An Improved Synthesis of Benzocycloalkanone Derivatives[1)]

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A convenient and improved annulation method for the synthesis of bicyclic ketones was developed. A 2,2-dimethyl-6-(2-phenylsulfonyl)ethylcyclohexanone was converted into a sulfonylester by the addition of ethyl acetate and subsequent dehydration. A Dieckmann type condensation of the sulfonylester followed by desulfonylation afforded the 8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-one in good yield. This annulation method was also applicable for the synthesis of the benzocyclooctanone derivative.

Key words annulation; sulfonylester; bicyclic ketone; retinal anlog

It is well known that (11*Z*)-retinal (**1**) and its (all-*E*)-isomer are a chromophore of protein pigments such as rhodopsin, bacteriorhodopsin, phoborhodopsin and so on.[2—6)] These proteins exhibit the significant functions in respective vital cells, in which the conformation of retinal chromophore plays an important role. In the past two decades, a number of reports have appeared on dealing with the synthesis of retinal analogs for examining the retinal-structure and protein environment around the retinal chromophore in the pigments.[7—17)] In order to investigate the conformation around the cyclohexene ring of chromophore in rhodopsin, especially to clarify the torsional angle around the C6—7 single bond, we have synthesized the bicyclic retinals (**2**), and from their binding experiments it was strongly supported that the tortional angle around the C6—7 single bond of the retinal is about 60—70° in the protein.[1,18)] In the preparation of bicyclic retinals (**2**), we used the bicyclic ketones (**5**) as the key intermediates and these ketones were prepared by the Dieckmann condensation of the diesters (**4**) derived from the keto ester (**3**).[1,17)] However, the yields of these cyclization were very low except for the 6—7 ring system because of a side reaction such as aromatization, therefore, this methodology is not suitable in the large scale preparation for supply in the extended research of the investigation on the interaction between the chromophore and proteins (Chart 1). To circumvent this problem, in this paper, we wish to describe a convenient and improved synthesis of the bicyclic ketones (**5a**, **5c**) from the sulfonylesters and subsequent desulfonylation.

Grimm and co-workers reported the construction of the bicyclo[6,4,0]dodecane ring system, the medium ring which was difficult to prepare by the usual Dieckmann condensation of the diester, by an intramolecular cyclization of sulfone stabilized carbanion in good yield.[19)] Applying for this methodology, we initially tried to prepare the 6—6 bicyclic ketone (**5a**). A Michael addition of the sodium salt of 2-methoxycarbonyl-6,6-dimethylcyclohxanone (**3**)[17)] to the phenyl vinyl sulfone smoothly proceeded to give the corresponding adduct in excellent yield. Treatment of this adduct with concentrated HCl in EtOH under relfux afforded the sulfonylketone (**6**) in a 74% yield by two steps from **3**. After the addition of the lithium salt of ethyl acetate to **6**, the resulting hydroxy sulfone was dehydrated with thionyl chloride to give the sulfonylester (**7**) in excellent yield. An intramolecular cyclization of **7** was achieved using a 2.2 eq of lithium bis(trimethylsilyl)amide according to the Grimm's procedure to afford the β-keto sulfone (**8**), while this crude product was used for the next reaction without a further purification. Desulfonylation of **8** was accomplished by treatment with excess tributyltin hydride and azobisiisobutylnitrile (AIBN) in toluene at 140 °C[20)] to produce the desired bicyclic ketone (**5a**) and the tetrahydronaphthalene derivative (**9**) in 67% and 20% yields, respectively (Chart 2). The latter compound would be produced from the initially formed **5a** by air oxidation under the reaction conditions. These structures were determined by comparison with the authentic specimens we had previously reported.[1)] It is remarkable that, from the viewpoint of the 6—6 comparable ring annulation, a cyclization using the sulfonylester is more superior than that of the Dieckmann condensation of the corresponding diester.

