3-PHENYLHEXAHYDRO-1(3H)-ISOBENZOFURANONES

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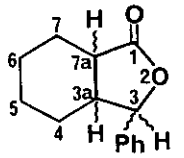
Abstract —— Highly stereoselective syntheses of four stereoisomers of 3-phenylhexahydro-1(3H)-isobenzofuranone (1) and the reevaluation of stereochemical assignments of these lactones are described.

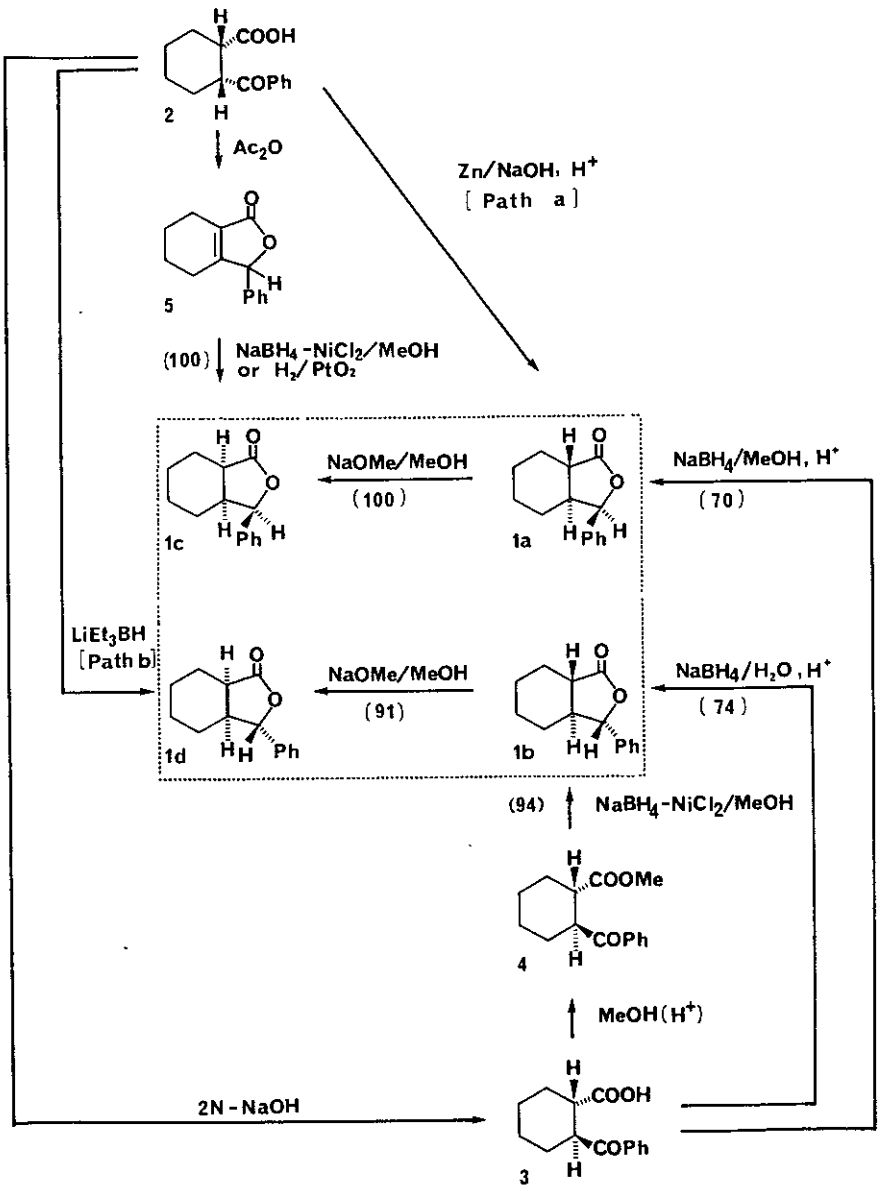
In the course of our investigations into chemical modification of pharmacologically active compounds, we have had an occasion to prepare the 3-phenylhexahydro-1(3H)-isobenzofuranones (**1**) which exist as four stereoisomers [(**1a**),(**1b**),(**1c**), and (**1d**)] with regard to the configurations of the chiral centers at C-3, C-3a, and C-7a, as shown in Fig. 1 and Scheme 1. Although the stereoselective syntheses of these four racemic stereoisomers are known,[1-3] the previous method consisting of reductive cyclization of keto acid (**2**) seems to give satisfactory and reproducible results only for the preparation of the stereoisomers (**1a**)[2] and (**1d**)[1] (see Path a and Path b). Quite recently, configurational assignments of these four stereoisomers have been presented through ^{1}H- and ^{13}C-nmr spectroscopic studies.[1]



