Preparation of An 8-Membered Ring via Intramolecular [2+2]Photocycloadduct: Formal Total Synthesis of (±)-Precapnelladiene

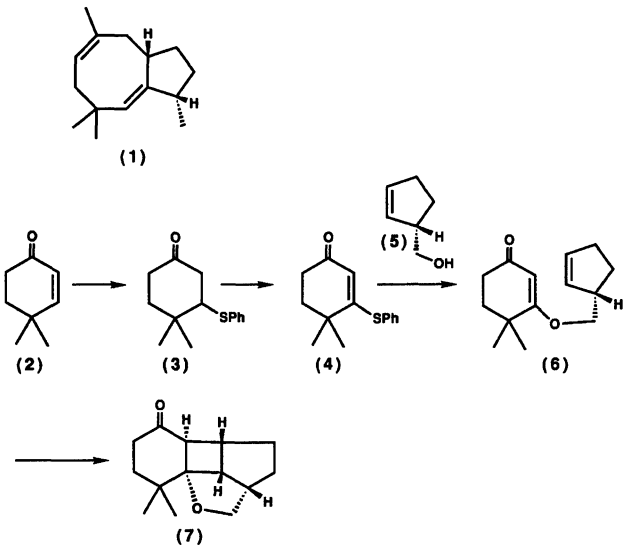
Yoshinobu INOUYE,* Michio SHIRAI, Tetsuyuki MICHINO, and Hiroshi KAKISAWA
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305
(Received June 12, 1992)

Synopsis. Irradiation of 4,4-dimethyl-3-[(2-cyclopentenyl)methoxy]-2-cyclohexen-1-one, prepared from 4,4-dimethyl-3-phenylthio-2-cyclohexen-1-one and (2-cyclopentenyl) methanol, gave a tetracyclic intramolecular [2+2]-photocycloadduct **7**. Treatment of **7** with iodotrimethylsilane followed with tributyltin hydride afforded 3,3,11-trimethylbicyclo[6.3.0]undecane-2,6-dione(**12**). Methylenation of **12** afforded 6-methylene-3,3,11-trimethylbicyclo[6.3.0] undecan-2-one, the known intermediate to precapnelladiene.

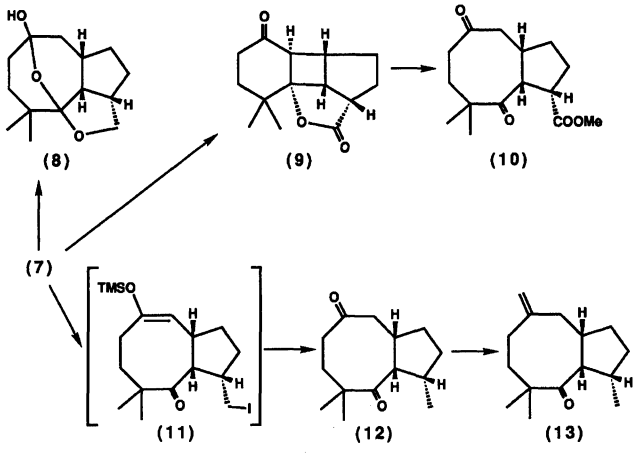
Construction of a 8-membered ring is one of the challenging problems; several methodologies have been successfully reported regarding the total syntheses of natural products.[1] Of those, precapnelladiene (**1**)[2] has been synthesized by three groups.[3] The key step to the 8-membered ring system in those syntheses was either a Claisen rearrangement[3a,3c] or a cleavage of the 5-5 ring system.[3b] In 1985, we reported that the intramolecular [2+2]photocycloaddition of 3-(3-alkenyloxy)-2-cyclohexen-1-one followed by the cleavage of the 6-4 ring system was an effective way to construct an 8-membered ring;[4] a 3β-trinortaxane skeleton was successfully prepared by using the bicyclo[3.3.1]non-3-en-2-one derivative.[4b] We wish to report here on a short-step formal total synthesis of precapnelladiene using this methodology.