Next we focused our attention on the synthesis of the 6—8 bicyclic ketone (**5c**). The precursor (**12**) of the ring closure reaction was derived from the keto ester (**4b**), prepared from **3** by alkylation and subsequent demethoxycarbonylation.[17)] Reduction of **4b** with $LiAlH_4$ followed by the successive protection of primary alcohol and PDC oxidation of secondary alcohol, produced the silyloxy ketone (**10**) in a 62% yield. After desilylation with tetrabutylammonium floride (TBAF), the resulting alcohol was treated with carbon tetrabromide and triphenylphosphine to give the keto bromide, which was converted to the solfonylketone (**11**) by the reaction with sodium phenylsulfinylamide in the presence of a phase transfer catalyst in a 64% yield. The sulfonylketone (**11**) was transformed into the sulfonylester (**12**) by the addition of the lithium salt of ethyl acetate followed by dehydration with thionyl chloride in an 89% yield. The ring closure of **12** and

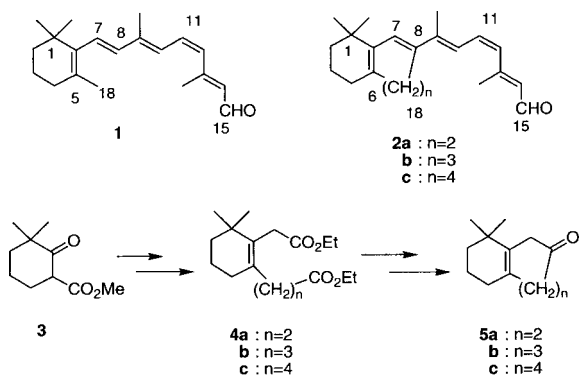

Chart 1

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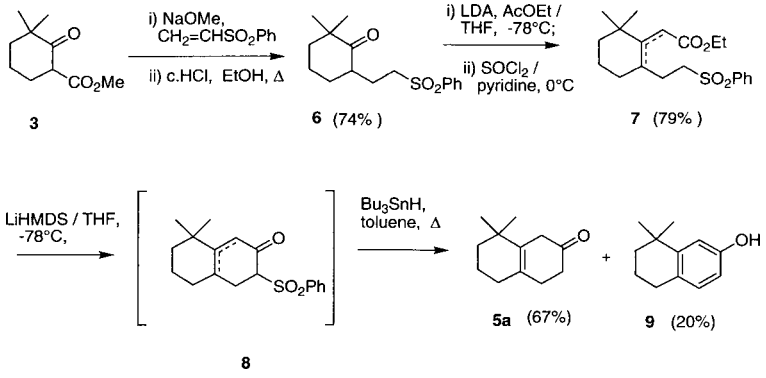

Chart 2

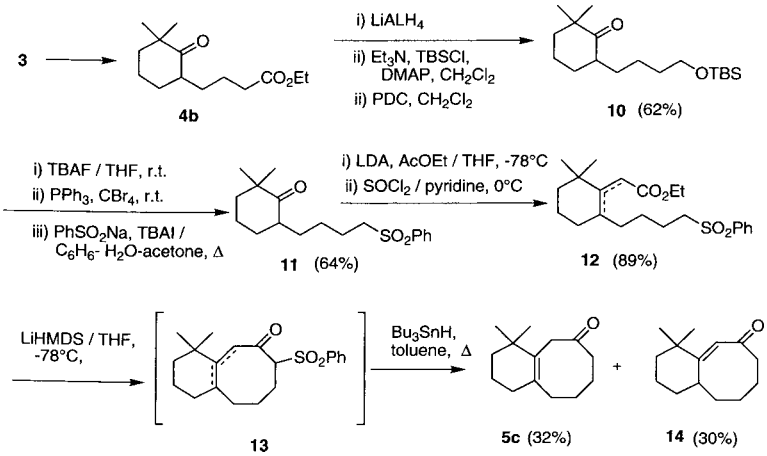

Chart 3

subsequent desulfonylation were performed by the same manner as described for the case of **7** to produce the desired 6—8 bicyclic ketone (**5c**) and its isomer of the double bond (**14**) in 32% and 30% yields, respectively (Chart 3).

