STEREOSELECTIVE SYNTHESES OF *cis*- AND *trans*-HEXAHYDROCYCLOPENTA[*c*]PYRAN-3(1*H*)-ONES

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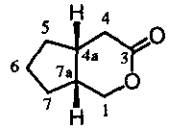
Abstracts ——— A new access to *cis*- and *trans*-hexahydrocyclopenta[*c*]pyran-3(1*H*)-ones (**1** and **2**) has been accomplished stereoselectively through 4-step and 5-step routes, respectively, starting from 2-(hydroxymethyl)cyclopentanone (**3**).

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.



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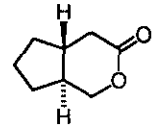

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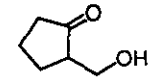

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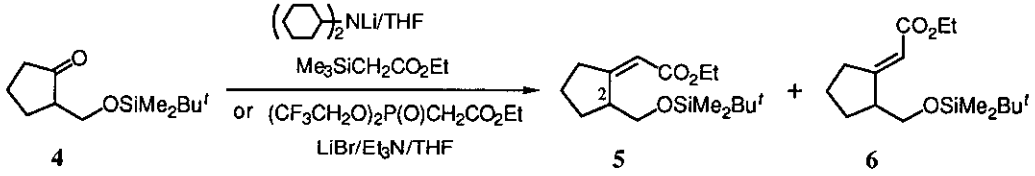
Carboxyolefination reaction of the cyclopentanone derivative (**4**), prepared from **3**[4] in 95% yield, by the Wittig reaction ($Ph_3P{=}CHCO_2Et$, benzoic acid, boiling toluene, 5 h)[5] or the Horner–Wadsworth–Emmons reaction [$(EtO)_2P(O)CH_2CO_2Et$, NaH, benzene, room temperature, 2.5 h][6] failed 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, $Me_3SiCH_2CO_2Et$, 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 $(CF_3CH_2O)_2P(O)CH_2CO_2Et$ and Et_3N in the presence of LiBr, developed recently by Rathke and Bouhlel,[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]



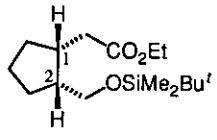
4 **5** **6**

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.



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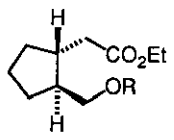
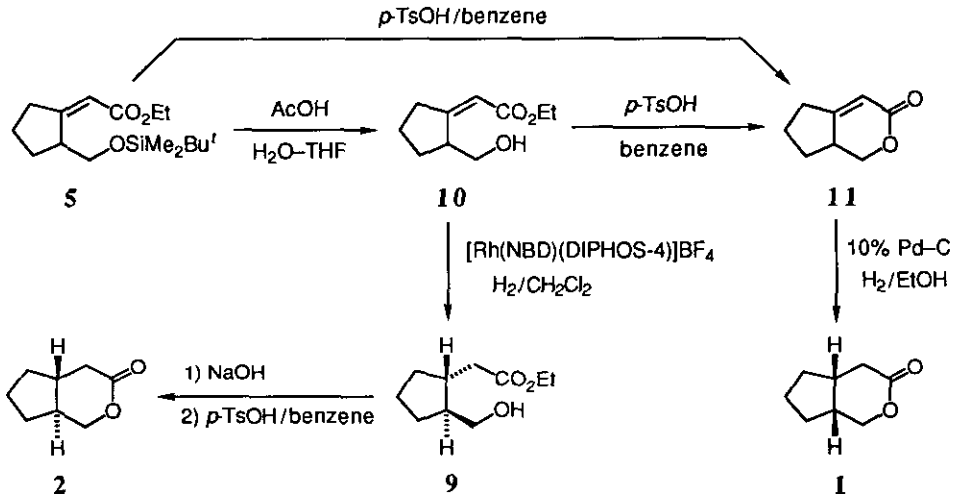


8: R = $SiMe_2Bu^t$
9: R = H

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(1*H*)-ones (**1** and **2**). Deprotection of **5** with AcOH–H_2O–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, H_2, 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 H_2 in CH_2Cl_2,[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.



NBD = 2,5-norbornadiene, DIPHOS-4 = 1,4-bis(diphenylphosphino)butane

In summary, the stereoselective syntheses of *cis*- and *trans*-(±)-hexahydrocyclopenta[*c*]pyran-3(1*H*)-ones (**1** and **2**) have been achieved from (±)-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 chromatography[11] 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 (^{1}H 500 MHz) nmr spectrometer. Chemical shifts are reported in

ppm downfield from internal Me_4Si. 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 H_2O (50 ml) and extracted with ether (4 × 40 ml). The ethereal extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by flash chromatography[11] [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); ir ν_{max}^{film} 1744 cm^{-1} (CO); ^1H nmr ($CDCl_3$) δ: 0.03 and 0.04 (6H, s each, $SiMe_2$), 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) (OCH_2).

