Synthetic Photochemistry. XVI. Alternative Syntheses of dl-Geijierone and dl-γ-Elemene

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Synthetic Photochemistry. XVI.[1] Alternative Syntheses of dl-Geijerone and dl-γ-Elemene

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Taking into an advantage of ready cyclohexenone formation from the photoadducts of enolized β-diketones with olefins, a new and versatile synthesis of elemenoids, monocyclic sesquiterpenoids, has been accomplished. The major photoadduct obtained by the reaction of methyl 2,4-diketopentanoate with isoprene, a formal element of terpenoids, was utilized to construct the functionalized cyclohexenone system having the proper functional groups for subsequent chemical transformations. Thus, racemic geijerone, a *trisnor*-elemenoid ketone, was obtained by a series of reactions, *i.e.*, zinc in acetic anhydride reduction of conjugated double bond, protection of the carbonyl group by the acetal formation, the Grignard methylation, dehydration of the tertiary alcohol, and finally a hydrolytic regenerations of the carbonyl group. Further conversion of geijerone into γ-elemene was verified by the Grignard reaction with isopropenyl magnesium bromide, an allylic displacement reaction with chloride, and the LAH reduction.

1. Introduction

In a course of studies on the photoaddition of methyl 2,4-diketopentanoate (**1**) with conjugated olefins, we have noticed that cycloheptatriene[2] and cyclopentadiene[3] yielded the $(2+2)\pi$ cycloadducts, and this observation suggests that the major cycloadducts with acyclic dienes are likely to be the similar $(2+2)\pi$ adducts, which are known to be convertible into cyclohexenone derivatives. Such functionality may be valuable for synthesizing natural products, especially, terpenoids or steroids. Currently, synthetic works of terpenoids are concentrated on physiologically active derivatives, *e. g.*, anti-tumour compounds, insect pheromones, *etc.*, and sesquiterpenoids are extremely rich source for them. In addition, since the sesquiterpenoids are biogenetically derived from farnesyl pyrophosphate (**A**), germacrene (**B**), a direct cyclization product of **A** with the ten-membered ring, should be the common precursor of many others, and must be an important target of syntheses. However, **B** and elemene (**C**) are mutu-

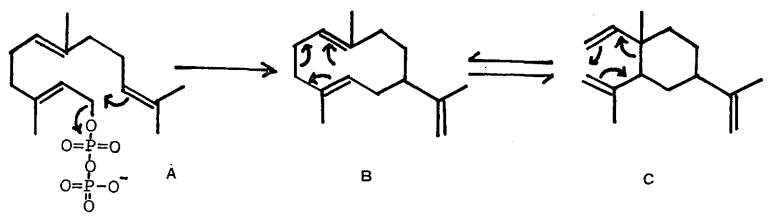

CHART 1

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ally interconvertible under conditions of Cope rearrangement *in vitro*, and isolations of many elemenoids have been suspected to be the artifacts. A novel synthesis of **C**, as a substitute for the synthesis of **B**, therefore must be worthwhile in the terpenoid chemistry.

This paper will describe an efficient approach to elemenoid sespuiterpenoids, geijerone (**3**,[4]) a *trisnor*-sesquiterpenoid ketone from *Juniperus communis L.*, which has been recently synthesized by Indian workers,[5] and γ-elemene (**4**),[6][7] starting from such a $(2+2)\pi$ photocycladdition of **1** with isoprene (**2**).

