Synthetic Photochemistry. XXXI. The Cycloaddition Reaction of Myrcene with 2,4-Dioxopentanoate : A Facile Synthesis of a Versatile Intermediate for Cycloneryl Derivatives

Okaishi, Koya

Hatsui, Toshihide
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Takeshita, Hitoshi
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Synthetic Photochemistry. XXXI.[1] The Cycloaddition Reaction of Myrcene with 2,4-Dioxopentanoate: A Facile Synthesis of a Versatile Intermediate for Cycloneryl Derivatives

Koya OKAISHI , Toshihide HATSUI , and Hitoshi TAKESHITA*

Abstract　Methyl 2,4-dioxopentanoate and myrcene smoothly afforded the photoadducts by irradiation with a high-pressure mercury lamp.　The $(2+2)\pi$ adducts were selectively resulted from the conjugated double bond moiety.　Reductive cyclization of the adduct afforded cycloneryl derivatives, whose further chemical conversion were carried out.

Previously we have accomplished total syntheses of protoilludenes[2] and some elemenoid sesquiterpenoids[3] by means of the photocycloaddition of enolized β-diketone with appropriate olefins.　Particularly, taking the advantage that the conjugated olefins are capable of forming photocycloadducts with 2,4-Dioxopentanoate (**1**), [3,4] we have carried out the photocycloaddition with isoprene (**A**) to efficiently construct the C_{10}-frameworks[3,5] which were convertible to the correct head-to-tail monoterpenoid (iridoids) and sesquiterpenoid (elemenoids) skeleton.　Thus, the new way of versatile C_5-homologation for the terpenoid

[Scheme 1]

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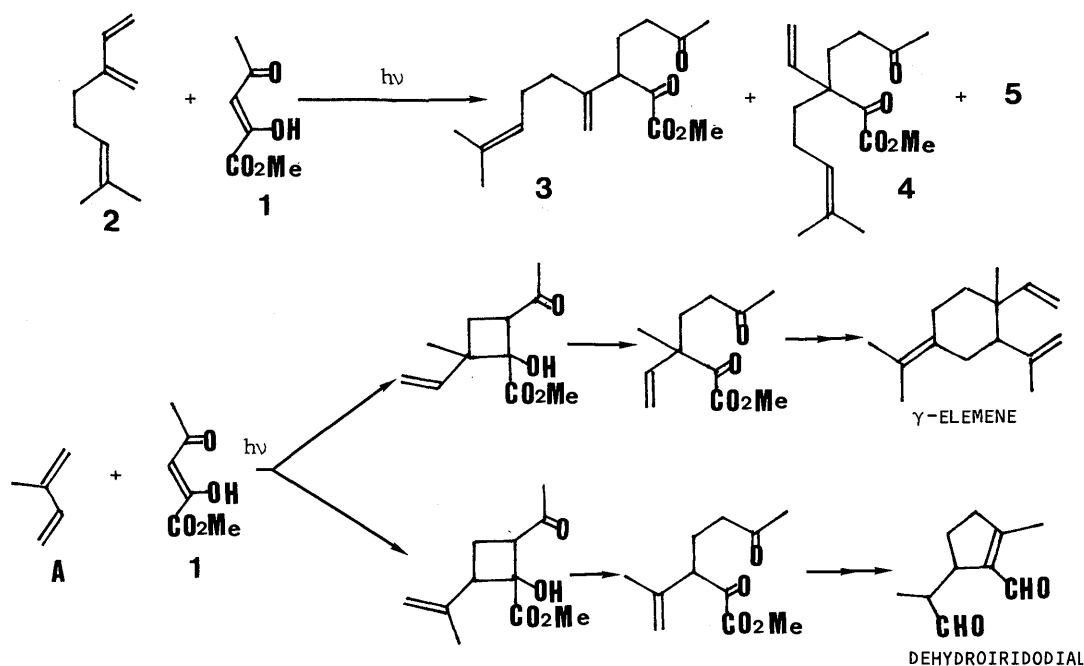
syntheses has been opened.

Threfore, it is interesting to check a further possibility to construct the sesquiterpene frameworks by the reaction of **1** and C_{10}-precursors. Herein, we wish to describe the results of the photocycloaddition of **1** with myrcene (**2**), an acyclic triene.

