

NEW REDUCTION REACTION OF BENZYLIC ALCOHOLS WITH ACID AND PROOF OF THE INTERMOLECULAR HYDRIDE SHIFT MECHANISM

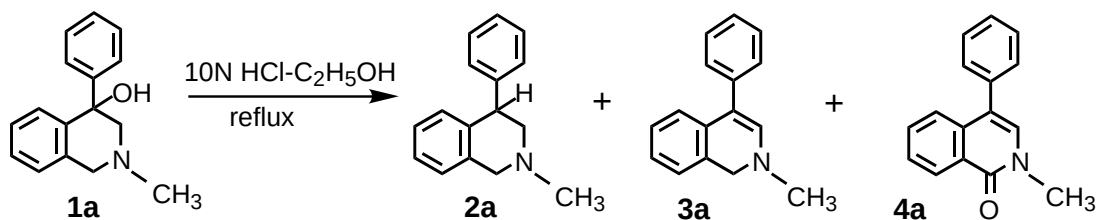
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Abstract - The new reduction reaction of the hydroxy groups of 4-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinolines (**1**) to the corresponding alkanes (**2**) with mineral and Lewis acids is reported. A stereoselective intermolecular hydride shift mechanism of the reduction was proved by reaction of the deuterated derivatives (**14** and **15**) of **1a** with 10N HCl-C₂H₅OH and BBr₃ in CH₃CN.

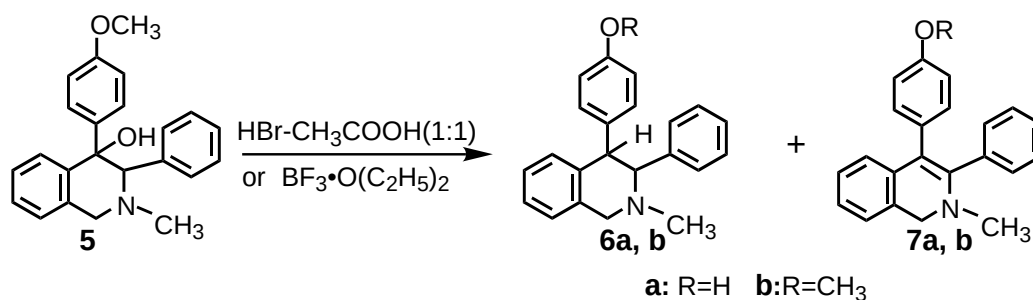
The general method for the preparation of alkanes from benzyl alcohols includes a reduction process and catalytic reduction of the hydroxy groups of benzyl alcohols¹ and the double bond of olefins² obtained from benzyl alcohols with acid was used. Recently, the convenient reductions of the hydroxy groups of benzyl alcohols with NaBH₄² and triethylsilane in TFA³ were reported. In the course of our study⁴ on the synthesis of 1,2-dihydro-3,4-diphenylisoquinolines as anti-breast cancer agents, we found a novel reduction of a tetrahydroisoquinoline derivative (**1a**)⁵ having a benzylic hydroxy group with boiling 10N HCl-EtOH to an alkane (**2a**) with a dehydrated compound (**3a**) and an amide (**4a**) (Scheme 1). This reaction and the mechanism are very interesting since the reduction proceeded without using a reducing reagent. In the previous paper,⁶ we reported the reduction of **1a** to **2a** proceed via **3a** with a stereoselective intermolecular hydride shift mechanism. In this paper, we report the reaction of some derivatives and the related compounds of **1a** with mineral and Lewis acids. In addition, the mechanism is discussed in detail by the results of the reaction of deuterated compounds of **1a** with 10N HCl-EtOH and BBr₃.

Scheme 1



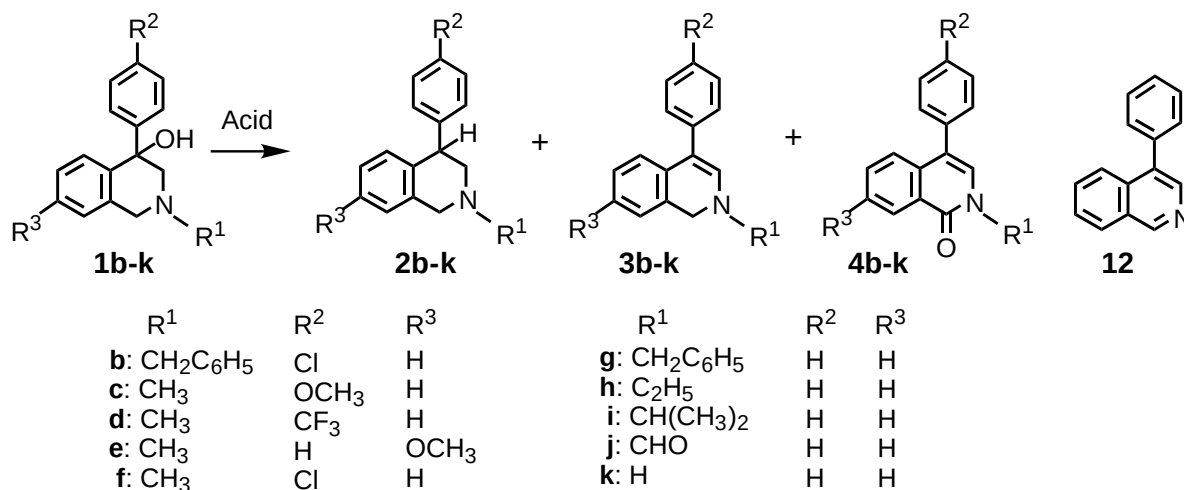
In our previous paper,⁴ we reported that the treatment of 3,4-diphenyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**5**) with boiling HBr-AcOH gave a reduced product (**6a**) even in low yield (14%) with 3,4-diphenyl-1,2-dihydroisoquinoline (**7a**) (35%) as a tamoxifen analogue. In order to examine the appropriate

