

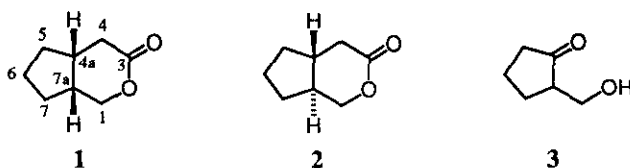
STEREOSELECTIVE SYNTHESSES OF *cis*- AND *trans*-HEXA-HYDROCYCLOPENTA[*c*]PYRAN-3(1*H*)-ONES

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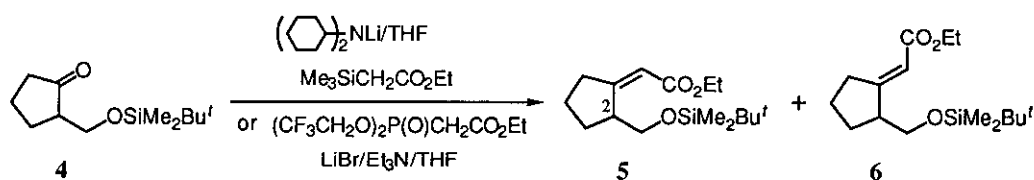
Abstracts ——— A new access to *cis*- and *trans*-hexahydrocyclopenta[*c*]pyran-3(1*H*)-ones (**1** and **2**) has been accomplished stereoselectively through 4-step and 5-step routes, respectively, starting from 2-(hydroxymethyl)cyclopentanone (**3**).

cis-Hexahydrocyclopenta[*c*]pyran-3(1*H*)-one (**1**) represents one of the parent frameworks common to a large number of cyclopentano-monoterpene lactones.¹ Some of these lactones are highly attractive to cats and other *Felidae* animals and are also known as potent insecticides.^{1c-e} Many synthetic efforts toward **1** and the related lactones have been made due to such unique activities.² In the present paper, we wish to report the stereoselective syntheses of (±)-**1** and its *trans*-isomer (**2**)³ from (±)-2-(hydroxymethyl)cyclopentanone (**3**) as a preliminary to racemic and chiral syntheses of cyclopentano-monoterpene lactones.



Carboxyolefination reaction of the cyclopentanone derivative (**4**), prepared from **3**⁴ in 95% yield, by the Wittig reaction ($\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, benzoic acid, boiling toluene, 5 h)⁵ or the Horner–Wadsworth–Emmons reaction [$(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, NaH, benzene, room temperature, 2.5 h]⁶ failed to give the desired α,β -unsaturated ester(s) (**5** and/or **6**) because of its ready enolization.⁷ However, on application of the Peterson olefination reaction (lithium dicyclohexylamide, $\text{Me}_3\text{SiCH}_2\text{CO}_2\text{Et}$, THF, -78°C , 1 h) reported by Nozaki and co-workers,^{7b}

4 afforded the (*Z*)- and (*E*)- α,β -unsaturated esters (**5** and **6**) in 61% and 9% yields, respectively. An alternative carboxyolefination reaction of **4** exploiting $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ and Et_3N in the presence of LiBr , developed recently by Rathke and Bouhlei,⁸ gave **5** and **6** in 42% and 39% yields, respectively. The assignments of geometry in **5** and **6** were based on the fact that the C(2)-proton (3.52 ppm) of the (*Z*)-isomer (**5**) resonates in CDCl_3 at lower field than the corresponding proton (2.72 ppm) of the (*E*)-isomer (**6**). A similar deshielding effect has been observed for the C(2)-proton of ethyl (*Z*)-2-(*tert*-butyldimethylsilyloxy)cyclopentylideneacetate relative to that of its (*E*)-isomer.^{5b}



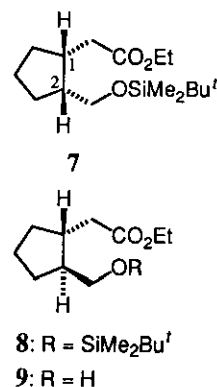
Hydrogenation of the (*Z*)-isomer (**5**) using Pd-C and H_2 (EtOH , 1 atm, room temperature, 1 h) gave a 48 : 52 mixture of the *cis*- and *trans*-esters (**7** and **8**) in 98% yield (Table I). A parallel result was also obtained with a similar hydrogenation of the (*E*)-isomer (**6**). On the other hand, catalytic hydrogenation of **6** employing Adams catalyst instead of Pd-C produced the *cis*-ester (**7**) in preference to the *trans*-ester (**8**). The structures of the *cis*- and *trans*-esters (**7** and **8**) were assigned on the basis of their ^1H nmr spectra in CDCl_3 . On irradiation of the C(2)-proton signal of **7**, a 12% NOE at the C(1)-proton signal was observed due to their *cis* relationship. In the case of Entry 1 in Table I, the mixture of **7** and **8** was treated with tetrabutylammonium fluoride to give the *cis*-lactone (**1**)² via cyclization that occurred simultaneously as well as the *trans*-alcohol (**9**) in 46% and 50% yields (from **5**), respectively.