In summary, we were able to demonstrate that the ring annulation using an intramolecular cyclization of the sulfone stabilized carbanion is an efficient and convenient route for the preparation of the bicyclic ketones (**5**), and this methodology is very useful for supplying the bicyclic retinals in large scale (g scale order) for the research field of the conformational analysis of retinal proteins.

Experimental

IR spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrometer. ^{1}H-NMR spectra were obtained on a Varian Gemini-200 or Gemini-300 NMR spectrometer in deuteriochloroform. ^{13}C-NMR spectra were obtained on a Gemini-300 NMR spectrometer in deuteriochloroform. Mass spectra were determined on a Hitachi M-4100 instrument. Column chromatography (CC) was performed using Merck silica gel 60. All reactions were carried out under a nitrogen atmosphere. THF and ether were purified by distillation from benzophenone-sodium ketyl under nitrogen. Commercially available chemicals were used without further purification except when otherwise noted. Diisopropylamine was purified by distillation from CaH_2. Standard workup means that the organic layers were finally washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated *in vacuo* below 30 °C using a rotary evaporator.

2,2-Dimethyl-6-(2-phenylsulfonyl)ethylcyclohexanone (6) To a stirred solution of the keto ester **3** (5.04 g, 27 mmol) in benzene (100 ml) and NaOMe (0.55 g, 8.2 mmol) was added a solution of phenyl vinyl sulfone (5.4 g, 54 mmol) in benzene (25 ml) at 0 °C under nitrogen, and the resulting mixture was stirred for an additional 3 h. The reaction was quenched with saturated aqueous NH_4Cl (60 ml) and then the organics were extracted with benzene (3×80 ml), followed by a standard workup. The residue was purified by CC (dichloromethane–ether, 19 : 1) to afford methyl 3,3-dimethyl-1-(2-phenylsulfonyl)ethyl-2-oxo-cyclohexanecarboxylate (8.9 g, 92%) as a pale yellow oil. [IR ($CHCl_3$) cm^{-1}: 2951, 1735, 1705, 1305, 1135; ^{1}H-NMR δ: 1.00 (3H, s, Me), 1.13 (3H, s, Me), 1.5—2.6 (10H, m, CH_2×5), 3.60 (3H, s, $CO_2\underline{CH_3}$), 7.5—7.9 (5H, m, ArH)].

A mixture of this keto ester (7.2 g, 20 mmol), EtOH (30 ml) and c.HCl (70 ml) was refluxed for 18 h. After cooling, water (150 ml) was added, and the organics were extracted with dichloromethane (3×80 ml), followed by a standard workup. The residue was purified by CC (Et_2O–dichloromethane, 1 : 49) to afford the keto sulfone **6** (4.8 g, 80%) as a pale yellow oil. IR ($CHCl_3$) cm^{-1}; 2935, 1702, 1313, 1154; ^{1}H-NMR δ: 1.00 (3H, s, Me), 1.14 (3H, s, Me), 1.2—1.8 (6H, m, CH_2×3), 1.9—2.1 (2H, m, CH_2), 2.6—2.8 (1H, m, CH), 2.3—3.5 (2H, m, CH_2) 7.5—7.7 (3H, m, ArH), 7.91 (2H, d, J=8 Hz, ArH); HR-MS *m/z*: 294.1289 (Calcd for $C_{16}H_{22}O_3S$: M$^+$ 294.1289).