2. Results and Discussions

Unlike the ordinary photocycloadducts, the adducts of β-diketones and olefins easily dealdolize into 2,6-heptanedione derivatives, and a convertibility into cyclohexenones under mild conditions makes the photoreaction more general as the synthetic mean, *e.g.*, particularly the terpenoid syntheses. Taking an advantage of this neat reaction, we have now completed a short-step total synthesis of elemenoid sesquiterpenoids. Thus, when a neat mixture of **1** and **2** was irradiated at 0 to 5°C by means of a 400 W high-pressure mercury lamp for 5 h, two photoadducts, **5** and **6**, were formed and separated by use of a large-scale high-pressure liquid chromatograph. The major product (**5**), a colorless oil, 48%, revealed a presence of a vinyl group in the ^{1}H-NMR [δ[8]: 1.32(3H s), 2.04 (2H, m), 2.14 (3H, s), 2.40 (2H, m), 3.82 (3H, s), 5.17 (1H, dd, J=17, 1 Hz), 5.27 (1H, dd, J=11, 1 Hz), and 5.93 (1H, dd, J=17, 11 Hz)], but the minor product (**6**), a colorless oil, 14%, showed a isopropylidene group [δ: 1.74 (3H, br. s), 1.92 (2H, m), 2.00 (1H, m), 2.12 (3H, s), 2.40 (2H, m), 3.82 (3H, s), 4.76 (1H, m), and 5.00 (1H, m)]. Predominant occurrence of the photoaddition at the disubstituted double bond, an unexpected behavior, is particularly appropriate for this synthetic plan; previous findings show that the photoreactivity of **1** is mainly controlled by a steric effect.[9]

The cyclohexenone **7**, obtained by cyclization of **5** with *p*-toluenesulfonic acid (TsOH), has been transformed into geijerone (**3**) as follows: **7** was reduced by zinc in acetic acid to unseparable mixture of dihydro derivatives (**8c** and **8t**), which were then converted into a mixture of acetals (**9c** and **9t**) with ethylene glycol and TsOH. Although a separation of **9c** and **9t** was possible by silica gel column chromatography to obtain analytically pure materials, the methylation reaction with a Grignard reagent was carried out without fractionation. The alcohols (**10t** and **10c**) thus formed, colorless oils, were easily separated on a silica gel column, and the structures were determined by NMR spectral analysis. The *trans*-isomer, **10t**, was then dehydrated by thionyl chloride in pyridine to **11t**, a colorless oil. By hydrolysis in acetone with TsOH, **11t** afforded a colorless oil, which was identified to be geijerone (**3**)[4][5] in respects of NMR comparisons. Similarly, **10c** was dehydrated into **11c**, and then hydrolyzed to *epi*-geijerone, **12**.

By the Grignard reaction with isopropenylmagnesium bromide in tetrahydrofuran (THF), **3** produced an epimeric mixture of hydroxyelemenes (**13** and **14**), and their stereochemical distinguishment was made on the basis of the NMR evidence: Thus, **13** [δ: 0.97 (3H, s), 1.70