Table I. Hydrogenation of the (*Z*)- and (*E*)- α,β -Unsaturated Esters (**5** and **6**)

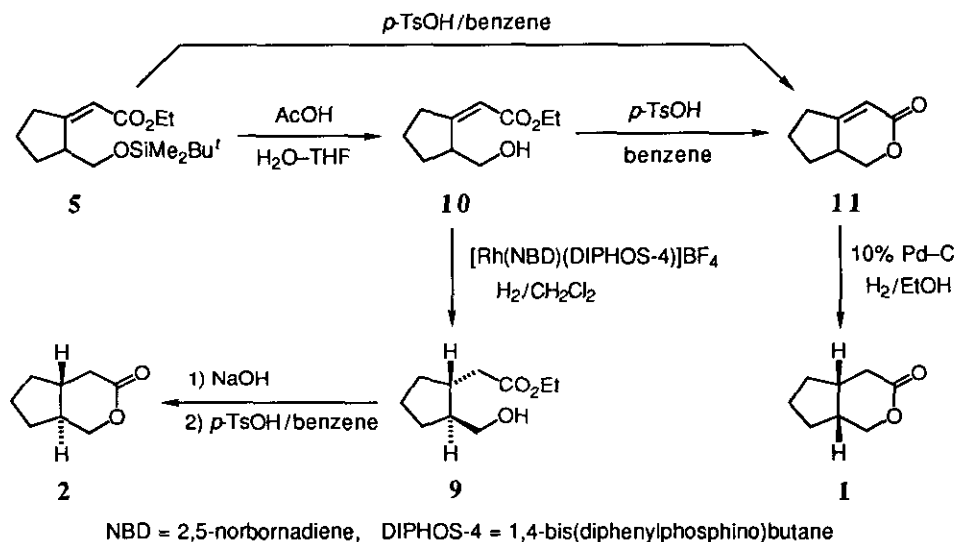
Entry ^{a)}	Substrate	Catalyst	Products (7 and 8)	
			Yield (%)	Isomeric ratio (7 : 8) ^{b)}
1	5	Pd-C	98	48 : 52
2	5	Pt	99	59 : 41
3	6	Pd-C	89	49 : 51
4	6	Pt	91	85 : 15

a) For details of the reaction conditions, see "Experimental".

b) Determined on the basis of ^1H nmr spectral analysis.



We next explored the stereoselective conversion of the (*Z*)-isomer (**5**), obtained as the major product from the above Peterson olefination reaction, into *cis*- and *trans*-hexahydrocyclopenta[*c*]pyran-3(*1H*)-ones (**1** and **2**). Deprotection of **5** with AcOH–H₂O–THF (3 : 1 : 1, v/v) provided the (*Z*)-alcohol (**10**) (93% yield), which was then subjected to acid-promoted cyclization (*p*-TsOH, benzene, room temperature, 2.5 h) to give the α,β -unsaturated lactone (**11**)⁹ in 88% yield. This lactone (**11**) was also prepared in one step (82% yield) from **5** by treatment with *p*-TsOH in benzene at room temperature for 6 h. Catalytic hydrogenation (Pd–C, H₂, EtOH, 1 atm, room temperature, 1 h) of **11** occurred exclusively from convex face to provide the desired *cis*-lactone (**1**)² as a sole isomer in 90% yield. On the other hand, the hydroxy-directed reduction of the homoallylic alcohol (**10**) was effected by using rhodium catalyst and H₂ in CH₂Cl₂,¹⁰ leading stereoselectively to the *trans*-alcohol (**9**) in 94% yield. Finally, alkaline hydrolysis of **9** and subsequent acid-catalyzed cyclization afforded the *trans*-lactone (**2**)^{2c-e} in 66% yield.