The photocycloaddition of **2** with **1** performed by means of a 400-W high-pressure tungsten lamp under a nitrogen atmosphere in an immersion apparatus equipped with a magnetic stirrer at 0−5°C, which was maintained by circulation of ice-cooled water. After 4 h, practically all of **1** have been consumed to give the photoadducts. The separation of these products was achieved by a preparative liquid chromatographic fractionation; the first fraction eluted from hexane-ethyl acetate (3 : 2) was the major product (**3**), a colorless liquid, in a 55% yield. The NMR of **3** revealed the characteristic isopropylidene signal remained, indicating thus the reaction occurred at one of the conjugated double bond, and the presence of the vinyl signals deduced its structure. The minor product (**4**) revealed similar NMR spectral features to **3**, but an important difference in the spectrum is a replacement of the vinyl signals in **3** to the isopropenyl signals. Therefore, its structure must be expressed as depicted in Scheme 1. Quite frequently, a third product (**5**) was detected; its yields were variable, and the formation was seemed to depend on the reaction conditions, and therefore, **5** is a secondary photoproduct. Such a by-product was already detected in the reaction of 2,4-dioxohexanoate with **2**,[6] and its formation will be independently reported.

The ratio of **3** and **4** was just reverse to the case of **1** with **A**, where the ratio of corresponding isomers was 4 : 1. In the present case, the electronically more reactive double bond in **2**, vinylidene group, is suffering a severe steric hindrance, and relatively high yield of **4** was observed.

Next, **4** was treated with zinc and titanium(IV) chloride in tetrahydrofuran (THF) to facilitate the intramolecular *retro*-ozonolysis leading to cyclopentane derivatives, which should have the same carbon arrangement with the cycloneryl derivatives, *i. e.*, cyclonerodiol, isolated from the microorganisms, *e. g.*, *Tricothecium roseum*.[7] and cyclonerotriol, from *Fusarium culmorum*.[8] Thus, **4** was treated with titanium (II) chloride, generated *in situ*, at − 5 °C; two 1,2-glycols (**6a** and **6b**) were obtained. Their stereostructures were solved by the ¹H- and ¹³C NMR comparisons with three glycols from the photoadducts of **1** with **A**,[5,9] whose stereochmistry has alredy established as *cis-cis* for **B** (yield from **A**; 8%), *cis-trans* for **C** (68%), and *trans-trans* for **D** (11%). Thus, **B** showed the characteristic ¹³C NMR siguals ascribable to the quarternary carbons bearing hydroxyl group at $\delta = 80.9$ and 88.5, which correspond to those appeared in the spectrim of **6b** at 83.5 and 89.6. In the same time, **C** revealed the signals at 81.5 and 85.2, which are in good agreement with the signals at 81.6 and 84.4 of **6a**. As a reference, those signals of **D** apperared at 84.5 and 85.1.

In addition, the ¹H NMR spectra also provided the supporting evidence; the chemical shift of the methyl group on the carbon bearing the tertiary hydroxyl group of **6a** appeared at 1.24, which is similar to that of **C** at 1.26, while the same signal of **6b** appeared at 1.10, which is also similar to that of **B** at 1.08. Again, the corresponding methyl signal of **D** was at 1.28.

Furthermore, in the series of the photoproducts from **1** and **A**, only the *cis*-1,2-glycols have been respectively reduced to a cyclopentene under the conditions.[9] Therefore, the fol-
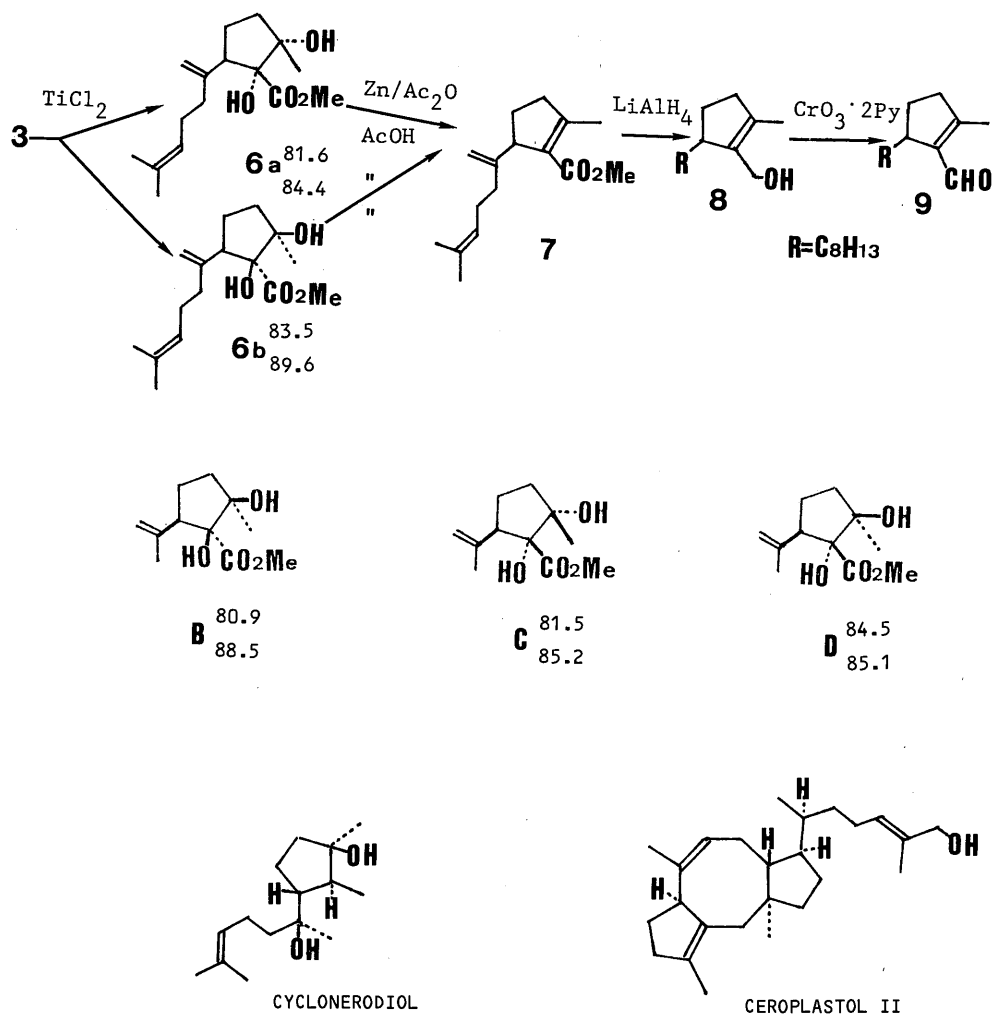
[Scheme 2]

