

Synthetic Photochemistry. XXVII.¹⁾ An Efficient Synthesis of Deoxytrisporone by Photocycloaddition

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Synopsis. Deoxytrisporone was synthesized from isobutene and methyl 2,4-dioxohexanoate to show the utility of the regioselective photocycloaddition of β -diketone for construction of polysubstituted cyclohexenones.

Deoxytrisporone (**1**)^{2,3)} is a fundamental trimethylcyclohexene derivative. We have accomplished its facile total synthesis by photocycloaddition of 2-methylpropene (**2**) with methyl 2,4-dioxohexanoate (**3**)⁴⁾ followed by a series of chemical conversions which will be described herein.

Photocycloaddition of **2** with **3** gave a single 1:1-adduct (**4**) in 56% yield. The structure of **4** was shown to be methyl 3,3-dimethyl-2,6-dioxooctanoate, on the basis of its NMR spectroscopic analysis⁵⁾ as well as its chemical conversion: Treatment of **4** with *p*-toluenesulfonic acid (TsOH) gave an α,β -unsaturated ketone, methyl 3-oxo- β -cyclogeranate (2,6,6-trimethyl-3-oxo-1-cyclohexene-1-carboxylate, **5**), which upon borohydride reduction yielded a dihydro derivative (**6**).⁶⁾

The keto ester (**5**) was converted to the 3,3-ethylenedithio derivative (**7**) of β -cyclocitral *via* corresponding derivatives (**8**, **9**) of methyl β -cyclogeranate and β -cyclogeraniol by consecutive reactions with 1,2-ethanedithiol and boron trifluoride, lithium aluminum hydride (LAH), and the Collins reagent. The dianionic species⁷⁾ generated from 3-methyl-2-butenic acid (**10**) and lithium diisopropylamide (LDA) was treated at -30°C with **7** to give 1:1-condensates from which, a crystalline δ -lactone (**11**) has been isolated in 74% yield. A mild sodium methoxide treatment of **11** quantitatively gave the (2*Z*,4*E*)-trienic acid (**12**) whose methyl ester (**13**) can be equilibrated to a 2:3-mixture with the (2*E*,4*E*)-ester (**14**) iodine in benzene.⁹⁾ Isolation of **14**, a colorless oil, from the mixture was accomplished by high-pressure liquid chromatography (HPLC).

The LAH-reduction of **14** quantitatively gave the colorless oily alcohol (**15**) which was immediately treated with silver nitrate⁹⁾ to form a colorless oil whose identity with **1** was confirmed by comparison of the H-NMR spectrum taken in a carbon tetrachloride solution.²⁾

Consequently, the alternative synthesis of **1** has been completed.

Experimental

Photocycloaddition of 2 with 3. Formation of **4**: In ethyl acetate (30 cm³), **2** (ca. 20 cm³), and **3** (10.0 g) were internally irradiated by means of a 100-W high-pressure mercury lamp at -50 to -60°C under N₂ atmosphere for 37 h. Silica-gel chromatography of the mixture from hexane–ethyl acetate (9:1) eluted a colorless oil, 6.7 g (56%) [Found: C, 61.76; H, 8.59%. Calcd for C₁₁H₁₈O₄: C, 61.66; H, 8.47%. δ =1.02 (3H, t, J =8 Hz), 1.21 (6H, s), 1.92 (2H, m), 2.36 (2H, m), 2.42 (2H, q, J =8 Hz), and 3.83 (3H, s). δ (C)=7.9, 23.5 (2C), 32.5, 35.9, 37.5, 45.5, 52.3, 164.0, 201.1, and 210.0. ν : 1715, 1740 cm⁻¹].

Dehydration of 4 to 5. A mixture of **4** (4.00 g) and TsOH (30 mg) was refluxed in benzene (20 cm³) for 17 h. Subsequent silica-gel chromatography gave, from hexane–ethyl acetate (4:1), a colorless liquid (**5**), 3.3 g (90%) [Found: C, 66.93; H, 8.28%. M. W., 196.1119. Calcd for C₁₁H₁₆O₃: C, 67.32; H, 8.22%; M. W., 196.1099. δ =1.24 (6H, s), 1.70 (3H, s), 1.90 (2H, m), 2.52 (2H, m), and 3.80 (3H, s). δ (C)=13.0, 26.8 (2C), 34.1, 34.2, 37.5, 51.6, 130.9, 154.7, 168.5, 198.3. ν : 1715, 1665 cm⁻¹].

