ )] and 13 [mp 205-206°C; IR max(nujol) 3400, 1715  $\text{cm}^{-1}$ ;  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.61(s,3H); MS m/z 202( $\text{M}^+$ )].



**14**  $\text{R}^1=\text{O}$ ,  $\text{R}^2=\text{Me}$

**15**  $\text{R}^1=\text{O}$ ,  $\text{R}^2=\text{Me}$

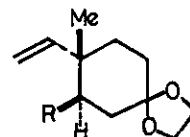
**16**  $\text{R}^1=\text{O}$ ,  $\text{R}^2=\text{H}$



**17**  $\text{R}=\text{CH}_2\text{OH}$

**18**  $\text{R}=\text{CHO}$

**19**  $\text{R}=\text{CH}=\text{CH}_2$



**20**  $\text{R}=\text{CH}_2\text{COCH}_3$

**21**  $\text{R}=\text{C}(\text{CH}_3)=\text{CH}_2$

The keto amide 14 was easily obtained from 12 by two steps [i.  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ , acetone, 81%. ii.  $\text{SOCl}_2$ ,  $\text{C}_6\text{H}_6$  followed by  $\text{Me}_2\text{NH}$ , ether, 84%]. Acetalization of 14 with ethylene glycol in the presence of a catalytic amount of p-toluenesulfonic acid followed by saponification with 5% aqueous sodium hydroxide gave 16 [mp 169-171°C;  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.54(s,3H), 2.93(s,3H), 3.11(s,3H), 3.48(dd, J=12 and 4.5 Hz,1H), 4.00(s,4H), 11.07(br,1H)] in 73% yield. Treatment of 16 with ethyl chloroformate in the presence of triethylamine at  $-30^\circ\text{C}$  and subsequent reduction of the resulting mixed anhydride with sodium borohydride at  $-10^\circ\text{C}$  afforded the desired alcohol 17 in 61% yield after purification by chromatography. Oxidation of 17 with pyridinium chlorochromate in dichloromethane led to the acetal aldehyde 18 [mp 64-66°C IR max (nujol) 2710, 1720, 1640  $\text{cm}^{-1}$ ;  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.47(s,3H), 2.92(s,3H), 3.10(s,3H), 3.32(dd, J=12 and 5 Hz,1H), 3.98(s,4H), 9.58(s,1H); MS m/z 255( $\text{M}^+$ )] in 85% yield. The Wittig reaction of 18 with methylenetriphenylphosphorane in benzene gave the vinylamide 19 in 54% yield which in turn was converted to the vinylketone 20 in 76% yield by the addition of methyl lithium.

Finally, dl-geijerone 1 was obtained from 20 by two steps [i.  $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$ , n-BuLi,  $\text{C}_6\text{H}_6$ , 43%. ii. 10% HCl, THF, 85%]. Spectral properties of the synthetic geijerone 1 were identical in all respects with those of a sample<sup>3b</sup> kindly provided by Professor A. Yoshikoshi. Since Yoshikoshi<sup>4d</sup> had reported the successful conversion of geijerone 1 into  $\gamma$ -elemene 2 by two steps, the present synthesis of dl-geijerone means a formal total synthesis of dl- $\gamma$ -elemene.

#### ACKNOWLEDGMENTS

We express our thanks to Professor A. Yoshikoshi, Chemical Research Institute of Non-aqueous Solution, Tohoku University, for his generous gift of spectra of dl-geijerone 1. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

#### REFERENCES

1. J. R. Hanson, "Terpenoids and Steroids" published by the Royal Society of Chemistry.
2. T. Wakamatsu, H. Hara, and Y. Ban, Tetrahedron Lett., 1227 (1979).
3. Isolation: a) A. F. Thomas, Helv. Chim. Acta, **55**, 2429 (1972). Synthesis: b) M. Kato, H. Kurihara, and Y. Yoshikoshi, J. C. S. Perkin I, 2740 (1979)
4. Isolation: a) J. H. Gough and M. D. Sutherland, Austral. J. Chem., **17**, 1270 (1964). b) R. Bernardi, C. Cardani, D. Ghiringhelli, and A. Selva, Chimica e Industria, **52**, 581 (1970). c) C. Gauteer and B. Keller-Wajtkiewicz, Helv. Chim. Acta, **54**, 183 (1971). Synthesis: d) see ref. 3 b).
5. For conjugate addition of an organocuprate to bicyclic cyclohexenones see G. Stork and E. W. Logusch, Tetrahedron Lett., 3361 (1979).
6. I. N. Nazarov and V. F. Kucherov, Izv. Akad. Nauk, SSSR, Otd. Khim. Nauk, 329 (1954).
7. R.E. Ireland, R. H. Mueller, and A. K. Willard, J. Am. Chem. Soc., **98**, 2868 (1976).
8. A. S. Narula, Tetrahedron Lett., 4119 (1981).
9. P. R. Bruck, R. D. Clark, R.S. Davidson, W. H. H. Gunter, P.S. Littlewood, and B. Lythgoe, J. Chem. Soc. C, 2529 (1967).

Received, 2nd February, 1987