(**1**)

Fig. 1

In this paper, we wish to report the highly stereoselective preparations and some chemical properties of the title lactones (1), as well as the reevaluation of stereochemical assignments of these lactones.



Scheme 1

Table 1. 3-Phenylhexahydro-1(3H)-isobenzofuranones(1a-d)

Compd.	Mp(°C)	Purity (%) [Ret. time (min.)][e]	Ir (cm^{-1})[f]	^{1}H-Nmr (ppm) on C-3[g]
1a	83-84[a]	100 [4.40]	1775	5.60 (J=7.0 Hz)
1b	86.5-88[b]	100 [5.88]	1775	4.98 (J=9.3 Hz)
1c	84-85[c]	100 [5.85]	1765	5.48 (J=4.4 Hz)
1d	53-54[d]	100 [3.68]	1765	5.19 (J=3.4 Hz)

[a] Lit. mp 82-83°C[1] and mp 80-88°C[2] (Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.56; H, 7.52.). [b] Lit. mp 79-81°C[1] (Found: C, 77.60; H,7.52). [c] Lit.[1] mp 68-70°C (Found:C, 77.52; H,7.51). [d] Reported as an oil in literature[1] (Found: C, 77.73; H, 7.34). [e] By HPLC performed by using a Waters M-45 solvent delivery system equipped with U6K injector and differential refractometer R-401 (Waters μ-porasil, 3.9 mm i.d. x 30 cm). [f] Obtained as KBr tablet. [g] Recorded in $CDCl_3$ (TMS as an internal standard) with 90 MHz.

According to the routes shown in Scheme 1, we synthesized the four 3-phenylhexahydro-1(3H)-isobenzofuranones (**1a**) - (**1d**) which are shown in Table 1. The alternative routes which we now successfully developed for the synthesis of the title compounds(**1a-d**) also gave high stereoselectivities (values in parentheses shown in Scheme 1 indicate the ratios of major isomers).

In these reactions, the route via cis hydrogenation of the unsaturated lactone (5) with $NaBH_4$ in the presence of $NiCl_2 \cdot 6H_2O$[5] in MeOH [(2) →(5) →(1c)] provides a new alternative method for (**1c**). The fact that the catalytic hydrogenation[6] of the unsaturated lactone (5) with PtO_2 also afforded (**1c**) with 100 % isomeric purity (by HPLC) though in low yield offers further corroborating evidence for the cis ring junction of the product (**1c**). With regard to the two routes for (**1b**) [(3) →(4) →(1b), and (3) →(1b)], it should be mentioned that the former reaction gave higher stereoselectivity (94%) than the reductive lactonization of (3) reported previously.[1]

