STEREOSELECTIVE ALKYLATION OF ESTER LACTONE. SYNTHESIS OF dl-GEIJERONE AND FORMAL SYNTHESIS OF dl-γ-ELEMENE

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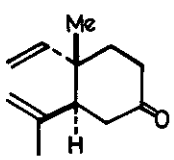
Abstract — Geijerone 1 was synthesized in racemic form via stereoselective alkylation of an ester lactone conformationally fixed with its bridged lactone ring. dl-γ-Elemene 2 has already been obtained from 1.

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[1]) in a number of biologically active natural products has prompted us to develop new methods for the elaboration of substituted cyclohexanes. We previously reported[2] a stereoselective alkylation of cyclohexenecarboxylate derivatives which provided a new process for the formation of cis-fused δ-valerolactone. In this communication we describe the control of the stereochemistry of substituents necessary in the synthesis of geijerone 1[3] and γ-elemene 2[4] which we achieved by imposing a rigid conformation on the cyclohexanecarboxylate (3 ⟶ 4).[5]



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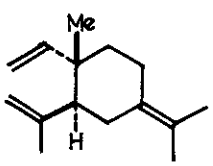

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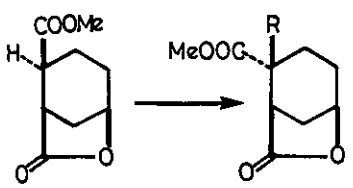
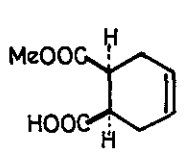


3 4

Treatment of cis-4-cyclohexene-1,2-dicarboxylic acid monomethyl ester 5[6] with iodine and potassium iodide in aqueous sodium carbonate afforded the iodolactone 6 [mp 83-86°C; IR max (nujol) 1765, 1720 cm^{-1}; ^1H NMR($CDCl_3$)δ 3.75(s,3H), 4.55(m,1H), 4.84(m,1H); MS m/z 310(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 cm^{-1}; ^1H NMR($CDCl_3$)δ 2.78(m,1H), 3.75(s,3H), 4.85(m, w/2=15 Hz,1H); MS m/z 184(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 cm^{-1}; ^1H NMR($CDCl_3$)δ 1.33(s,3H), 2.77(m,1H), 3.74(s,3H), 4.80(m,1H); MS m/z 198(M^+)] and 17% of the isomeric lactone 8 [mp 68.5-69.5°C; IR max (nujol) 1765, 1720 cm^{-1}; ^1H NMR($CDCl_3$)δ 1.35(s,3H), 2.95(m,1H), 3.74(s,3H), 4.76(m,1H); MS m/z 198(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.



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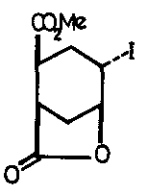

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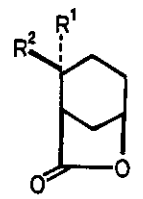
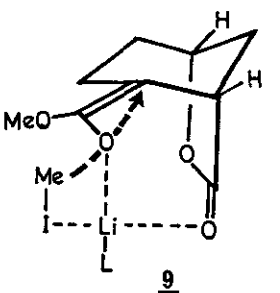


7 R^1=CO_2Me, R^2=Me

8 R^1=Me, R^2=CO_2Me



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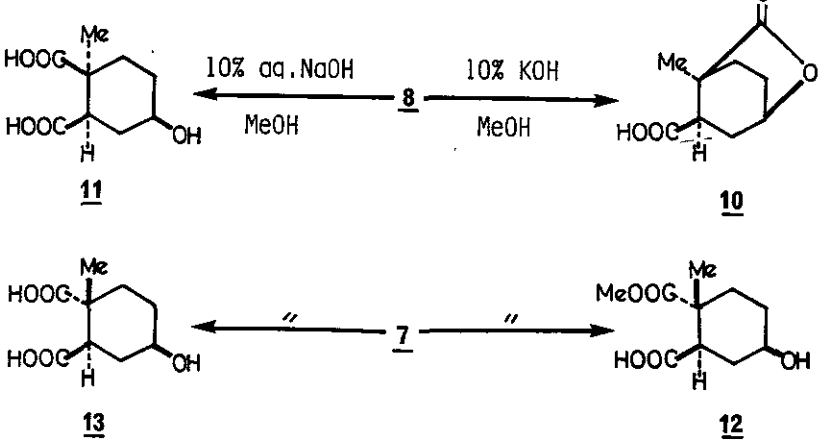
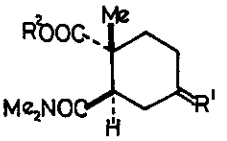
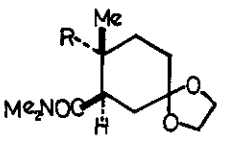


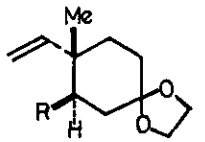
It is obviously of interest to note that alkylation of the anion obtained by deprotonation of 3 in the presence of HMPT occurred stereoselectively on the more hindered convex site. This degree of control should be proceeded with selective formation of the geometric enolate 9(E-enolate) rather than its isomeric enolate(Z-enolate), in which lithium cation is separated far from carbonyl oxygen, by the effects known as solvation of the coordinating HMPA.[7,8] 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.[9] 144-145°C)] and 11[mp 181-182°C(lit.[9] 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 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.24(s,3H), 3.02(dd, J=13 and 4 Hz,1H), 3.66(s,3H); MS m/z 216(M^+)] and 13 [mp 205-206°C; IR max(nujol) 3400,1715cm^{-1}; ^1H NMR($CDCl_3$)δ 1.61(s,3H);MS m/z 202(M^+)].

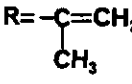


14 R^1=O , R^2=Me
15 R^1=  , R^2=Me
16 R^1=  , R^2=H



17 R=CH_2OH
18 R=CHO
19 R=$CH=CH_2$



20 R=CH_2COCH_3
21 R= 

The keto amide 14 was easily obtained from 12 by two steps [i. CrO_3, H_2SO_4, acetone, 81%. ii. $SOCl_2$, C_6H_6 followed by Me_2NH, 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; ^1H NMR($CDCl_3$)δ 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°C and subsequent reduction of the resulting mixed anhydride with sodium borohydride at -10°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 cm^{-1}; ^1H NMR($CDCl_3$)δ 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(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 methyllithium.

Finally, dl-geijerone 1 was obtained from 20 by two steps [i. $Ph_3P^+CH_3Br^-$, n-BuLi, C_6H_6, 43%. ii. 10% HCl, THF, 85%]. Spectral properties of the synthetic geijerone 1 were identical in all respects with those of a sample[3b] kindly provided by Professor A. Yoshikoshi. Since Yoshikoshi[4d] had reported the successful conversion of geijerone 1 into γ-elemene 2 by two steps, the present synthesis of dl-geijerone means a formal total synthesis of dl-γ-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 acknowleged.

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Received, 2nd February, 1987