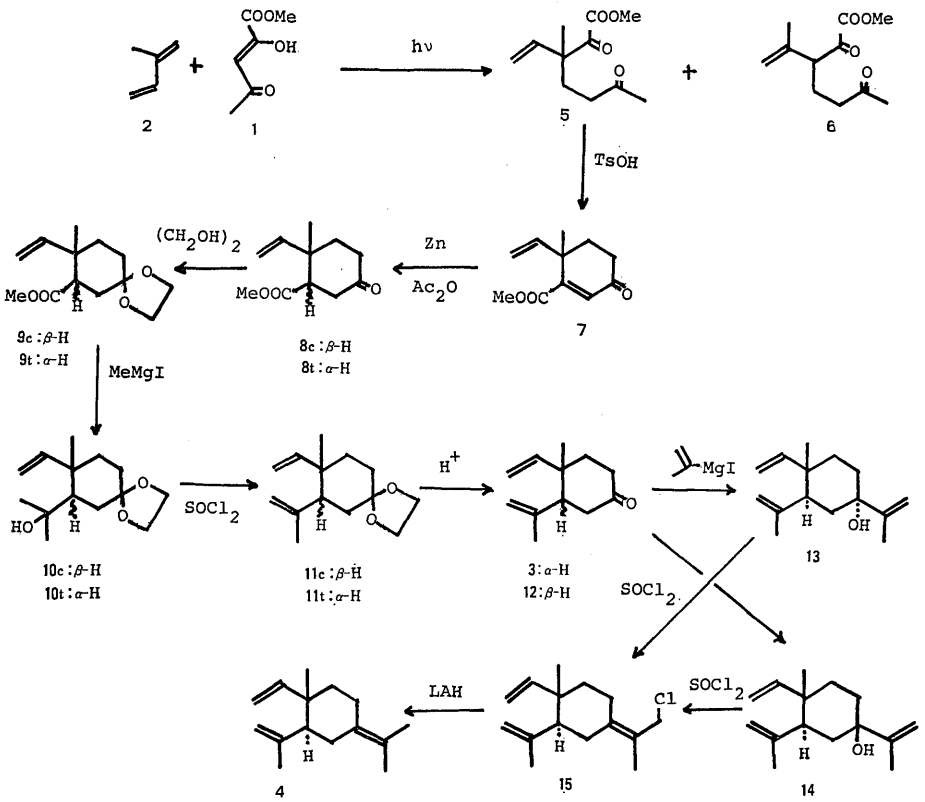


CHART 2

(3H, s), 1.82 (3H, s), 2.45 (1H, dd, J=12, 3 Hz), 4.57 (1H, br. s), 4.80 (3H, br. s), 4.96 (1H, dd, J=17.5, 1 Hz), 4.98 (1H, dd, J=10.5, 1 Hz), and 5.04 (1H, dd, J=17.5, 10.5 Hz)] revealed a characteristic signal ascribable for the methine proton at the carbon bearing isopropenyl group at δ 2.45, and an appearance of this low-field signal could be better explained in terms of an anisotropy from the tertiary hydroxy group of the 1,3-diaxial relationship. On the other hand, **14** [δ: 1.09 (3H, s), 1.68 (3H, s), 1.79 (3H, s), 4.58 (1H, br. s), 4.80 (2H, br. s), 4.97 (1H, dd, J=17, 1 Hz), 4.98 (1H, dd, J=10.5, 1 Hz), 5.02 (1H, br. s), and 5.72 (1H, dd, J=17, 10.5 Hz)] lacks this feature. Therefore, the structures were depicted as shown. **13** is a tertiary allyl alcohol, and therefore likely to cause an allyl rearrangement reaction by a nucleophilic reagent. Indeed, when **13** was treated with thionyl chloride in pyridine, the major product was shown to be such a product, **15**, 15-chloro-γ-elemene.[10] According to the NMR [δ: 1.08 (3H, s), 1.72 (3H, br. s), 1.79 (3H, br. s), 4.12 (2H, s), 4.62 (1H, br. s), 4.84 (1H, br. s), 4.89 (1H, dd, J=10.5, 1 Hz), 4.92 (1H, dd, J=17.5, 1 Hz), and 5.76 (1H, dd, J=17.5, 10.5 Hz)] spectrum, **15** is a single compound. The location of the chlorine atom was tentatively assigned on the basis of a sterical preference for an attack of chloride ion as depicted. The LAH reduction of **15** yielded γ-elemene (**4**)[6] in

a good yield.

Consequently, present investigation constitutes alternative total synthesis of **3** and **4** by photochemical construction of carbon frame-work. A formation of **15** by the allyl rearrangement from **13** or **14** would be a synthetic value in view of an easy introduction of oxygen function at the isopropylidene moiety of elemenoids.

3. Experimental Scction

Photocycloaddition Reaction of Methyl 2,4-Diketopentanoate (**1**) *with Isoprene* (**2**). **1** (2.6 g) and **2** (100 cm^3) were internally irradiated at 0 to 5°C under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp for 5 h. The reaction mixture was then chromatographed on a prepacked silica gel column (System 500 Apparatus, Waters Associates) and eluted by hexane: ethyl acetate (85 : 15), to give **5**, a colorless oil, 1.82 g (48 %) [Found : C, 62.32 ; H, 7.69 %. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60 %. δ(C) : 19.6(q), 29.7(q), 30.6(t), 38.1(t), 51.8(s), 52.2(q), 117.1(t), 138.9(d), 163.5 (s), 197.9(s), and 206.7(s). $\nu_{C=O}$: 1740, 1725 cm^{-1}], and **6**, a colorless oil, 520 mg (14 %) [Found: C, 62.38; H, 7.63 %. δ (C) : 20.9(q), 22.5(t), 29.7(q), 40.4(t), 52.6(q), 54.1(d), 116.6(t), 140.5(s), 161.9 (s), 192.5(s), and 207.3(s). $\nu_{C=O}$: 1740, 1725 cm^{-1}].