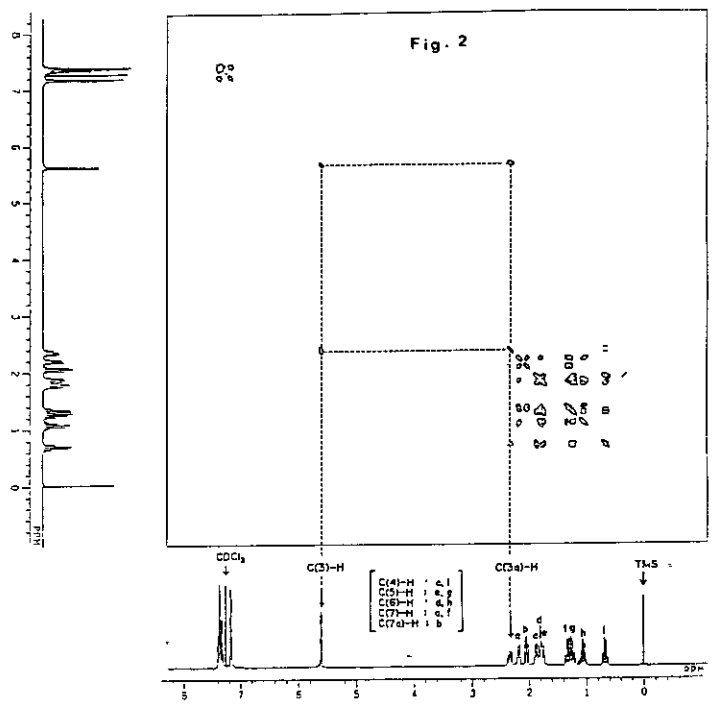
All stereoisomers (**1a-1d**) were obtained as colourless crystals, and showed different retention times by high performance liquid chromatography (HPLC). That both trans isomers (**1a** and **1b**) showed C=O absorption at slightly higher frequencies (10 cm^{-1}) than the corresponding cis isomers [(**1c**) and (**1d**), respectively] in ir spectra may be attributable to the higher ring strain of γ-lactone for the trans ring junction rather than those for cis junction.[7] In fact, the trans isomers (**1a**) and (**1b**) on treatment with sodium methoxide are easily epimerized into the corresponding cis isomers [(**1c**) and (**1d**), respectively] in excellent yields.

The spectroscopic results easily determine the structures of those products as 3-phenylhexahydro-1(3H)-isobenzofuranones. The ^{13}C-nmr data which we obtained with those pure samples are summarized in the Table 2. Although these assignments were supported by the procedure including deuterium exchange experiments, the results of the configurational assignments for the products, especially regarding the carbon resonances for C-3a and C-7a, were found to be somewhat different from the values reported recently. Thus, Eisenbraun[1] had assigned two signals appearing at high field (δ 37.8-46.6 ppm) and at low field (δ 42.2-51.8 ppm) to C-3a and C-7a resonances, respectively.[1] The final confirmation of our assignments in Table 2 was supplied by nmr analysis using the technique of two dimensional (2D) shift

Table 2. ^{13}C-Nmr Chemical Shifts (δ , ppm) for 3-Phenylhexahydro-1(3H)-isobenzofuranones (1a-d)[a,b]

C \ Compd.	1a	1b	1c	1d
1	177.6	176.5	177.3	178.2
3	82.0	85.4	81.7	83.1
3a	46.7[c]	51.9[c]	41.0[c]	43.0[c]
4	27.5	27.0	23.6	26.9
5	(25.0)	(24.8)	(23.6)	23.0
6	(25.2)	(25.3)	(22.7)	23.0
7	(25.3)	(25.0)	(23.1)	23.0
7a	40.2	46.5	42.4[c]	37.9[c]

[a] Recorded as 1.39 mol solutions in $CDCl_3$ using TMS as an internal standard(100 MHz). Four ^{13}C resonances ascribable to the aromatic carbons were observed at δ 125.0-138.6 ppm. [b] The final assignments in parentheses, which were interchangeable (by 1D nmr with 100 MHz), were confirmed by 2D nmr spectroscopic analysis (400 MHz). [c] Confirmable through deuterium exchange.