4,4-Dimethyl-2-cyclohexen-1-one (**2**)[5] was converted to 4,4-dimethyl-3-phenylthio-2-cyclohexen-1-one (**4**) via a thiophenol addition followed by oxidation with *N*-chlorosuccinimide.[6] Coupling of **4** with (2-cyclopentenyl)-methanol (**5**)[7] was performed in the presence of potassium hydride in DMSO to give 3-[(2-cyclopentenyl)-methoxy]-4,4-dimethyl-2-cyclohexen-1-one (**6**). Irradiation of **6** with a 400 W high-pressure mercury-arc lamp in hexane gave only one adduct **7** in 70% based on the recovery of the starting **6**[8] (Scheme 1).

Cleavage of the 6-4 ring system in **7** could be achieved in several ways. A $BF_3 \cdot OEt_2$ treatment of **7** in dichloromethane gave **8** in 83% yield, while oxidation of **7** with ruthenium tetraoxide (to give **9** in 78% yield) followed by hydrolysis and methylation gave **10** in 63% yield. On the other hand, treatment of **7** with iodotrimethylsilane (Me_3SiI)[9] in $CDCl_3$ gave a corresponding 8-membered compound **11**, as monitored by ^1H NMR analysis (a new doublet of $J=6.3$ Hz at $\delta=3.08$ shows the presence of the $-CH_2I$ group). However, an attempted isolation of **11** or its hydrolysis product failed due to easier formation of an intramolecular diacetal followed by displacement of the iodide by the hydroxyl group to give **8**. It was, thus, necessary to remove the iodine prior to hydrolysis. The reaction mixture of **7** with Me_3SiI in dry benzene was treated directly with tributyltin hydride to afford the desired diketone **12** in 98% yield when the product was purified by the chromatography on alumina. A Wittig reaction of **12** afforded a methylene compound **13** in 88% yield. The spectroscopic data of **13** were completely in accord with those of the authentic sample.[3b] Since **13** had been converted to precapnelladiene (**1**) in three steps,[3b] the preparation of **13**, thus, established a formal total synthesis of precapnelladiene (**1**) (Scheme 2).



Scheme 1.



Scheme 2.

Experimental

The melting points are uncorrected. IR spectra were taken on a JASCO IR Report-100 spectrophotometer. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$, except when otherwise stated, either on a JEOL FX90Q (90 MHz) or on a Brucker AM500 (500 MHz) spectrometer; chemical shifts were recorded relative to the TMS as an internal standard. Column chromatographies were performed using Merck Silica gel 60, except for the others, as stated, while Flash chromatographies using a Wakogel C-300 with the stated solvent. Recycle HPLC was performed on a JAI LC-908 chromatogram with columns JAIGEL-1H and -2H using chloroform as an eluent. Microanalyses were obtained at the Analytical Center, University of Tsukuba.

4,4-Dimethyl-3-(phenylthio)cyclohexanone (3). To a solution of 10.0 g of 4,4-dimethyl-2-cyclohexen-1-one (**2**)[5] and 10.6 g (1.2 equiv) of thiophenol in 130 ml of chloroform, there was added 25 µl of 2% $Et_3N/CHCl_3$; the mixture was stirred for 3 d at room temperature. After the whole had been filtered through a silica-gel column, the solvent was evaporated to give crystals. Recrystallization from hexane gave 12.9 g (68%) of **3**.

3; mp 64—65°C; ^1H NMR δ=1.23 (s, 3H), 1.29 (s, 3H), 1.50—2.00 (m, 3H), 2.20—2.80 (m, 3H), 3.18 (dd,1H, J=9.9 and 6.3 Hz), and 7.00—7.60 (m, 5H). Found: C, 71.67; H, 7.78%. Calcd for $C_{14}H_{18}OS$: C, 71.74; H, 7.76%.