Cyclization of **5**. **5** (320 mg) was dissolved in anhydrous benzene (30 cm^3) containing TsOH (*ca.* 5 mg), and azeotropically dehydrated to give a colorless oil, which was further purified by silica gel column chromatography, **7**, 258 mg (88%) [Found: C, 67.75; H, 7.29 %. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27 %. δ: 1.46 (3H, s), 3.78 (3H, s), 5.03 (1H, dd, J=10.5, 1 Hz), 5.16(1H, dd, J=17.5, 1 Hz), 5.91(1H, dd, J=17.5, 10.5 Hz), and 6.55 (1H, s). δ(C) : 24.9 (q), 34.1(t), 36.4(t), 40.3(s), 52.1(q), 114.4(t), 132.4(t), 132.4(d), 153.8 (s), 166.6(s), and 198.8(s). $\nu_{C=O}$: 1730, 1670 cm^{-1}].

Zinc in Acetic Anhydride Reduction of **7**. **7** (110 mg) was dissolved in acetic anhydride (20 cm^3), and heated together with zinc dust (5 g) at 80 to 100°C for 5 h. Then, the mixture was washed several times with ether. This ethereal extract was passed through a silica gel column to give oily keto ester (**8**), a colorless oil, 93 mg (85 %) [Found: C, 67.22; H, 8.25 %. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22 %. Despite an intensive effort, separation of the stereoisomers, **8t** [δ: 1.17 (3H, s), 3.65(3H, s), 5.13 (1H, dd, J=10, 1.5 Hz), 5.16 (1H, dd, J=17.5, 1.5 Hz), and 5.88 (1H, dd, J=17.5, 10 Hz). $\nu_{C=O}$: 1745, 1710 cm^{-1}], and **8c** [δ: 1.26 (3H, s), 3.64 (3H, s), 5.11 (1H, dd, J= 10.5, 1.5 Hz), 5.15 (1H, dd, J=17.5, 1.5 Hz), and 6.12 (1H, dd, J=17.5, 10.5 Hz). $\nu_{C=O}$: 1745, 1708 cm^{-1}], was unsuccessful.

Reaction of **8** *with Ethylene Glycol*: *Formation of* **9**. The mixture of **8t** and **8c**(1 :1, 395 mg) was dissolved in anhydrous benzene (40 cm^3) containing ethylene glycol (4 cm^3) and TsOH (55 mg), and refluxed for 6 h. The mixture was then neutralized by sodium carbonate and extracted by ether. After an evaporation of the solvent, a brief silica gel chromatography of the extract gave a colorless oil, **9**, 474 mg (98 %). As anlytical samples, a coloress oil, **9t** [Found: C, 65.09; H, 8.40 %. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39 %. δ: 1.14 (3H, s), 3.59 (3H, s), 3.92 (4H, s), 5.01 (1H, dd, J=10.5, 1 Hz), 5.09 (1H, dd, J=17.5, 1 Hz), and 5.84 (1H, dd, J=17.5, 10.5 Hz)], and a colorless

oil, **9c** [δ: 1.14 (3H, s), 3.64 (3H, s), 3.92 (4H, s), 4.95 (1H, dd, J=11, 1 Hz), 5.07 (1H, dd, J=17, 1 Hz), and 6.19 (1H, dd, J=17, 11 Hz)], were isolated by repeated silica gel column chromatography.