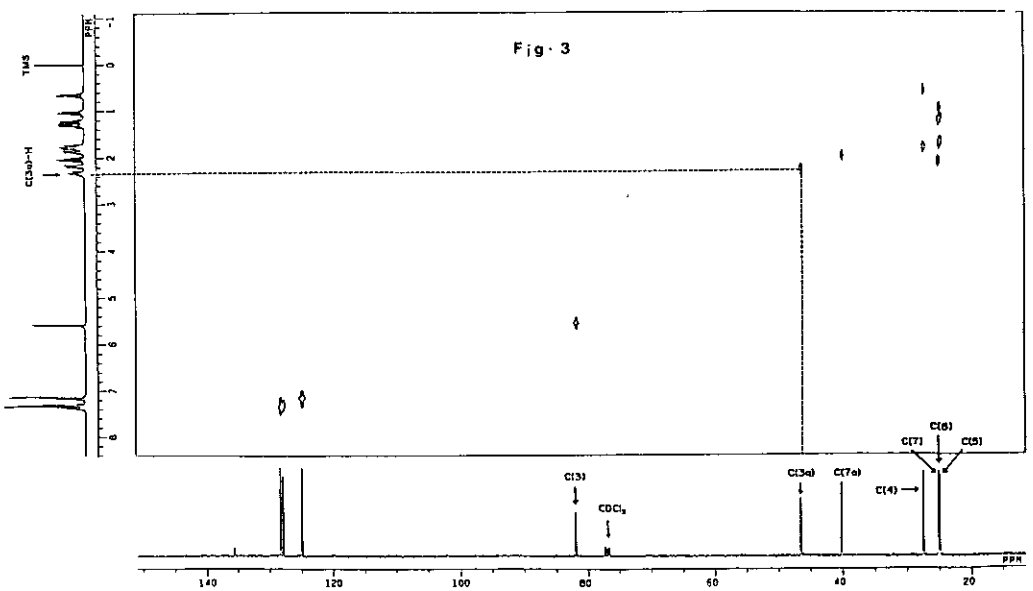


Fig. 2 and Fig. 3. 2D-Homonuclear (^{1}H-^{1}H) (Fig. 2) and Heteronuclear (^{13}C-^{1}H) (Fig. 3) Shift Correlation Spectra of **1a**.

correlation spectra with 400 MHz.[8] Fig. 2 and Fig. 3 are the examples for the compound (**1a**). From 2D-homonuclear (^1H-^1H) shift correlation spectrum (Fig. 2), it is apparent that the proton appearing at δ 2.35 ppm, coupling with the proton (δ 5.60 ppm, doublet, J=7.0 Hz) on C-3, might be assigned to the proton on C-3a. Consequently, the carbon resonance at δ 46.7 ppm can be assigned to the signal of C-3a in 2D-heteronuclear (^{13}C-^1H) shift correlation spectrum (Fig. 3). Similarly, the results using 2D-nmr spectra permitted chemical shift assignment of ^{13}C signal appearing at δ 40.20 ppm for C-7a of the lactone (**1a**).

The assignments of ^{13}C resonance listed in Table 2 were also borne out by the experiments that employed deuterated compounds. For example, the ^{13}C-nmr spectra of the lactone (**1d**) and two deuterated compounds **C3a-D-1d** and **C7a-D-1d** are shown in Fig. 4. The deuterated compound (**C7a-D-1d**) is the sole product from the isomerization of (**1b**) with NaOMe/DOMe, and the compound (**C3a-D-1d**) is the product from the isomerization of the deuterated compound (**C3a-D-1b**), prepared by the procedure for (**1b**) with the deuterated compound (**C2-D-3**)(Scheme 2).

With regard to the ^1H-nmr spectra of the products (**1a-d**), the observed chemical shifts of a proton on C-3 and coupling constants between a proton on C-3 and a proton on C-3a are listed in the Table 1 for reference.

From the viewpoint of stereoselective synthesis, it could be emphasized that the two routes [(**3**) → (**4**) → (**1b**) and (**2**) → (**5**) → (**1c**)] gave the most satisfactory and reproducible results with high stereoselectivities, together with the previous procedure for (**1a**) and (**1d**) [the routes (**2**) → (**1a**) and (**2**) → (**1d**), respectively]. Reductive lactonizations with the trans keto acid (**3**) described in this paper, except for the route (**3** → **4** → **1b**), must result in the products(**1a-b**) via the intermediate trans hydroxy acids (**6a-b**) (see Fig. 5). In contrast to the easy isolation of the pure hydroxy acid (**6a**),[2] isolation of the hydroxy acid (**6b**) was difficult because of the contamination by the lactone (**1b**) which simultaneously formed in the course of purification. This fact indicates that the rate of lactonization of (**6b**) appears to be faster than that of (**6a**). For the preparation of the pure (**1a**) and (**1b**), appropriate work-up that took the above properties into consideration gave satisfactory