lowing conversion of **6** to the olefn, **7**, should explain that, both **6a** and **6b** were *cis*-glycols as depicted (Scheme 2).

When the glycols, as a mixture of **6a** and **6b**, were warmed in acetic acid and acetic anhydride with zinc powder, desired cyclopentene (**7**) was obtained in some 70% yield. This **7** can be termed as methyl cyclonero-1,6(14),10-trienoate, having the fundamental requirement for further conversions to natural product, cyclonerodiol or cyclonerotriol.

The **7** was easily transformed to several cycloneryl derivatives; by an LAH-reduction, it give a primary alcohol (**8**), which was oxidized to an unsaturated aldehyde (**9**) by Collins oxidation in dichloromethane. Obviously, they are useful C_{15}-synthones for the sesterterpenoids such as ophiobollines and ceroplastols, whose synthesis is our current interest.[10]

Experimental

The elemental analyses were performed at the Research Institute of Industrial Science, or at the Analyses Center, Faculty of Science, Kyushu University. The NMR spectra were measured by a JEOL FX 100 Spectrometer in CDCl₃ solution, unless otherwise specified, and the chemical shifts experessed were in δ unit from the internal Me₄Si. The mass spectra were measured by a JEOL 01SG-2 Spectrometer. The IR spectra were taken in CHCl₃ solutions using Jasco IR-A 102 Spectrometer.

Photochmical Reaction of 1 with 2. An EtOAc solution (20 cm³ of **1** (500 mg) and **2** (30 cm³) was irradiated by means of a 400-W high-pressure mercury lamp through a Pyrex glass filter at 0–5 °C for 4 h. Then, the volatile materials were removed by distillation *in vacuo* from the mixture, and the resulted residue was chromatographed on a prepacked silica-gel chromatography by use of a System 500 Apparatus, Nippon Waters Co., to give **3**, 450 mg (46%) [Found: C, 68.41; H, 8.57%. Calcd for C₁₆H₂₄O₄: C, 68.54; H, 8.63%. ¹H NMR δ =1.5–2.2 (6H, m), 1.61(3H, s), 1.67(3H, s), 2.11(3H, s), 2.3–2.5(2H, m), 3.76(1H,t, J = 8 Hz), 3.80(3H,s), 4.85(1H, s), 5.00(1H, s), 5.10(1H, br. s), ¹³C NMR δ = 17.7, 23.4, 25.6, 29.9, 35.4 40.9, 52.8, 53.2, 114.7, 123.3, 132.2, 144.6, 162.0, 192.5, and 207.6. ν :1720, 1230, 920 cm⁻¹], and **4**, 160 mg (16%) [¹H NMR δ =1.60(3H, s), 1.67(3H, s), 1.8–3.0(8H, m), 2.14(3H, s), 3.82(3H, s), 4.76(1H, s), 5.12(1H, dd, J=18, 1 Hz), 5.32(1H, dd, J= 12, 1 Hz), and 5.92(1H, dd, J=18, 12 Hz). ν : 1720, 1220, 910 cm⁻¹], together with **5**, 220 mg (22%).