Ethyl (6,6-dimethyl-2-((2-phenylsulfonyl)ethyl)cyclohexen-1-yl)acetate (7) To a stirred solution of LDA, prepared from *n*-BuLi (1.6 M hexane solution, 13 ml, 20.8 mmol) and diisopropylamine (2.1 g, 21 mmol) in THF (30 ml), was added a solution of ethyl acetate (1.8 ml, 21 mmol) in THF (7 ml) at −70 °C, and the resulting mixture was stirred for an additional 30 min. A solution of the sulfonylketone **6** (2.2 g, 7.5 mmol) in THF (10 ml) was added at −70 °C and the mixture was further stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (40 ml), and after the removal of THF *in vacuo*, the organics were extracted with dichloromethane (3×70 ml), followed by a standard workup. The residue was purified by CC (dichloromethane–hexane, 3 : 97) to give the hydoxyester (2.65 g, 93%) as a mixture of diastereoisomer. [^{1}H-NMR δ: 0.88 (3H, s, Me), 1.29 (3H, t, J=7 Hz, $CO_2CH_2\underline{CH_3}$), 1.2—2.1 (9H, m, CH_2×4 and CH), 2.34 (1H, d, J=16 Hz, $\underline{CH_2}COO$), 2.54 (1H, d, J=16 Hz, $\underline{CH_2}COO$), 3.0—3.3 (2H, m, $\underline{CH_2}SO_2$), 4.16 (2H, q, J=7 Hz, $CO_2\underline{CH_2}CH_3$), 4.38 (H, s, OH, disappeared with D_2O), 7.5—7.7 (3H, m, ArH), 7.88 (2H, d, J=8 Hz, ArH)].

To a solution of the hydroxy ester (2.6 g, 6.8 mmol) in pyridine (24 ml) was added thionyl chloride (1.3 ml, 18 mmol) at 0 °C, and the resulting mixture was stirred for 10 min. The reaction was quenched with 5% HCl (50 ml)

in an ice bath, and the organics were extracted with dichhoromethane (3×50 ml), followed by a standard workup. The residue was purified by CC (dichloromethane–hexane, 1 : 49) to give the sulfonylester **7** (2.18 g, 88%) as a colorless oil. NMR analysis indicated that the *endo* and *exo* isomers of the double bond were present in a ratio of 5 : 1. Analytical samples were obtained respectively by further CC using the same eluent.

endo-Isomer: IR ($CHCl_3$) cm^{-1}; 2936, 1727, 1315, 1142; ^{1}H-NMR δ: 0.92 (6H, s, Me×2), 1.25 (3H, t, J=7 Hz, $CO_2CH_2\underline{CH_3}$), 1.3—1.6 (4H, m, CH_2×2) , 1.91 (2H, t, J=7 Hz, CH_2), 2.3—2.5 (2H, m, CH_2), 2.97 (2H, s, CH_2CO), 3.1—3.3 (2H, m, $\underline{CH_2}SO_2$), 4.08 (2H, q, J=7 Hz, $CO_2\underline{CH_2}CH_3$), 7.5—7.7 (3H, m, ArH), 7.91 (2H, d, J=8 Hz, ArH); HR-MS *m*/*z*: 364.1702. (Calcd for $C_{20}H_{28}O_4S$: M^+ 364.1707).

exo-Isomer: ^{1}H-NMR δ: 0.98 (3H, s, Me), 1.03 (3H, s, Me), 1.25 (3H, t, J=7 Hz, $CO_2CH_2\underline{CH_3}$), 1.3—1.9 (9H, m, CH_2×4, CH), 3.1—3.3 (2H, m, $\underline{CH_2}SO_2$), 4.08 (2H, q, J=7 Hz, $CO_2\underline{CH_2}CH_3$), 5.78 (1H, s, =CH), 7.5—7.7 (3H, m, ArH), 7.91 (2H, d, J=8 Hz, ArH).