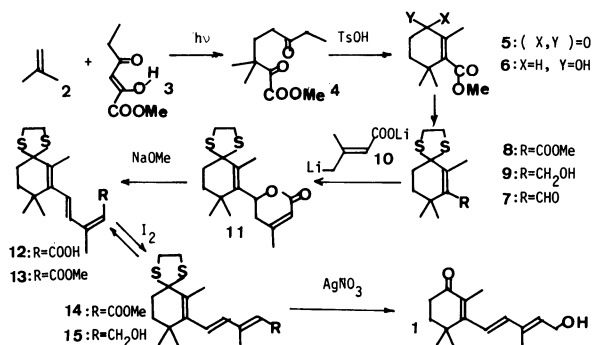
NaBH₄-reduction of 5. In methanol (4.5 cm³), **5** (1.00 g) was reduced with NaBH₄ (300 mg) for 1 h at 15 – 20°C to give a colorless liquid (**6**), 920 mg (91%) [δ =1.06 (3H, s), 1.09 (3H, s), 1.2–2.0 (4H, m), 1.73 (3H, s), 2.73 (1H, br), 3.72 (3H, s), and 3.94 (1H, t, J =5 Hz)].

The Reaction of 5 with 1,2-Ethanedithiol. In anhydrous CH₂Cl₂ (5 cm³), **5** (500 mg) and BF₃–etherate (1 cm³) were kept at 15 – 20°C for 35 h. The mixture was washed with 5% NaOH and then with water, and the solvent was removed to leave colorless needles (**8**), mp 89 – 91°C , 700 mg ($\approx 100\%$) [Found: M. W., 272.0878. Calcd for C₁₃H₂₀O₂S₂: 272.0904. δ =1.05 (6H, s), 1.65 (3H, m), 1.88 (3H, s), 2.28 (2H, m), 3.28 (4H, s), and 3.71 (3H, s). δ (C)=17.4, 28.0 (2C), 33.1, 38.0, 40.0, 40.6 (2C), 51.2, 69.6, 133.4, 139.3, 170.1. ν : 2900, 1725 cm⁻¹].

The LAH-reduction of 8. In anhydrous ether (50 cm³), **8** (700 mg) was reduced with LAH (400 mg) at 15 – 20°C for 3 h to give colorless needles (**9**), mp 88 – 89°C , 625 mg ($\approx 100\%$) [Found: M. W., 244.0951. Calcd for C₁₂H₂₀OS₂: 244.0952. δ =1.04 (6H, s), 1.37 (1H, br, s), 1.65 (2H, m), 2.04 (3H, s), 2.22 (2H, m), 3.31 (4H, s), and 4.08 (2H, s). δ (C)=16.0, 27.9 (2C), 34.0, 38.4, 40.1, 40.4 (2C), 59.1, 71.5, 133.9, 142.2. ν : 3300 cm⁻¹].

Oxidation of 9. A mixture of **9** (600 mg) with Collins reagent (3 g, 5 equiv.) in CH₂Cl₂ (5 cm³) was kept at 15 – 20°C for 3.5 h with stirring. Then, the mixture was chromatographed on a silica-gel column to give a colorless oil (**7**), 430 mg (72%) [Found: M. W., 242.0808. Calcd for C₁₂H₁₈OS₂: 242.0798. δ =1.18 (6H, s), 1.62 (2H, m), 2.24 (2H, m), 2.32 (3H, s), 3.37 (4H, s), and 10.06 (1H, s). δ (C)=16.1, 27.6 (2C), 33.1, 39.5, 39.6, 41.1 (2C), 71.9, 142.3, 152.5, and 193.9. ν : 1675 cm⁻¹].

Reaction of 7 with 10 and LDA. To tetrahydrofuran (THF, 1 cm³) containing diisopropylamine (12 mg), commercially available *n*-BuLi (1.8 cm³ of 1 M solution) was added at -45°C , and kept stirring for 1 h, while the temperature



was gradually raised to 18°C. After cooling the mixture to -40°C, **10** (120 mg) was added to the mixture in a 1-h period, and maintained at 15–20°C for 1 h. To the mixture, **7** (120 mg) was introduced at -30°C and was kept under stirring for 9 h, then the temperature was gradually raised to 15°C. The mixture was treated with 10% HCl, and extracted with ether. The ethereal extract was washed with aqueous NaHCO₃, and chromatographed on a silica-gel column to give colorless needles (**11**), mp 153–154.5°C, 119 mg (74%) [Found: M. W., 324.1220. Calcd for C₁₇H₂₄O₂S₂: 324.1218. δ =1.00 (3H, s), 1.12 (3H, s), 1.67 (2H, m), 1.98 (3H, br. s), 2.05 (3H, s), 2.22 (2H, m), 3.30 (4H, s), 4.96 (1H, dd, J =13, 5 Hz), and 5.79 (1H, br. s). δ (C)=17.6, 22.9, 27.3, 28.3, 34.4, 34.6, 38.6, 39.8, 40.4, 40.7, 72.2, 75.6, 116.3, 136.0, 139.0, 157.3, and 165.2. ν : 2925, 1705 cm⁻¹].

