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

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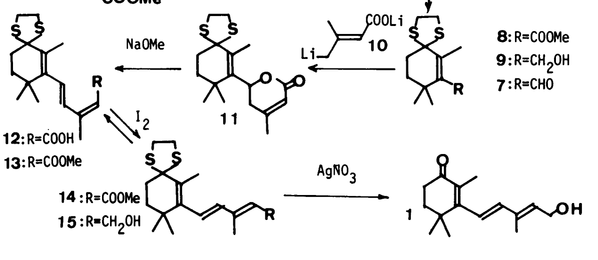
Synopsis. Deoxytrisporone was synthesized from isobutene and methyl 2,4-dioxohexanoate to show the utility of the regioselective photocycloaddition of β-diketone for construction of polysubstituted cyclohexenones.

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 analysis[5)] 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 species[7)] generated from 3-methyl-2-butenoic 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.[8)] 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 nitrate[9)] 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 cm^3), **2** (*ca.* 20 cm^3), and **3** (10.0 g) were internally irradiated by means of a 100-W high-pressure mercury lamp at −50 to −60 °C under N_2 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 $C_{11}H_{18}O_4$: 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 cm^3) 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 $C_{11}H_{16}O_3$: 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}].

*$NaBH_4$-reduction of **5**.* In methanol (4.5 cm^3), **5** (1.00 g) was reduced with $NaBH_4$ (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 CH_2Cl_2 (5 cm^3), **5** (500 mg) and BF_3-etherate (1 cm^3) 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 (≈100%) [Found: M. W., 272.0878. Calcd for $C_{13}H_{20}O_2S_2$: 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 cm^3), **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 (≈100%) [Found, M. W., 244.0951. Calcd for $C_{12}H_{20}OS_2$: 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 CH_2Cl_2 (5 cm^3) 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 $C_{12}H_{18}OS_2$: 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 cm^3) containing diisopropylamine (12 mg), commercially available *n*-BuLi (1.8 cm^3 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 $NaHCO_3$, 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 $C_{17}H_{24}O_2S_2$: 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 cm^3), **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 chromatgraphed on a silica-gel column to give a colorless oil (**13**), 38 mg (91%) [Found: M. W., 338.1376. Calcd for $C_{18}H_{26}O_2S_2$: 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 cm^3), and **13** (10 mg) and I_2 (2 mg) were kept at 15—20 °C for 72 h. After washings with $Na_2S_2O_3$, 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 $C_{18}H_{26}O_2S_2$: 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 cm^3), 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 cm^3), and hydrolyzed with aqueous $AgNO_3$ (5 mg) at −5 °C for 2 h. The mixture was then washed with aqueous NH_4Cl, 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^{CCl_4}=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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