8,8-Dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-one (5a) and 8,8-Dimethyl-5,6,7,8-tetrahydro-2-naphthol (9) To a stirred solution of LiHMDS, prepared from *n*-BuLi (1.6 M hexane solution, 7.6 ml, 12.1 mmol) and hexamethyldisilazane (1.9 g, 11.9 mmol) in THF (20 ml), was added a solution of sulfonylester **7** (2.0 g, 5.5 mmol) in THF (40 ml) at −70 °C, and the resulting mixture was stirred for an additional 2 h. The reaction was quenched with saturated aqueous NH_4Cl (40 ml) and after the removal of THF *in vacuo*, the organics were extracted with dichloromethane (3×70 ml), followed by a standard workup to give the crude cyclized product **8** (1.9 g) as a pale yellow oil.

To a stirred solution of the cyclized sulfone **8** (1.9 g) and (n-Bu)$_3$SnH (7.0 g, 22 mmol, 4 eq of **8**) in toluene (60 ml) was added dropwise a solution of azobisisobutylnitrile (0.66 g, 4.0 mmol) in toluene (15 ml) under reflux. The resulting mixture was further stirred for 10 min under reflux, and then cooled to come to room temperature. After the removal of toluene *in vacuo*, the residue was purified by CC (ether–hexane, 15 : 75) to give the bicyclic ketone **5a** (1.45 g, 67%) and the naphthol **9**. (0.19 g, 20%). These compounds were identical with the authentic specimens obtained by the Dieckmann condensation in the literature.[1)]

Ketone **5a**: IR ($CHCl_3$) cm^{-1}; 1705; ^{1}H-NMR δ: 0.98 (6H, s, Me×2), 1.4—1.5 (2H, m, CH_2), 1.5—1.7 (2H, m, CH_2), 1.9—2.0 (2H, m, [CH_2×1/2]×2), 2.2—2.5 (4H, m, CH_2 and [CH_2×1/2]×2), 2.84 (2H, br s, CH_2), ^{13}C-NMR δ: 19.1, 27.5 (2C), 30.7, 34.2, 39.1, 41.2, 42.0, 128.3, 132.8, 212.2. HR-MS *m*/*z*: 178.1362. (Calcd for $C_{12}H_{18}O$: M^+ 178.1357).

Naphthol **9**: IR ($CHCl_3$) cm^{-1}; 3598, 3343, 2933, 1610; ^{1}H-NMR δ: 1.24 (6H, s, Me×2), 1.5—1.9 (4H, m, CH_2×2), 2.71 (2H, t, J=6 Hz, CH_2), 4.53 (1H, s, OH), 6.62 (1H, dd, J=8, 2.5 Hz, ArH), 6.83 (1H, d, J=2.5 Hz, ArH), 6.96 (1H, d, J=8 Hz, ArH), ^{13}C-NMR δ: 19.8, 29.9, 31.8 (2C), 33.9, 39.1, 111.8, 112.7, 128.3, 129.9, 147.3, 153.0.

2,2-Dimethyl-6-((1,1-dimethyl)ethyldimethylsilyloxy)butylcyclohexanone (10) A solution of the keto ester **4b** (2 g, 8.3 mmol) in dry ether (10 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (822 mg, 21 mmol) in ether (30 ml) at 0 °C under nitrogen, and the resulting mixture was stirred for an additional 15 min. The excess of $LiAlH_4$ was destroyed by the addition of moist Et_2O and water, and the mixture was extracted with Et_2O. The extract was washed with brine, dried and concentrated to afford the crude dialcohol, which was used for the next reaction without further purification.

A solution of TBDMSCl (1.87 g, 12 mmol) in dichloromethane (10 ml) was added to a stirred mixture of the crude alcohol, DMAP (130 mg, 1.1 mmol), and Et_3N (1.51 ml, 11 mmol) at 0 °C. The resulting mixture was stirred for an additional 3 h at room temperature. The reaction was quenched with saturated NH_4Cl (50 ml), and the organics were extracted with dichloromethane (3×50 ml), followed by a standard workup to give the silyloxyalcohol.