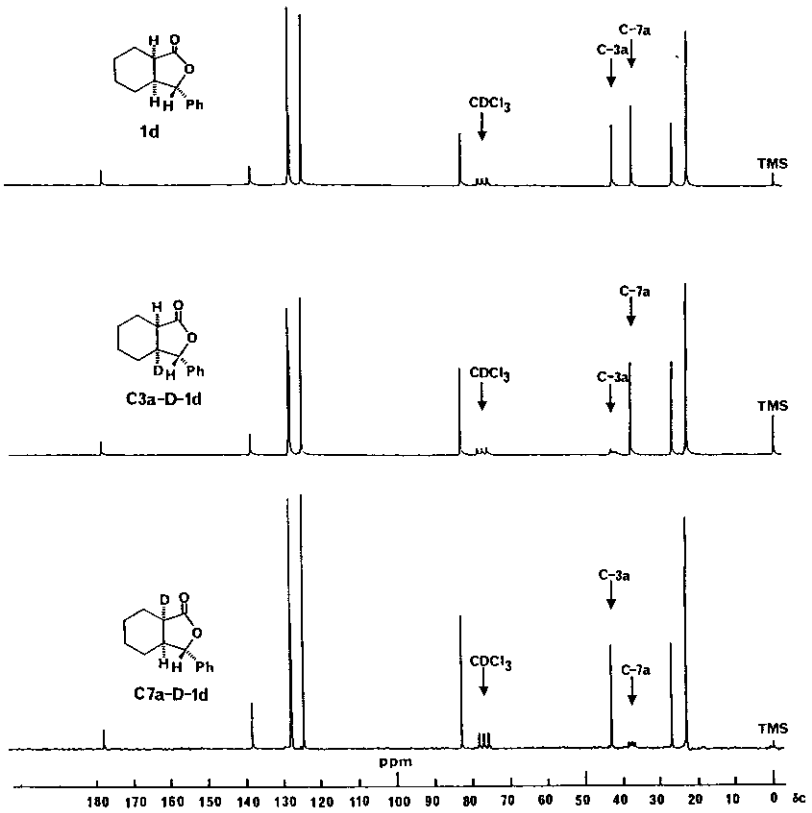
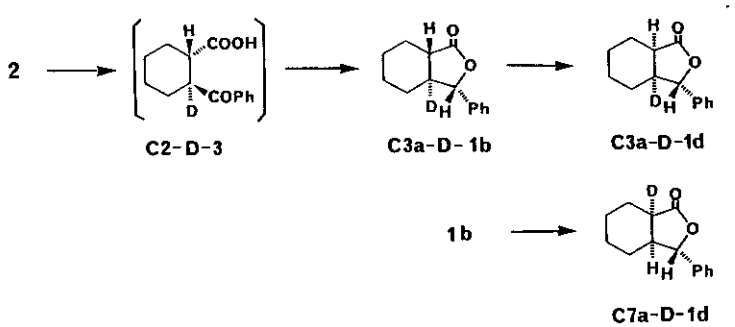


Fig. 4. ^{13}C-Nmr Spectra (100 MHz) of the Compounds **1d**, **C3a-D-1d**, and **C7a-D-1d**.



Scheme 2

results (see EXPERIMENTAL).

Further chemical transformations of the stereoisomers (1a-d) and pharmacological evaluations will be published elsewhere in detail.

6a 6b

Fig. 5

EXPERIMENTAL

Melting points were uncorrected. Ir spectra were obtained on a Hitachi 250 spectrometer. ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Hitachi R-22 instrument and on a JNM FX-100 instrument, respectively, using tetramethylsilane as an internal standard. High performance liquid chromatography (HPLC) was performed by using the Waters M-45 solvent delivery system equipped with U6K injector and differential refractometer R-401 (Waters μ-porasil, 3.9 mm i.d. X 30 cm, using hexane/Et_2O=8/2 as solvent).