(*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 N_2, 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 trimethylsilylacetate[12] (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 NH_4Cl (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 $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil, which was subjected to flash chromatography[11] [hexane–AcOEt (40 : 1, v/v)]. Earlier fractions furnished **5** (364 mg, 61%) as a colorless oil, ms *m/z*: 298 (M^+); ir ν_{max}^{film} 1713 cm^{-1} (ester CO); ^1H nmr ($CDCl_3$) δ: 0.02 and 0.04 (6H, s each, $SiMe_2$), 0.88 (9H, s, *tert*-Bu), 1.27 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 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)-CH_2O], 4.15 (2H, q, J = 7 Hz, $OC\underline{H_2}Me$), 5.80 [1H, ddd, J = 2 Hz each, C(1)=C$\underline{H}CO_2Et$].

Later fractions of the above chromatography gave **6** (51 mg, 9%) as a colorless oil, ms *m/z*: 298 (M^+); ir ν_{max}^{film} 1713 cm^{-1} (ester CO); ^1H nmr ($CDCl_3$) δ: 0.04 and 0.05 (6H, s each, $SiMe_2$), 0.89 (9H, s, *tert*-Bu), 1.27 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 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)-CH_2O], 4.15 (2H, q, J = 7 Hz, O$\underline{CH_2}$Me), 5.81 [1H, ddd, J = 2.5 Hz each, C(1)=C$\underline{H}CO_2Et$].

(ii) *Via* the Rathke–Bouhlel Modification of the Horner–Wadsworth–Emmons Reaction: A mixture of ethyl bis-(2,2,2-trifluoroethoxy)phosphinylacetate [$(CF_3CH_2O)_2P(O)CH_2CO_2Et$][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 Et_3N (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 $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography[11] 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 ^{1}H 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; ^{1}H nmr ($CDCl_3$) *cis*-isomer (**7**) δ: 0.029 and 0.033 (s each, $SiMe_2$), 0.88 (s, *tert*-Bu), 1.25 (t, J = 7 Hz, $OCH_2\underline{Me}$), 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) ($C\underline{H_2}CO_2Et$), 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)-CH_2O], 4.12 (q, J = 7 Hz, O$\underline{CH_2}$Me); *trans*-isomer (**8**) δ: 0.04 (s, $SiMe_2$), 0.89 (s, *tert*-Bu), 1.25 (t, J = 7 Hz, $OCH_2\underline{Me}$), 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) ($C\underline{H_2}CO_2Et$), 3.50 (dd, J = 10 and 6.5 Hz) and 3.55 (dd, J = 10 and 6 Hz) [C(2)-CH_2O], 4.12 (q, J = 7 Hz, O$\underline{CH_2}$Me). On the basis of the ^{1}H 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 ^{1}H 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–H_2O–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 H_2O and ether. The ethereal extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by flash chromatography[11] [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 ($CDCl_3$) δ: 1.28 (3H, t, *J* = 7 Hz, $OCH_2\underline{Me}$), 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)-$C\underline{H}_2OH$], 3.60 [1H, m, C(2)-H], 4.16 (2H, q, *J* = 7 Hz, $OC\underline{H}_2Me$), 5.92 [1H, ddd, *J* = 2 Hz each, C(1)=$C\underline{H}CO_2Et$].

5,6,7,7a-Tetrahydrocyclopenta[*c*]pyran-3(1*H*)-one (11). (i) From **10**: A mixture of **10** (111 mg, 0.60 mmol), *p*-TsOH·H_2O (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·H_2O (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 $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil, which was purified by flash chromatography[11] [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 ($CDCl_3$) 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(1*H*)-one (1) and *trans*-2-(Hydroxymethyl)cyclopentaneacetic 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·$3H_2O$ (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 chromatography[11] [hexane–AcOEt (2 : 1, v/v)] of the residual slightly brownish oil gave a colorless oil, which was further subjected to flash chromatography[11] [CH_2Cl_2–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 ($CDCl_3$) 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, $OCH_2\underline{Me}$), 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) ($C\underline{H}_2CO_2Et$), 3.54 (2H, d, J ≈ 6.5 Hz, $C\underline{H}_2OH$), 4.14 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$).

(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 **1**[2] (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 tetrafluoroborate[10] (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 chromatography[11] [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(1*H*)-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 chromatography[11] [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} 1726 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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