In summary, the stereoselective syntheses of *cis*- and *trans*-(\pm)-hexahydrocyclopenta[*c*]pyran-3(*1H*)-ones (**1** and **2**) have been achieved from (\pm)-2-(hydroxymethyl)cyclopentanone (**3**) via the (*Z*)- α,β -unsaturated ester (**5**) as a common intermediate in 43% (4 steps) and 33% (5 steps) overall yields, respectively.

EXPERIMENTAL

General Notes. Flash chromatography¹¹ was performed with the solvents indicated using Merck silica gel 60 (No. 9385). Spectra reported herein were recorded on a JASCO A-202 ir spectrophotometer, a Hitachi M-80 mass spectrometer, or a JEOL JNM-GSX-500 (¹H 500 MHz) nmr spectrometer. Chemical shifts are reported in

ppm downfield from internal Me₄Si. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-dd's, m = multiplet, q = quartet, s = singlet, t = triplet.

2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]cyclopentanone (4). A mixture of 2-(hydroxymethyl)cyclopentanone (3)⁴ (2.28 g, 20.0 mmol), imidazole (3.40 g, 49.9 mmol), and DMF (10 ml) was stirred under ice-cooling, and *tert*-butylchlorodimethylsilane (3.62 g, 24.0 mmol) was added. After having been stirred at room temperature for 1 h, the reaction mixture was poured into H₂O (50 ml) and extracted with ether (4 × 40 ml). The ethereal extracts were washed with saturated aqueous NaCl, dried over MgSO₄, and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by flash chromatography¹¹ [hexane–AcOEt (8 : 1, v/v)] and subsequent distillation gave **3** (4.35 g, 95%) as a colorless oil, bp 120–122°C (19 mmHg); ν_{\max}^{film} 1744 cm⁻¹ (CO); ¹H nmr (CDCl₃) δ : 0.03 and 0.04 (6H, s each, SiMe₂), 0.86 (9H, s, *tert*-Bu), 1.7–2.3 (7H, m, ring protons), 3.74 (1H, dd, *J* = 10 and 3.5 Hz) and 3.86 (1H, dd, *J* = 10 and 5 Hz) (OCH₂).

(Z)-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]cyclopentylidene]acetic Acid Ethyl Ester (5) and (E)-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]cyclopentylidene]acetic Acid Ethyl Ester (6). (i) *Via* the Peterson Olefination Reaction: A stirred solution of dicyclohexylamine (0.8 ml, 4.0 mmol) in dry THF (20 ml) was cooled to –78°C in an atmosphere of N₂, and a 1.38 M solution (2.9 ml, 4.0 mmol) of *n*-BuLi in hexane was added dropwise. After the mixture had been stirred at the same temperature for 20 min, ethyl trimethylsilylacetate¹² (0.73 ml, 4.0 mmol) was added over 4 min, and stirring was continued for 25 min. A solution of **4** (457 mg, 2.0 mmol) in dry THF (2 ml) was then added over 10 min and the reaction mixture was stirred at –78°C for 1 h. The reaction was quenched by adding saturated aqueous NH₄Cl (4 ml). After having been warmed to room temperature, the aqueous layer was separated from the organic layer and extracted with ether (4 × 20 ml). The ethereal extracts and the above organic layer were combined, washed with saturated aqueous NaCl, dried over MgSO₄, and concentrated *in vacuo* to leave a colorless oil, which was subjected to flash chromatography¹¹ [hexane–AcOEt (40 : 1, v/v)]. Earlier fractions furnished **5** (364 mg, 61%) as a colorless oil, *ms m/z*: 298 (M⁺); ν_{\max}^{film} 1713 cm⁻¹ (ester CO); ¹H nmr (CDCl₃) δ : 0.02 and 0.04 (6H, s each, SiMe₂), 0.88 (9H, s, *tert*-Bu), 1.27 (3H, t, *J* = 7 Hz, OCH₂Me), 1.55–2.05 [4H, m, C(3)-H's and C(4)-H's], 2.37 and 2.48 [2H, m each, C(5)-H's], 3.52 [1H, m, C(2)-H], 3.56 (1H, dd, *J* = 9 and 7.5 Hz) and 3.73 (1H, dd, *J* = 9 and 3.5 Hz) [C(2)-CH₂O], 4.15 (2H, q, *J* = 7 Hz, OCH₂Me), 5.80 [1H, ddd, *J* = 2 Hz each, C(1)=CHCO₂Et].