The silyloxyalcohol was dissolved in dichloromethane (70 ml) and then PDC (15 g, 39 mmol) was added all at once. The resulting mixture was stirred for an additional 8 h and then filtered with Celite. The filtrate was successively washed with 10% HCl, 10% $NaHCO_3$, brine and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by CC (ether–hexane, 1 : 9) to give the silyloxyketone **10** (1.63 g, 62%, 3 steps) as a colorless oil. IR ($CHCl_3$) cm^{-1}; 2932, 1700; ^{1}H-NMR δ: 0.03 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiCMe_3$), 1.03 (3H, s, Me), 1.17 (3H, s, Me), 1.2—2.2 (12H, m, CH_2×6) , 2.50 (1H, quint, J=7 Hz, CH), 3.59 (2H, t, J=6.5 Hz, OCH_2); HR-MS *m*/*z*: 312.2481. (Calcd for $C_{18}H_{36}O_2Si$: M^+ 312.2482).

2,2-Dimethyl-6-(4-phenylsulfonyl)butylcyclohexanone (11) To a stirred solution of the silyloxyketoe **10** (1.49 g, 4.8 mmol) in THF (30 ml) was added a solution of TBAF (1.0 M solution in THF, 1.38 ml, 1.38 mmol) at 0 °C under nitrogen, and the resulting mixture was stirred for an additional 4 h. The reaction was quenched with saturated aqueous NH_4Cl (30 ml) and then the organics were extracted with ether (3×50 ml), followed by a standard workup. The residue was purified by CC (ether–hexane, 1 : 1) to give the hydroxyketone (928 mg, 98%).

To a stirred solution of PPh_3 (1.04 g, 4.0 mmol) and CBr_4 (1.09 g, 3.3 mmol) in dichloromethane, a solution of the hydroxyketone (519 mg, 2.6 mmol) in dichloromethane (25 ml) was added at 0 °C. The resulting mixture was stirred for an additional 10 min, and after the removal of dichloromethane *in vacuo*, ether was added and the precipitate was filtered off using Celite. The filtrate was concentrated *in vacuo* to give the crude bromoketone (1.65 g), which was used in the next reaction without purification.

The above bromoketone was dissolved in H_2O–acetone–benzene (120 : 90 : 90, 50 ml), and to this solution were added $PhSO_2Na$ (820 mg, 5.0 mmol) and TBAI (360 mg, 1.0 mmol). The resulting mixture was heated at 110 °C for 14 h. After cooling, the organics were extracted with dichloromethane (3×70 ml), followed by a standard workup. The residue was purified by CC (dichloromethane–hexane, 3 : 97) to give the sulfonylketone **11** (960 mg, 65%) as a pale yellow oil. IR ($CHCl_3$) cm^{-1}; 2934, 1700, 1307, 1149; ^{1}H-NMR δ: 1.02 (3H, s, Me), 1.14 (3H, s Me), 1.2—2.1 (12H, m, CH_2×6), 2.42 (1H, quint, J=7 Hz, CH), 3.0—3.2 (2H, m, $\underline{CH_2}SO_2$), 7.5—7.7 (3H, m, ArH), 7.89 (2H, d, J=8 Hz, ArH); HR-MS *m*/*z*: 322.1592. (Calcd for $C_{18}H_{26}O_3S$: M^+ 322.1601).