The two-dimensional nmr (2D-nmr) heteronuclear (^{13}C-^{1}H) shift correlation spectra were recorded on a JEOL GX-400 spectrometer with 5-mm probe and Me_4Si as an internal standard at 25°C in $CDCl_3$, equipped with a G MHD 80R(JEOL) computer system. 2D experiments were controlled and data processed with the standard VCHSHF software package of PLEXUS (JEOL) data system, using a magnetic disc of 32 megabyte storage capacity. Time domain matrices $S(t_1, t_2)$ of 256 x 2048 points were used, with spectral widths in the f_1 and f_2 domains of 3800 and 14000 Hz respectively. 2D-homonuclear chemical shift correlation (COSY) spectra were also performed on above apparatus with 5mm probe and Me_4Si as an internal standard at 25°C in $CDCl_3$. 2D experiments were controlled and processed with the standard VCOSYN software package of PLEXUS(JEOL) data system. Time domain matrices $S(t_1, t_2)$ of 512 x 1024 points were used, with spectral widths in the f_1 and f_2 domains of 3750 and 3750 Hz respectively.

Preparations of Cis and Trans 2-Benzoylcyclohexanecarboxylic Acids [(2) and (3)]

The starting compound (2), mp 139-140°C (lit.[2] mp 139-140°C) was prepared by the procedure reported by Fieser and Novello[2]. The trans keto acid (3), mp 151-152°C (lit.[9] mp 151-152°C), was obtained as colourless needles from epimerization of (2) with 2N-NaOH, according to the method by Jucker and Süess.[9]

Reduction of Trans Keto Acid(3) with Sodium Borohydride($NaBH_4$)

Method A: $NaBH_4$ (0.37 g, 0.01 mol) was added to a solution of trans keto acid (3) (4.64 g, 0.02 mol) and dissolved NaOH (1.64 g) in methanol (50 ml). The mixture was allowed to stand overnight at room temperature, $NaBH_4$ (0.22 g, 0.006 mol) was added and then kept for 5 days at room temperature. After concentration of the solvent with a rotary evaporator, the resulting residue was acidified with hydrochloric acid (10 %) with ice cooling and the separated hydroxy acids were extracted with ether (150 ml). The ethereal layer [**(6a)+(6b)**] was washed with brine, dried over anhydrous magnesium sulfate, and after evaporation of the solvent, the residue was treated with a catalytic amount of p-toluenesulfonic acid in benzene under reflux. Work up gave a mixture of lactones (**1a** and **1b**). The ratio (**1a:1b**) was 70:30 by HPLC and the yield was 3.8 g (88 %).

The following procedure for lactonization of the above mixture of hydroxy acids [**(6a)+(6b)**] gave the pure lactone (**1a**). Thus, the ethereal layer obtained above was stirred vigorously with hydrochloric acid (20 %) (30 ml) for 40 min. After removal of the aqueous layer, the ethereal layer was extracted with aq. sodium carbonate (5%). The aqueous layer was acidified with hydrochloric acid (10 %) under cooling and extracted with ether and then the ether extract was washed with brine. After evaporation of the solvent, lactonization of the residue in refluxing benzene with a catalytic amount of p-toluenesulfonic acid gave 2.24 g(51.9%) of a mixture of the lactones (**1a**/**1b**=95/5). Recrystallization of this material from diisopropyl ether gave pure (**1a**), the physical properties of which are summarized in the Table 1.

Method B: $NaBH_4$ (0.37 g, 0.01 mol) was added to a solution of trans keto acid (3) (4.64 g, 0.02 mol) in water (30 ml) in the presence of NaOH (1.64 g). The

mixture was kept overnight at 8°C and then additional $NaBH_4$ (0.22 g, 0.006 mol) was introduced. After standing for 9 days at 8°C, the resulting mixture was acidified with hydrochloric acid (10 %), and the separated hydroxy acids [**(6a)+(6b)**] were extracted with ether. The residue obtained after evaporation of the solvent was treated with p-toluenesulfonic acid in benzene under reflux to afford a mixture of the lactones [**(1a)** and **(1b)**]. The yield was 3.68 g (85.2 %), and the ratio was found to be 26:74 (**1a:1b**) by HPLC.