Later fractions of the above chromatography gave **6** (51 mg, 9%) as a colorless oil, *ms m/z*: 298 (M⁺); ν_{\max}^{film} 1713 cm⁻¹ (ester CO); ¹H nmr (CDCl₃) δ : 0.04 and 0.05 (6H, s each, SiMe₂), 0.89 (9H, s, *tert*-Bu), 1.27 (3H, t, *J* = 7 Hz, OCH₂Me), 1.5–1.9 [4H, m, C(3)-H's and C(4)-H's], 2.72 [1H, m, C(2)-H], 2.78 and 2.90 [2H,

m each, C(5)-H's], 3.52 (1H, dd, $J = 10$ and 8 Hz) and 3.65 (1H, dd, $J = 10$ and 6 Hz) [C(2)-CH₂O], 4.15 (2H, q, $J = 7$ Hz, OCH₂Me), 5.81 [1H, ddd, $J = 2.5$ Hz each, C(1)=CHCO₂Et].

(ii) *Via the Rathke–Bouhler Modification of the Horner–Wadsworth–Emmons Reaction*: A mixture of ethyl bis-(2,2,2-trifluoroethoxy)phosphinylacetate [(CF₃CH₂O)₂P(O)CH₂CO₂Et]¹³ (2.49 g, 7.5 mmol), LiBr (780 mg, 9.0 mmol), and dry THF (15 ml) was stirred in an atmosphere of Ar for 5 min, and Et₃N (1.25 ml, 9.0 mmol) was added. After the mixture had been stirred for 10 min, a solution of **4** (570 mg, 2.5 mmol) in dry THF (5 ml) was added over 5 min. The reaction mixture was stirred at room temperature for 24 h and then quenched with 1 N aqueous HCl (6 ml). The aqueous layer was separated from the organic layer and extracted with ether (3 × 40 ml). The ethereal extracts and the above organic layer were combined, washed successively with saturated aqueous NaHCO₃ and saturated aqueous NaCl, dried over MgSO₄, and concentrated *in vacuo*. Flash chromatography¹¹ of the residual oil was carried out as described above under method (i) to give **5** (316 mg, 42%) and **6** (288 mg, 39%), which were identical [by comparison of the ir and ¹H nmr spectra and tlc behavior] with authentic samples prepared by method (i), respectively.

Hydrogenation of the (Z)-Isomer (5). (i) Entry 1 in Table I: A solution of **5** (430 mg, 1.44 mmol) in EtOH (15 ml) was hydrogenated over 10% Pd–C (150 mg) at atmospheric pressure and room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to leave a mixture (425 mg, 98%) of **7** and **8** as a colorless oil; ¹H nmr (CDCl₃) *cis*-isomer (**7**) δ: 0.029 and 0.033 (s each, SiMe₂), 0.88 (s, *tert*-Bu), 1.25 (t, $J = 7$ Hz, OCH₂Me), 1.3–1.8 [m, C(3)-H's, C(4)-H's, and C(5)-H's], 2.13 [m, C(2)-H], 2.21 (dd, $J = 15$ and 9.5 Hz) and 2.51 (dd, $J = 15$ and 6 Hz) (CH₂CO₂Et), 2.38 [m, C(1)-H], 3.48 (dd, $J = 10.5$ and 6 Hz) and 3.54 (dd, $J = 10.5$ and 6.5 Hz) [C(2)-CH₂O], 4.12 (q, $J = 7$ Hz, OCH₂Me); *trans*-isomer (**8**) δ: 0.04 (s, SiMe₂), 0.89 (s, *tert*-Bu), 1.25 (t, $J = 7$ Hz, OCH₂Me), 1.3–1.9 [m, C(2)-H, C(3)-H's, C(4)-H's, and C(5)-H's], 1.99 [m, C(1)-H], 2.18 (dd, $J = 14.5$ and 9.5 Hz) and 2.55 (dd, $J = 14.5$ and 5.5 Hz) (CH₂CO₂Et), 3.50 (dd, $J = 10$ and 6.5 Hz) and 3.55 (dd, $J = 10$ and 6 Hz) [C(2)-CH₂O], 4.12 (q, $J = 7$ Hz, OCH₂Me). On the basis of the ¹H nmr spectrum, this oil was a 48 : 52 mixture of **7** and **8**.

(ii) Entry 2 in Table I: A solution of **5** (64 mg, 0.21 mmol) in EtOH (2 ml) was hydrogenated over Adams catalyst (6 mg) at atmospheric pressure and room temperature for 1 h. Removal of the catalyst by filtration and evaporation of the filtrate under reduced pressure left a colorless oil (64 mg, 99%), which was found to be a 59 : 41 mixture of the *cis*- and *trans*-isomers (**7** and **8**) on ¹H nmr spectral analysis.