Ethyl (6,6-dimethyl-2-((4-phenylsulfonyl)butyl)cyclohexen-1-yl)acetate (12) This was prepared from the ketone **11** (517 mg, 1.6 mmol) by the addition of ethyl acetate (0.42 ml, 4.4 mmol) and subsequent dehydration with thionylcloride (0.53 g, 4.4 mmol) by the same manner as described for the preparation of **6**. The crude product was purified by CC (dichloromethane–hexane, 1 : 49) to give the sulfonylester **12** (555 mg, 94%) as a pale yellow oil. NMR analysis indicated that the *endo* and *exo* isomers of double bond were present in a ratio of 5 : 2. Analytical samples were obtained respectively by further CC using the same eluent.

endo-Isomer: IR ($CHCl_3$) cm^{-1}; 2935, 1728, 1306, 1142; ^{1}H-NMR δ: 0.93 (6H, s, Me×2), 1.22 (3H, t, J=7 Hz, $CO_2CH_2\underline{CH_3}$), 1.2—1.8 (10H, m, CH_2×5), 1.83 (2H, t, J=6.5 Hz, CH_2), 2.97 (2H, s, CH_2CO), 3.0—3.2 (2H, m, $\underline{CH_2}SO_2$), 4.07 (2H, q, J=7 Hz, $CO_2\underline{CH_2}CH_3$), 7.5—7.7 (3H, m, ArH), 7.91 (2H, d, J=8 Hz, ArH); HR-MS *m*/*z*: 392.2039. (Calcd for $C_{22}H_{32}O_4S$: M^+ 392.2020).

exo-Isomer: ^{1}H-NMR δ: 1.08 (3H, s, Me), 1.10 (3H, s, Me), 1.22 (3H, t, J=7 Hz, $CO_2CH_2\underline{CH_3}$), 1.3—2.0 (13H, m, CH_2×6, CH), 3.0—3.2 (2H, m, $\underline{CH_2}SO_2$), 4.07 (2H, q, J=7 Hz, $CO_2\underline{CH_2}CH_3$), 5,76 (1H, sm =CH), 7.5—7.7 (3H, m, ArH), 7.91 (2H, d, J=8 Hz, ArH).

4,4-Dimethyl-1,2,3,4,7,8,9,10-octahydrobenzocycloocten-6(5*H*)-one (5c) and 4,4-Dimethyl-1,2,3,4,8,9,10,10a-octahydrobenzocycloocten-6(7*H*)-one (14) These were prepared from the sulfonylester **12** (517 mg, 1.6 mmol) by treatment with LiHMDS, prepared from *n*-BuLi (1.6 M hexane solution, 1.7 ml, 2.5 mmol) and hexamethyldisilazane (0.53 ml, 2.5 mmol) in THF (10 ml), and subsequent desulfonylation with tributyltinhydride (1.35 g, 4.6 mmol) and AIBN (80 mg, 0.5 mmol) by the same manner as described for the preparation of **5a**. The crude product was purified by CC (ether–hexane, 15 : 85) to give the bicyclic ketones **5c** (86 mg, 32%) and **14** (70 mg, 30%) as pale yellow oils. Endo-isomer **5c** was identical with the authentic specimen obtained by the Dieckmann condensation in the literature.[1)]

endo-Isomer **5c**: IR ($CHCl_3$) cm^{-1}; 1690; ^{1}H-NMR δ 0.98 (6H, s, Me×2), 1.4—1.5 (2H, m, CH_2), 1.5—1.8 (6H, m, CH_2×3), 2.0—2.1 (4H, m, CH_2×2), 2.4—2.5 (2H, m, CH_2), 3.15 (2H, s, CH_2). HR-MS *m*/*z*: 206.1690. (Calcd for $C_{19}H_{32}O_4$: M^+ 206.1669).

exo-Isomer **14**: ^{1}H-NMR δ: 1.24 (3H, s, Me), 1.26 (3H, s, Me), 1.3—2.5 (14H, m, CH_2×7), 3.1—3.3 (1H, m, CH), 6.55 (1H, m, =CH). ^{13}C-NMR δ: 21.5, 22.0, 25.2, 27.3, 31.5, 34.1, 38.1, 40.0, 41.4, 44.0, 118.8, 160.2, 212.5. HR-MS *m*/*z*: 206.1678. (Calcd for $C_{19}H_{32}O_4$: M^+ 206.1669).

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