The Grignard Methylation Reaction of **9**. To an anhydrous ether solution of methylmagnesium iodide (prepared from 11.64 g of methyl iodide), an ether solution of **9** (1.01 g) was added in drop by drop. The product obtained by a usual work up was chromatographed on a silica gel column to give colorless needles, mp 75–76.5°C, **10t**, 320 mg (40 %) [Found: C, 69.80; H, 9.99 %. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07 %. δ: 1.18 (3H, s), 1.19 (3H, s), 1.22 (3H, s), 1.5–2.1 (7H, m), 3.94 (4H, m), 4.96 (1H, dd, J=10.5, 1 Hz), 5.01 (1H, dd, J=17.5, 1 Hz), and 6.06 (1H, dd, J=17.5, 10.5 Hz)], and a colorless oil, **10c** (310 mg, 39 %) [Found: C, 69.71; H, 9.93 %. δ: 1.21 (3H, s), 1.22 (3H, s), 1.5–2.05 (7H, m), 3.94 (4H, *m*), 5.05 (1H, dd, J=10.5, 1.5 Hz), 5.07 (1H, dd, J=17.5, 1.5 Hz), and 6.42 (1H, dd, J=17.5, 10.5 Hz)], along with the recovered **9** (226 mg, 22 %).

Preparation of Geijerone (**3**): *Dehydration and Hydrolysis of* **10t**. **10t** (78 mg) was disolved in pyridine (2 cm³) and thionyl chloride (*ca.* 10 mg) and heated at 80°C for 30 min. After a removal of the volatile material, an extraction of the mixture by ether gave a colorless oil, **11t**, 60 mg [δ: 1.02 (3H, s), 1.71 (3H, br. s), 3.94 (4H, s), 1.5–2.1 (7H, m), 4.58 (1H, br. s), 4.82 (1H, br. s), 4.82 (1H, dd, J=10.5, 1 Hz), 4.98 (1H, dd, J=17.5, 1 Hz), and 5.81 (1H, dd, J=17.5, 10.5 Hz)], which was then hydrolyzed by refluxing in aqueous acetone containing a small amount of TsOH for 1 h. An ether extraction of the mixture afforded a colorless oil, 44 mg (81 % from **10t**), which showed the appropriate NMR [δ: 1.17 (3H, s), 1.72 (3H, br. s), 4.62 (1H, br. s), 4.90 (1H, m), 5.01 (1H, dd, J=10, 1 Hz), 5.02 (1H, dd, J=17, 1 Hz), and 5.83 (1H, dd, J=17, 10 Hz). δ(C): 18.3(q), 24.3(q), 37.5(t), 37.6(t), 39.3(s), 43.3(t), 52.1(d), 111.7(t), 113.5(t), 145.2(s), 147.2 (d), 211.1(s)] spectral figures for those of geijerone (**3**).

Preparation of epi-*Geijerone* (**12**). A pyridine solution (20 cm³) of **10c** (310 mg) was treated with thionyl chloride (*ca.* 30 mg) at 80°C for 3 h, and the mixture was heated *in vacuo* to remove the solvent. The residue thus obtained was purified by silica gel chromatography to give a colorless oil, **11c** [Found: M.W., 222.1630. Calcd for $C_{14}H_{22}O_2$: 222.1691]. A brief contact of this oily **11c** with aqueous acetone and HCl gave a colorless oil, **12**, 200 mg [Found: M. W., 178.1377. Calcd for $C_{12}H_{18}O$: 178.1358. δ: 1.18 (3H, s), 1.71 (3H, br. s), 4.68 (1H, br. s), 4.87 (1H, br. s), 5.13 (1H, dd, J=17.5, 1.5 Hz), 5.17 (1H, dd, J=10.5, 1.5 Hz), and 6.31 (1H, dd, J=17.5, 10.5 Hz). δ(C): 22.5(q), 26.5(q), 38.1(t), 39.0(s), 43.6(t), 54.3(d), 64.2(t), 114.1 (2C, t), 140.6(d), 144.8(s), 211.4(s)].

2, 4-Dinitrophenylhydrazone of **12**. Obtained as yellow orange crystals, mp 160–161 °C [Found: C, 60.27; H, 6.22; N, 15.48%, Calcd for $C_{18}H_{22}O_4$: C, 60.32; H, 6.19; N, 15.63 %].