Hydrogenation of the (E)-Isomer (6). Hydrogenation of **6** was effected as described above for the (Z)-isomer (**5**). The results are given in Table I.

(Z)-[2-(Hydroxymethyl)cyclopentylidene]acetic Acid Ethyl Ester (10). A stirred mixture of **5** (839 mg, 2.8 mmol) and AcOH-H₂O-THF (3 : 1 : 1, v/v) (32 ml) was heated at 45°C for 2 h. After cooling, the reaction mixture was concentrated *in vacuo*. The resulting oil was partitioned by extraction with a mixture of H₂O and ether. The ethereal extracts were washed successively with saturated aqueous NaHCO₃ and saturated aqueous NaCl, dried over MgSO₄, and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by flash chromatography¹¹ [hexane-AcOEt (2 : 1, v/v)] provided **10** (479 mg, 93%) as a colorless oil, *ms m/z*: 184 (M⁺); *ir* ν_{\max}^{film} cm⁻¹: 3420 (OH), 1709 (ester CO), 1648 (C=C); ¹H nmr (CDCl₃) δ : 1.28 (3H, t, *J* = 7 Hz, OCH₂Me), 1.6–1.9 [4H, m, C(3)-H's and C(4)-H's], 2.43 and 2.58 [2H, m each, C(5)-H's], 2.7 (1H, br, OH), 3.54 (1H, dd, *J* = 9 and 8.5 Hz) and 3.66 (1H, dd, *J* = 9 and 6 Hz) [C(2)-CH₂OH], 3.60 [1H, m, C(2)-H], 4.16 (2H, q, *J* = 7 Hz, OCH₂Me), 5.92 [1H, ddd, *J* = 2 Hz each, C(1)=CHCO₂Et].

5,6,7,7a-Tetrahydrocyclopenta[*c*]pyran-3(1H)-one (11). (i) From **10**: A mixture of **10** (111 mg, 0.60 mmol), *p*-TsOH-H₂O (11 mg, 0.06 mmol), and benzene (2 ml) was stirred at room temperature for 2.5 h. The reaction mixture was then worked up as described below under method (ii), giving **11**⁹ (73 mg, 88%) as a colorless oil. The *ir* and ¹H nmr spectra and tlc mobility of this oil were identical with those of an authentic sample obtained by method (ii).

(ii) From **5**: A mixture of **5** (185 mg, 0.62 mmol), *p*-TsOH-H₂O (18 mg, 0.09 mmol), and benzene (2 ml) was stirred at room temperature for 6 h. The reaction mixture, after addition of benzene (5 ml), was washed successively with saturated aqueous NaHCO₃ and saturated aqueous NaCl, dried over MgSO₄, and concentrated *in vacuo* to leave a colorless oil, which was purified by flash chromatography¹¹ [hexane-AcOEt (2 : 1, v/v)] to give **11**⁹ (70 mg, 82%) as a colorless oil, *ms m/z*: 138 (M⁺); *ir* ν_{\max}^{film} cm⁻¹: 1721 (CO), 1658 (C=C); ¹H nmr (CDCl₃) δ : 1.25 [1H, m, C(7)-H], 1.75–2.1 [3H, m, C(6)-H's and C(7)-H], 2.45–2.7 [2H, m, C(5)-H's], 2.87 [1H, m, C(7a)-H], 3.97 (1H, dd, *J* = 13 and 10.5 Hz) and 4.56 (1H, dd, *J* = 10.5 and 6 Hz) [C(1)-H's], 5.81 [1H, ddd, *J* = 2 Hz each, C(4)-H].

cis-Hexahydrocyclopenta[*c*]pyran-3(1H)-one (1) and trans-2-(Hydroxymethyl)cyclopentane-acetic Acid Ethyl Ester (9). (i) From a mixture of **7** and **8**: A solution of a 48 : 52 mixture (425 mg) of **7** and **8**, obtained from Entry 1 in Table I (*vide supra*), in THF (5 ml) was stirred under ice-cooling, and a solution of tetrabutylammonium fluoride·3H₂O (892 mg, 2.8 mmol) in THF (10 ml) was added dropwise over 20 min. After having been stirred at room temperature for 5 h, the reaction mixture was concentrated *in vacuo*. Flash chromatography¹¹ [hexane-AcOEt (2 : 1, v/v)] of the residual slightly brownish oil gave a colorless oil, which was further subjected to flash chromatography¹¹ [CH₂Cl₂-EtOH (40 : 1, v/v)]. Earlier fractions afforded **1**² (92 mg, 46% from **5**) as a colorless oil, *ms m/z*: 140 (M⁺); *ir* ν_{\max}^{film} 1744 cm⁻¹ (CO); ¹H nmr (CDCl₃) δ : 1.25–2.0 [6H, m, C(5)-H's, C(6)-H's, and C(7)-H's], 2.32 (1H, dd, *J* = 15 and 6.5 Hz) and 2.61 (1H, dd, *J* = 15 and