NaOMe-treatment of 11. In methanol (1 cm³), **11** (40 mg) and NaOMe (8 mg) were kept at 15–20°C for 6.5 h. After acidification with 10% HCl, the mixture was extracted with ether; removal of the organic layer left the carboxylic acid (**12**), which was immediately esterified with diazomethane, and chromatographed on a silica-gel column to give a colorless oil (**13**), 38 mg (91%) [Found: M. W., 338.1376. Calcd for C₁₈H₂₆O₂S₂: 338.1373. δ =1.05 (6H, s), 1.65 (2H, m), 1.98 (3H, d, J =1 Hz), 2.04 (3H, d, J =1 Hz), 2.25 (2H, m), 3.32 (4H, s), 3.68 (3H, s), 5.66 (1H, br. s), 6.48 (1H, d, J =18 Hz), and 7.58 (1H, d, J =18 Hz). δ (C)=18.4, 20.8, 28.6 (2C), 34.4, 38.9, 40.1, 40.7 (2C), 50.9, 71.9, 116.9, 131.4, 131.9, 134.8, 142.1, 151.1, and 166.7. ν : 2900, 1715, 1620, 1450, 1435 cm⁻¹].

Treatment of 13 with Iodine. In anhydrous benzene-ether (1:1, 1 cm³), and **13** (10 mg) and I₂ (2 mg) were kept at 15–20°C for 72 h. After washings with Na₂S₂O₃, the mixture was separated by HPLC on μ -Polasil with hexane-ethyl acetate (80:1); less polar fractions yielded colorless needles, mp 115–116°C (**14**), 4.8 mg (48%) [Found: C, 63.96; H, 7.76%. M. W., 338.1378. Calcd for C₁₈H₂₆O₂S₂: C, 63.86; H, 7.76%. M. W., 338.1373. δ =1.00 (6H, s), 1.68 (2H, m), 1.91 (3H, d, J =1 Hz), 2.26 (2H, m), 2.31 (3H, d, J =1 Hz), 3.31 (4H, s), 3.70 (3H, s), 5.75 (1H, br. s), 6.08 (1H, d, J =16, and 6.48 (1H, d, J =16 Hz). δ (C)=13.5, 18.2, 28.5 (2C), 34.4, 38.4, 40.0, 40.5 (2C), 50.9, 71.6, 118.6, 131.0, 133.5, 137.4, 142.0, 152.1, and 167.2. ν : 1715, 1420, 1230, 1150, 980, 875, 840 cm⁻¹]. The more polar fractions yielded recovered **13**, 3.2 mg (32%).

LAH-reduction and Hydrolysis of **14** (as a Mixture with **13**) to **1**.

To the above mixture of **13** and **14** (10 mg) in anhydrous ether (5 cm³), LAH (3 mg) was added and kept at 15–20°C for 1 h; the mixture was then extracted with benzene and water, and chromatographed on a silica-gel column to give a colorless liquid, **15**, 5.1 mg (54%) [Found: m/e , 310 (M⁺). δ =1.00 (6H, s), 1.6–1.75 (2H, m), 1.89 (3H, s), 1.94 (3H, s), 2.2–2.3 (2H, m), 3.32 (4H, s), 4.28 (2H, d, J =8 Hz), 5.55 (1H, t, J =8 Hz), 6.12 (1H, d, J =16 Hz), and 6.34 (1H, d, J =16 Hz) together with 1.82 (3H, s), 5.62 (1H, t, J =8 Hz), and 6.04 (1H, s) of the contaminated *Z,E*-isomer]. This was dissolved in ether (1.5 cm³), and hydrolyzed with aqueous AgNO₃ (5 mg) at -5°C for 2 h. The mixture was then washed with aqueous NH₄Cl, and chromatographed on a silica-gel column; the eluant from ethyl acetate-hexane (1:9) gave a colorless liquid, 3.7 mg (98%), whose NMR figures [δ ^{CDCl₃}=1.17 (6H, s), 1.76 (3H, s), 1.85 (3H, s), 2.40 (2H, m), 4.22 (2H, d, J =7 Hz), 5.75 (1H, br. t, J =7 Hz), and 6.15 (1H, s). ν : 1665 cm⁻¹] were in accord to those reported of **1**.²

References

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