The following procedure for lactonization of the mixture of hydroxy acids gave the pure lactone (**1b**): An ether extract obtained above was treated with hydrochloric acid (20%) (30 ml) for 20 min under vigorous stirring. The ethereal solution separated from the aqueous layer was washed with aq. sodium carbonate (5 %) and then with brine. After drying over anhydrous magnesium sulfate, evaporation of the solvent gave 2.9 g (67.1 %) of a mixture of (**1a**) and (**1b**), the ratio of which was 8:92 (**1a:1b**) by HPLC. Recrystallization of this material from diisopropyl ether afforded pure(**1b**) as colourless prisms. The physical properties of this compound are listed in Table 1.

When the above procedure for pure (**1b**) was employed under the same reaction conditions in D_2O starting with the keto acid **C2-D-3** (prepared by employing the isomerization reaction described by Jucker and Süess[9] under $NaOD/D_2O$), the compound (**C3a-D-1b**); mp 86.5-88°C (from iso-Pr_2O) was the main product; m/z 217 (M^+), ir(KBr) 1775 cm^{-1} (C=O). In ^1H-nmr spectrum, this compound showed a sharp singlet at δ 4.98 ppm , ascribable to the benzylic proton, by which the deuterated proton on C-3a is easily confirmed.

Preparation of Trans Methyl 2-Benzoylcyclohexanecarboxylate (**4**)

The trans keto ester (**4**) was obtained according to the procedure by Hagishita and Kuriyama.[10] Recrystallization from hexane gave the trans keto ester (**4**), mp 51-52°C (lit.[10] mp 55-57°C), in 92 % yield.

Reduction of the Keto Ester (**4**) with $NaBH_4$-$NiCl_2 \cdot 6H_2O$

To a stirred solution of the keto ester (**4**) (2.46 g, 0.01 mol) and $NiCl_2.6H_2O$ (1.20 g, 0.005 mol) in methanol (50 ml) was added $NaBH_4$ (1.9 g, 0.05 mol) in small portion over a period of 4 h at -10°C. The black precipitate was

filtered off through a short column of alumina using methanol as an eluent. The methanolic solution obtained was acidified with hydrochloric acid (20 %). Removal of the methanol afforded a residue, which was dissolved in benzene (50 ml) containing p-toluenesulfonic acid (0.5 g) and was heated under reflux for 1 h. The resulting solution was washed with aq. sodium carbonate (5 %), brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a mixture of (**1a**) and (**1b**), mp 78-81°C, in 94 % yield. The ratio of **1a/1b** was 6/94 by HPLC. One recrystallization of this material from diisopropyl ether gave pure (**1b**) as colourless prisms, mp 86.5- 88°C. This compound was identical with the pure sample obtained from the method B described above.

Isomerization of the Trans Lactones (**1a** and **1b**).

Isomerization of (**1a**): A mixture of trans lactone (**1a**) (100 % isomeric purity) (2.16 g, 0.01 mol) and methanolic sodium methoxide, prepared from 0.3 g of sodium and 20 ml of anhydrous methanol, was refluxed for 3.5 h. The resulting solution was concentrated under reduced pressure, diluted with water, and acidified with hydrochloric acid (10 %) under cooling. The mixture was extracted with ether, and the extract was washed with aq. sodium carbonate, brine, and dried over anhydrous magnesium sulfate. Evaporation afforded the cis lactone (**1c**) (100 % isomeric purity by HPLC) as a colourless crystalline solid. The yield was 1.83 g (84.7 %). Recrystallization from diisopropyl ether gave colourless needles, mp 84-85°C (lit.[1] mp 68-70°C), which was sufficient for the analytical use. Other physical data of this compound were shown in Table 1.

Isomerization of (**1b**): The reaction was carried out under the same conditions described for the isomerization of the trans (**1a**). Work up in similar fashion gave 1.70 g (78.7 %) of the cis lactone (**1d**) [with the contamination of the starting trans lactone (**1b**) (9%) by HPLC]. Column chromatography of alumina, using hexane/ether (8/2) as an eluent, gave the analytical sample, mp 53-54°C (lit.[1] oil), the data of which were shown in the Table 1.