6.5 Hz) [C(4)-H's], 2.4–2.55 [2H, m, C(4a)-H and C(7a)-H], 4.01 (1H, dd, $J = 11.5$ and 7 Hz) and 4.28 (1H, dd, $J = 11.5$ and 5 Hz) [C(1)-H's].

Later fractions from the above second chromatography provided **9** (135 mg, 50% from **5**) as a colorless oil, ms m/z : 186 (M^+); ir ν_{\max}^{film} cm^{-1} : 3420 (OH), 1727 (ester CO); ^1H nmr (CDCl_3) δ : 1.26 (3H, t, $J = 7$ Hz, OCH_2Me), 1.25–2.1 (9H, m, ring protons and OH), 2.33 (1H, dd, $J = 15.5$ and 7 Hz) and 2.44 (1H, dd, $J = 15.5$ and 7.5 Hz) ($\text{CH}_2\text{CO}_2\text{Et}$), 3.54 (2H, d, $J = 6.5$ Hz, CH_2OH), 4.14 (2H, q, $J = 7$ Hz, OCH_2Me).

(ii) From **11**: A solution of **11** (73 mg, 0.53 mmol) in EtOH (3 ml) was hydrogenated over 10% Pd-C (35 mg) at atmospheric pressure and room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give **12** (67 mg, 90%) as a colorless oil, which was identical [by comparison of the ir and ^1H nmr spectra and tlc behavior] with the sample of **1** obtained by method (i).

(iii) From **10**: A solution of **10** (94 mg, 0.51 mmol) in CH_2Cl_2 (10 ml) was hydrogenated over (bicyclo-[2.2.1]hepta-2,5-diene)-[1,4-bis(diphenylphosphino)butane]rhodium tetrafluoroborate¹⁰ (18 mg) at 3.9 atm and room temperature for 1 h. The reaction mixture was then concentrated *in vacuo*. The orange residue was purified by flash chromatography¹¹ [hexane-AcOEt (1 : 1, v/v)] to give **9** (89 mg, 94%) as a colorless oil. The ir and ^1H nmr spectra and tlc behavior of this sample were identical with those of the sample of **9** prepared by method (i).

trans-Hexahydrocyclopenta[c]pyran-3(1H)-one (2). A mixture of **9** (46 mg, 0.25 mmol), EtOH (1 ml), and 1 N aqueous NaOH (1 ml) was stirred at room temperature for 50 min. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in H_2O (1 ml). The aqueous solution was acidified (pH 1) with 10% aqueous HCl and extracted with ether (5×5 ml). The ethereal extracts were washed with saturated aqueous NaCl, dried over MgSO_4 , and concentrated *in vacuo* to leave a colorless oil, which was dissolved in benzene (5 ml). The benzene solution, after addition of *p*-TsOH· H_2O (5 mg, 0.026 mmol), was heated under reflux for 1 h. After cooling, the mixture was washed successively with saturated aqueous NaHCO_3 and saturated aqueous NaCl, dried over MgSO_4 , and concentrated *in vacuo*. Purification of the residual oil by flash chromatography¹¹ [CH_2Cl_2 -EtOH (30 : 1, v/v)] furnished **2^{2c-e}** (23 mg, 66%) as a colorless oil, ms m/z : 140 (M^+); ir ν_{\max}^{film} cm^{-1} (CO); ^1H nmr (CDCl_3) δ : 1.15–1.3 [2H, m, C(6)-H's], 1.65–1.75 [2H, m, C(4a)-H and C(7a)-H], 1.8–2.0 [4H, m, C(5)-H's and C(7)-H's], 2.27 (1H, dd, $J = 18$ and 12.5 Hz) and 2.90 (1H, dd, $J = 18$ and 5 Hz) [C(4)-H's], 4.07 (1H, dd, $J = 11$ Hz each) and 4.60 (1H, dd, $J = 11$ and 5 Hz) [C(1)-H's].

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