4,4-Dimethyl-3-phenylthio-2-cyclohexen-1-one (4). To a solution of 2.78 g of **3** in 250 ml of benzene, 1.72 g (1.00 equiv) of *N*-chlorosuccinimide (freshly recrystallized twice from acetic acid) was added and the whole was stirred at room temperature for 50 h under protection from light. After evaporating the solvent, the residue was chromatographed with CH_2Cl_2 to afford 2.07 g (75%) of **4**.

4; mp 97—98°C (from hexane); ^1H NMR δ=1.45 (s, 6H), 1.94 (t, 2H, J=6.3 Hz), 2.42 (t, 2H, J=6.3 Hz), 5.32 (s, 1H), and 7.45 (br.s, 5H). Found: C, 72.36; H, 6.99%. Calcd for $C_{14}H_{16}OS$: C, 72.37; H, 6.94%.

4,4-Dimethyl-3-[(2-cyclopentenyl)methoxy]-2-cyclohexen-1-one (6). To 220 mg of KH placed in a three-necked flask, 5 ml of dry DMSO was added little by little under an argon atmosphere. After the reaction had ceased, 540 mg of (2-cyclopentenyl)methanol (**5**)[7] in 10 ml of dry DMSO was added drop by drop. After 30 min, 1.10 g of **4** in 25 ml of DMSO was added drop by drop and the whole was stirred at room temperature overnight. After water had been added, the products were taken in ether; the ether layer was then washed with brine, dried over anhydrous Na_2SO_4, and was evaporated to give crude products. Chromatography with CH_2Cl_2-ether (9:1) gave 1.03 g (ca. 100%) of **6**.

6; oil; IR (CCl_4) 1660, 1595, 1195, and 1160 cm^{-1}; ^1H NMR δ=1.22 (s, 6H), 1.3—2.2 (m, 4H), 2.2—2.5 (m, 4H), 3.08 (m, 1H), 3.65 (d, 2H, J=6 Hz), 5.20 (s, 1H), 5.62 (m, 1H), and 5.82 (m, 1H). Found: C, 76.04; H, 9.36%. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%.

Photocyclization of 6. A solution of 440 mg of **6** in 320 ml of freshly distilled and degassed hexane (for HPLC) was irradiated in a Pyrex tube for 3.5 h[8] with a high-pressure mercury-arc lamp (400 W). Evaporating the solvent gave 500 mg of an oil. The column chromatography with CH_2Cl_2-ether and HPLC with chloroform (3 times recycles) afforded 215 mg (49%; 70% based on the recovery of starting **6**) of **7** and 113 mg (30%) of the recovered **6**.

7; mp 68—69°C (from pentane); IR (KBr) 1690 and 1055 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ=0.773 (S, 3H), 0.955 (s, 3H), 1.202 (ddd, 1H, J=14.2, 5.5, 3.6 Hz), 1.45—1.65 (m, 4H), 1.65—1.75 (m, 1H), 1.950 (dtd, 1H, J=7.5, 5.3, 1.7 Hz), 2.27—2.31 (m, 2H), 2.35 (m, 1H), 2.571 (br.d, 1H, J=5.3 Hz), 2.592 (br.dd, 1H, J=8.5, 7.5 Hz), and 3.6 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ=20.3 (q), 22.0 (q), 31.3 (t), 32.2 (t), 34.0 (d), 34.0 (t), 35.5 (d), 45.5 (d), 48.3 (d), 57.1 (d), 76.5 (t), 87.5 (s), and 213.3 (s). Found: C, 76.44; H, 9.13%. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%.

BF_3·OEt_2 Treatment of 7. To a solution of 10 mg of **7** in 2 ml of dry CH_2Cl_2, 0.6 ml of BF_3·OEt_2 was added ; the mixture was stirred at room temperature for 1 h. Ether was added and the whole was washed with aq $NaHCO_3$, water, and then dried over anhydrous Na_2SO_4. After evaporating the solvent, the residue was chromatographed with CH_2Cl_2-ether (9:1) to afford 9 mg (83%) of **8**.