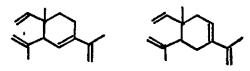
Reaction of **3** *with Isopropenylmagesium Bromide*. To anhydrous THF soltion (20 cm³) of isopropenymagesium bromide (prepared from 96 mg of isopropenyl bromide), an anhydrous THF solution (20 cm³) of **3** (53 mg) was added in drop by drop. After a hydrolysis by aqueous NH_4Cl, the mixture was extracted by

ether, and chromatographed on a silica gel column. A colorless oil obtained, 55 mg (84 %), was shown to be a 1 : 1-mixture by the NMR spectrometry, and fractionated to a colorless oil, **13**, 29 mg [Found: M. W., 220.1823. Calcd for $C_{15}H_{24}O$: 220.1823. ν: 3550, 3050, 2960 cm^{-1}], and another colorless oil, **14**, 26 mg [Found: M. W., 220.1822. ν: 3550, 3100, 2950 cm^{-1}].

The Formation of γ-Elemene (**4**) *from* **13**. A pyridine solution (5 cm^3) of **13** (28 mg) and thionyl chloride (20 mg) was heated at 60°C for 2 h. Evaporation of the mixture left a brownish oily residue which was extracted by ether and dried on sodium sulfate. From the extract, isolated after silica gel chromatography was a chlorohydrocarbon, **15**, a colorless oil, 22 mg (86 %) [*m/e*, 238, 240 (M^+). δ: 1.08 (3H, s), 1.72 (3H, s), 1.79 (3H, s), 4.12 (2H, s), 4.62 (1H, br. s), 4.84 (1H, br. s), 4.98 (1H, dd, J=10, 1 Hz), 4.92 (1H, dd, J=17.5, 1 Hz), and 5.76 (1H, dd, J=17.5, 10 Hz)].[10] Then, **15** (20 mg) was dissolved in THF (5 cm^3) and was reduced by LAH (15 mg) at room temperature. Silica gel column chromatography of the mixture yielded a colorless oil, **4**, 15 mg (68 %) [δ: 1.05 (3H, s), 1.65 (6H, s), 1.70 (3H, s), 4.59 (1H, br. s), 4.79 (1H, br. s), 4.85 (1H, dd, J=10.5, 1 Hz), 4.87 (1H, dd, J=17.5, 1 Hz), and 5.76 (1H, dd, J=17.5, 10.5 Hz)], which was identical with those of the authentic sample.[5]

4. References and Notes

1) Part XV: H. Takeshita, I. Kouno, H. Iwabuchi, M. Iino, and D. Nomura, Preceding Paper.
2) H. Takeshita, A. Mori, and Y. Toyonaga, *Bull. Chem. Soc. Jpn.*, **48**, 307 (1975).
3) H. Takeshita, A. Mori, and S. Itô, *Bull. Chem. Soc. Jpn.*, **47**, 1767 (1974).
4) A. F. Thomas, *Helv. Chim. Acta.* **55**, 2429 (1972).
5) S. D. Sharma, A. S. Sethi, and M. L. Sharma, *Indian J. Chem.*, **15B**, 958 (1977).
6) C. Ganter and B. K-Wojtkiewicz, *Helv. Chim. Acta*, **54**, 183 (1971).
7) For a recent account of general syntheses of elemenoids: M. Kodama, S. Yokoo, Y. Matsuki, and S. Itô, *Tetrahedron Lett.*, **1979**, 1687.
8) All the NMR spectra were taken in $CDCl_3$ solutions by an FX 100 Model apparatus, JEOL Co., and the chemical shifts were expressed in δ scale from the internal standard, TMS.
9) Within a series of cyclic olefins, **1** was utterly unreactive with trisubstituted double bonds, and this was interpreted in terms of a steric hindrance (Unpublished work in our laboratory).
10) As by-products, dehydrated hydrocarbons, $C_{15}H_{22}$, tetraenes, were obtained in small amount. The NMR spectral analysis indicated to be a mixture, **i** and **ii**, but no attempt for their separation has been successful sofer.



i **ii**