When above reaction was carried out with MeOD the deuterated compound (**C7a-D-1d**); mp 53-54°C, m/z 217 (M^+), ir (KBr) 1765 cm^{-1}(C=O), was obtained as the main product. A benzylic proton was observed at δ 5.19 ppm as a doublet (J=3.4

Hz). The use of the deuterated compound (C3a-D-1b) in above reaction with MeOH resulted in the formation of the product (C3a-D-1d) predominantly; mp 53-54°C, m/z 217 (M^+), ir (KBr) 1765 cm^{-1} (C=O). A benzylic proton was observed at 5.19 ppm as a sharp singlet. The ^{13}C-nmr spectra of these compounds were shown in Fig. 4 .

4,5,6,7-Tetrahydro-3-phenyl-1(3H)-isobenzofuranone (5).

A mixture of the cis keto acid (2) (10.4 g, 0.045 mol) and acetic anhydride (13.5 g) was heated under reflux for 2 h. After removal of acetic anhydride under reduced pressure, the residue was treated with aq. sodium carbonate (5 %) for 2 h under stirring. The mixture was filtered, washed with water, dried and then the solvent was evaporated. Column chromatography of the residue using alumina with ether as an eluent gave 8.84 g (92.2%) of the unsaturated lactone (5); mp 63-65°C , ir (KBr) 1760 (C=O), 1680 (C=C) cm^{-1}, ^1H-nmr ($CDCl_3$)δ7.4 -7.1 (m, 5H, ArH), 5.7 (s, 1H, a benzylic proton), 2.4-1.4 (m, 8H, other aliphatic protons)ppm, ^{13}C-nmr ($CDCl_3$) δ 173.5, 164.0, 135.2, 128.8 (x 3), 126.5(x 2), 125.6, 84.3, 23.0, 21.4 (x 2), 20.0 ppm. Anal. Calcd. for $C_{14}H_{14}O_2$: C,78.48; H,6.59. Found: C, 78.50; H, 6.44.

Reduction of the Unsaturated Lactone (5) with $NaBH_4$-$NiCl_2 \cdot 6H_2O$ in Methanol.

To a solution of the compound (5) (2.14 g, 0.01 mol) and $NiCl_2 \cdot 6H_2O$ (0.24 g, 0.001 mol) in methanol (36 ml) was added $NaBH_4$ (1.13 g, 0.03 mol) in small portions over a period of 4 h with stirring at -10°C. After addition of $NaBH_4$, the suspension of insoluble black material was filtered through a short column of alumina and washed with methanol. Concentration of the filtrate under reduced pressure gave an oily residue. The residue was mixed with H_2O (15 ml), acidified with aq. HCl (ca. 10 %) under ice-cooling, and then extracted with Et_2O. The ethereal extract was washed with aq. sodium carbonate (5 %), brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 1.80 g (83.3 %) of the lactone (1c)(100 % isomeric purity by HPLC); mp 84-85°C (from isopropyl ether). Other data are listed in Tables 1 and 2.

Catalytic Hydrogenation of (5).

The mixture of the unsaturated lactone (5) (2.14 g, 0.01 mol) and PtO_2 (0.6 g)

catalyst in ethyl acetate (30 ml) was hydrogenated at atmospheric pressure and room temperature. The above catalytic hydrogenation may not be recommended as the procedure for (1c), because of the simultaneous reductive cleavage of C(3)-O bond and further hydrogenation of the aromatic ring under the reaction conditions. Thus, use of an equimolar amount of hydrogen resulted in the recovery of starting compound (5), and introduction of hydrogen till disappearance of (5) only resulted in the formation of a trace amount of the desired compound. Therefore, the reaction was stopped after absorption of 380 ml of hydrogen, and the catalyst was removed by filtration from the mixture, the filtrate was then concentrated under reduced pressure to give a solid, to which ether was added. The ethereal solution was washed with aq. sodium carbonate (5 %), brine, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, two recrystallizations of the residue from diisopropyl ether gave (1c) as colourless prisms in 31 % yield. The product was identical with the sample obtained from the isomerization of (1a).

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