8; oil; ^1H NMR δ=0.91 (s, 3H), 1.10 (s, 3H), 1.4—2.0 (m, 10H), 2.0—3.0 (m, 4H), 3.52 (t, 1H, J=9 Hz), and 4.08 (t, 1H, J=9 Hz); ^{13}C NMR (125 MHz) δ=20.8 (q), 24.7 (q), 29.0 (t), 34.2 (t), 34.5 (t), 35.0 (t), 35.3 (s), 37.2 (t), 38.8 (d), 43.8 (d), 45.7 (d), 72.8 (t), 98.6 (s), and 112.9 (s).

RuO_4 Oxidation of 7. To a solution of 40 mg of **7** in 4 ml of pure CCl_4(#), 0.48 ml of RuO_4/CCl_4 (1 g/10 ml CCl_4, 61% active) was added and the whole was stirred for 30 min at room temperature. The mixture was cooled in an ice-water bath and excess RuO_4 was destroyed by the addition of 2-propanol. After filtration through the silica-gel column, chromatography with CH_2Cl_2-ether (9:1) gave 33 mg (78%) of a lactone **9**.

9; mp 64—66°C; IR ($CHCl_3$) 1769 and 1702 cm^{-1}; ^1H NMR δ=0.95 (s, 3H), 1.05 (s, 3H), 1.5—2.7 (m, 11H), and 3.1—3.4 (m, 3H). Found: C, 72.00; H, 7.99%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%.

Methyl 6,6-Dimethyl-3,7-dioxobicylo[6.3.0]undecane-9-carboxylate (10). The lactone **9** (63 mg) was refluxed with 12 ml of 10% KOH and 12 ml of DMSO under argon for 3 h. After the addtion of water, the aqueous layer was washed with benzene. 1 M HCl (1M=1 mol dm^{-3}) was added to make the pH 2—3 and the products were taken in ether. After being dried over anhydrous Na_2SO_4, evaporating the solvent gave a crude acid. The acid was treated with diazomethane and then purified by column chromatography (silica gel, CH_2Cl_2-ether=9:1) to give a methyl ester **10** (45 mg, 63%).

10; oil; IR ($CHCl_3$) 1735 and 1705 cm^{-1}. Found: C, 67.54; H, 8.37%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

3,3,11-Trimethylbicyclo[6.3.0]undecane-2,6-dione (12). To a solution of 100 mg (0.454 mmol) of **7** in 1 ml of dry benzene, 80 µl (0.562 mmol) of Me_3SiI was added under an argon atmosphere; the mixture was stirred at room temperature for 5 h. To the resulting brown solution, 180 µl of Bu_3SnH (0.670 mmol) was added and the whole was stirred for 1.5 h. Hexane (1 ml) was added and the mixture

(#) Purification of CCl_4: A mixture of 100 ml of CCl_4 and 50 ml of saturated aqueous KOH solution was stirred vigorously for 4—5 h. The CCl_4 was washed with water until neutral. The procedure was repeated twice. After it had been dried over $MgSO_4$, pure CCl_4 distilled at ordinary pressure.

was chromatographed on alumina (20 g) with hexane-benzene (1 : 1) to give 99 mg (98%) of crystalline **12**.

12; mp 70—71°C (from pentane); IR (KBr) 1697 and 1685 cm^{-1}; ^1H NMR (500 MHz) δ=0.880 (d, 3H, J=7 Hz), 1.098 (s, 3H), 1.139 (s, 3H), 1.57—1.90 (m, 5H), 2.15—2.33 (m, 4H), 2.405 (ddd, 1H, J=11.4, 5.3, and 1.7 Hz), 2.44—2.51 (m, 1H), 2.540 (td, 1H, J=12.5 and 1.7 Hz), and 3.333 (t, 1H, J=6.3 Hz); ^{13}C NMR (125 MHz) δ=16.5 (q), 21.7 (q), 26.5 (q), 30.8 (t), 31.8 (t), 38.1 (t), 40.2 (d), 41.3 (t), 44.8 (d), 45.1 (t), 48.8 (s), 51.6 (d), 214.2 (s), and 218.2 (s). Found: C, 75.58; H, 9.99%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