Redective Cyclization of 3. To a THF solution (20 cm³) of TiCl₄ (850 mg), a THF suspension (10 cm³) of Zn power (590 mg) was added over 2 h period at −10 °C under an N₂ atmosphere. Then, a THF solution (5 cm³) of **3** (840 mg) was added and stirred at 0–5 °C for 2 h. The mixture was subsequently diluted with water, washed with aqueous NaOH, and extracted with CHCl₃. The organic extract was chromatographed on silica-gel column to give **6a**, 215 mg (45%) [Found: C, 68.22; H, 9.45%, Calcd for C₁₆H₂₆O₄: C, 68,05; H, 9.28%. ¹H NMR δ = 1.24(3H,s), 1.4–2.2(9H, m) 1.58(3H, s),1.65(3H, s), 3.11(2H, br. s), 3.77(3H, s), 4.92(2H, s), and 5.02(1H, br. s.). ¹³C NMR δ =17.7, 24.7, 25.6, 26.1, 26.6, 36.0, 38.9, 50.4, 52.2, 81.6, 84.4, 112.1, 123.9, 131.6, 147.2, and 174.8. ν : 3400, 1740, 1230 cm⁻¹], and **6b**, 215 mg (25%) [Found: C, 68.29; H, 9.45% ¹H NMR δ = 1.10(3H, s), 1.4–2.2(8H, m), 1.54(3H, s), 1.61(3H, s), 2.85(1H, br. s), 3.68(3H, s), 3.78(2H, m), 3.88(1H, s), 5.30(1H, d, J = 2 Hz), and 5.05(1H, d, J = 2 Hz). ¹³C NMR δ =17.6, 23.2, 24.9, 25.6, 28.2, 34.3, 35.9, 52.4, 80.5, 89.6, 113.4, 124.8, 131.0, 141.8, and 175.2. ν : 3400, 1720, 1220 cm ⁻¹].

Reductive Elimination of 6a to cyclopentene Derivative (7). To a mixed solution of Ac₂O (20 cm³) and AcOH (50 cm³) and AcOH (50 cm³) of **6a** (150 mg), Zn powder (2 g) was added and refluxed for 2 h. The mixture was then washed and extracted with ether to give **7**, 80 mg (61%) [Found: C, 77.50; H, 9.90%. Calcd for C₁₆H₂₄O₂ C, 77.37; H, 9.74%. ¹H NMR δ = 1.5–2.6(8H, m), 1.61(3H, s), 1.67(3H, s), 2.12(3H, s), 3.6(1H, br, s), 3.64(3H, s), 4.60(1H, br. s), 4.64(1H, br. s) and 5.10(1H, br. s). ¹³C NMR δ =16.3, 17.7, 25.7, 26.5, 29.4, 35.1, 39.1, 50.7, 52.1, 107.3, 124.4, 129.7, 131.3, 152.3, 156.5, and 166.4].

LAH-reduction of 7. An ether solution (50 cm³) of **7** (250 mg) was reduced with LAH (25 mg) at 35 °C for 2 h. The usual work up, hydrolysis and ether extraction, afforded a colorless liquid, **8**, 220 mg (99%) [Found: C, 82.11; H, 10.87. Calcd for C₁₅H₂₄O: C, 81.76;

H, 10.98. ^{1}H NMR δ =1.5–2.4(9H, m), 1.60(3H, s), 1.72(3H, s) 3.4(1H, br. s), 3.97(1H, d, J = 12 Hz), 4.19(1H, d, J=12 Hz), 4.74(2H, s), and 5.68(1H, br. s).　^{13}C NMR δ =13.9, 17.6, 25.5, 26.4, 28.8, 33.3, 37.5, 53.8, 57.8, 108.7, 124.2, 128.2, 135.7, 138.1, and 152.6. ν : 3620, 880 cm^{-1}]

　　Collins Oxidation of 8.　　A CH$_2$Cl$_2$ solution (20 cm^3) of **8** (200 mg) was mixed with Collins reagent (910 mg) and kept at 25–30 °C for 2 h.　Then the mixture was diluted with water, extracted with CHCl$_3$, and chromatographed on a silica-gel column to give a colorless oil, **9**, 193 mg (97%) [^{1}H NMR δ = 1.4–2.3 (5H, m), 1.63(3H, s), 1.71(3H, s), 2.21(3H, s), 2.3–2.8(4H, m), 4.52(1H, br. s), 4.64(1H, s), 5.2(1H, br. s), and 9.84(1H, s). ^{13}C NMR δ = 14.4, 17.6, 25.3, 26.3, 29.1, 34.6, 39.2, 49.8, 107.6, 124.2, 131.3, 139.4, 151.0, 163.0, and 187.7].

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