6-Methylene-3,3,11-trimethylbicyclo[6.3.0]undecan-2-one (13). To a suspension of 55 mg (0.154 mmol) of methyltriphenylphosphonium bromide in 0.5 ml of dry THF, 100 μl (0.146 mmol) of a butyllithium/hexane solution was added; the mixture was stirred for one hour at room temperature. To the resulting light-orange solution, 23 mg (0.103 mmol) of **12** in 0.75 ml of THF was added; the whole was stirred for one hour at room temperature. Pentane (5 ml) was added and the precipitates were removed by filtration. Evaporating the solvent gave crystals, which were purified through a short alumina column with hexane to afford 20 mg (88%) of a crystalline **13**.

13; mp 66—67°C (from MeOH); IR (KBr) 3080, 1690, 1640, and 895 cm^{-1}; ^1H NMR (500 MHz) δ=0.865 (d, 3H, J=6.7 Hz), 1.023 (s, 3H), 1.051 (s, 3H), 1.59—1.82 (m, 6H), 2.05—2.35 (m, 6H), 3.343 (t, 1H, J=6.0 Hz), 4.678 (d, 1H, J=2.0 Hz), and 4.838 (br.s, 1H); ^{13}C NMR (125 MHz) δ=16.2 (q), 21.2 (q), 27.1 (q), 30.2 (t), 31.7 (t), 35.2 (t), 37.7 (t), 39.9 (d), 40.2 (d), 48.2 (s), 48.8 (d), 51.4 (d), 114.6 (t), 148.3 (s), and 218.8 (s).

The IR, ^1H, and ^{13}C NMR spectra of **13** were identical with those of the known compound.[3b)]

We are deeply indebted to Professor Goverdhan Mehta, University of Hyderabad, for sending his IR, ^1H, and ^{13}C NMR spectra of **13** and precapnelladiene (**1**).

References

1) See for example: G. Majetich, D. Lowery, V. Khetani, J.-S. Song, K. Hull, and C. Ringold, *J. Org. Chem.*, **56**, 3988(1991), and references cited therein.

2) E. Ayanoglu, Y. Gebreyesus, C. M. Beechan, and C. Djerassi, *Tetrahedron*, **35**, 1035(1979).

3) a) W. A. Kinney, M. J. Coghlan, and L. A. Paquette, *J. Am. Chem. Soc.*, **107**, 7352(1985); b) G. Mehta and A. N. Murthy, *J. Org. Chem.*, **52**, 2875(1987); c) N. A. Petasis and M. A. Patane, *Tetrahedron Lett.*, **31**, 6799(1990).

4) a) T. Kojima, Y. Inouye, and H. Kakisawa, *Bull. Chem. Soc. Jpn.*, **58**, 1738(1985); b) T. Kojima, Y. Inouye, and H. Kakisawa, *Chem. Lett.*, **1985**, 323.

5) E. L. Eliel and C. A. Lubach, *J. Am. Chem. Soc.*, **79**, 5986(1957).

6) a) P. Bakuzis and M. L. F. Bakuzis, *J. Org. Chem.*, **46**, 235(1981); b) Y. Inouye, T. Kojima, J. Owada, and H. Kakisawa, *Bull. Chem. Soc. Jpn.*, **60**, 4369(1987).

7) a) O. L. Chapman, K. C. Mattes, R. S. Sheridan, and J. A. Klun, *J. Am. Chem. Soc.*, **100**, 4878(1978); b) We prepared ethyl (2-cyclopentenyl)acetate according to the following method: C. A. Bunnell and P. L. Fuchs, *J. Am. Chem Soc.*, **99**, 5184(1977).

8) Prolonged irradiation caused the decomposition of **7** and we stopped the reaction prior to the complete disappearance of **6**.

9) M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761(1977).