Scheme 2

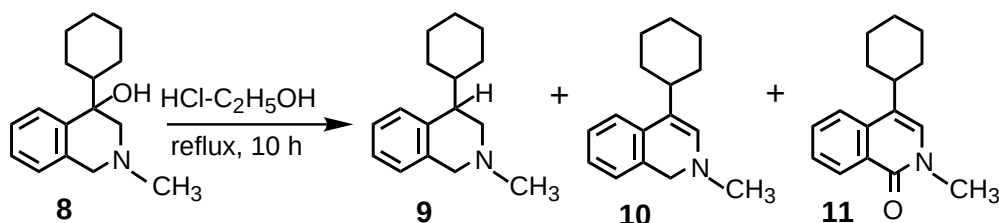


acid such as 10N HCl-C₂H₅OH, 2% CF₃SO₃H-C₆H₆, 85% H₂SO₄ and reaction conditions (reaction temperature and time) for the new reduction, the prototype compound (**1a**) was selected as a substrate for the reaction. The treatment of **1a** with 10N HCl-C₂H₅OH under reflux for 10 h gave the best result and the reduction product (**2a**), the dehydrated compound (**3a**), and the oxygenated compound (**4a**) of **3a** were obtained in 48%, 7%, and 17% yields, respectively (Table 1). The treatment of some derivatives (**1b-e**)⁵ (Scheme 3) of **1a** in the similar reaction conditions gave the reduced compounds (**2b-e**) in 37-48% yields (Table 1). It is interesting to note that treatment of the 4-cyclohexyl derivative (**8**) replaced the phenyl group of **1a** under the similar conditions gave a reduced compound (**9**) (40 %) with an olefin (**10**) and an amide (**11**) (Scheme 4). These facts show that the hydroxy groups of 4-alkylated 4-hydroxy-1,2,3,4-tetrahydroisoquinolines could be reduced by this method.

Scheme 3



Scheme 4



During the synthetic study on anti-breast cancer agents, we also observed⁷ the reduction reaction of the 4-hydroxyisoquinoline (**5**) with boron trifluoride etherate to an isoquinoline (**6b**) with a dehydrated product (**7b**), indicating the possibility of reduction reaction with Lewis acid. Thus, we examined the appropriate boron trihalide and the reaction conditions for the reduction using **1a** as a substrate (Table 2). As a best result, the reduced compound (**2a**) was obtained in 57% yield by using BBr₃ under reflux in CH₃CN with **3a** and **4a** (Entry 8), whereas the reaction at room temperature gave a poor yield of **2a** (Entry 7). The use of other Lewis acids such as AlCl₃, FeCl₃, TiCl₄, SnCl₄, ZnI₂, and CuCl₂ for the reduction gave no good results.

In the similar conditions to that of **1a** as above, a variety of 4-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinolines (**1b, d-k**)⁵ were treated with BBr₃ in CH₃CN (Table 3). The reaction of *N*-alkylated derivatives (**1b,d,f-i**) afforded the reduced products (**2b,d,f-i**) in moderate yields, respectively. The methoxyisoquinoline (**1e**) gave the low yield of 7-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**13**), which was accompanied by the cleavage⁸ of the methoxy group of **2e**. On the other hand, the reaction of *N*-formyl compound (**1j**) did not give a reduced compound (**2j**) but afforded the dehydrated compound (**3j**) in good yield with 4-phenylisoquinoline (**12**), suggesting the importance of the basicity of the nitrogen atom for the reduction reaction. The reaction of the secondary amine (**1k**) gave 4-phenylisoquinoline (**12**) in 53 % yield with the reduced compound (**2k**).

Table 1. Reaction of 4-Hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinolines (**1a-e**) with 10N HCl-EtOH under Reflux.

Starting material 1	Reaction time (h)	Product (%) ^{a)}		
		2	3	4
a (HCl salt)	10	48	7	17
b (HCl salt)	10	48	4	7
c	7	45	---	12
d	10	37	3	8
e	8	46	---	10

a) Isolated yield.

Table 2. Reaction of **1a** with Lewis Acids.

Entry	Reaction condition				Product(%) ^{a)}		
	Lewis acid	Solvent	Temp.	Time (h)	2a	3a	4a
1	BF ₃ •Et ₂ O	CH ₂ Cl ₂	rt	72	13	----	6
2	BF ₃ •Et ₂ O	CH ₂ Cl ₂	reflux	7	15	3	6
3	BF ₃ •Et ₂ O	CH ₃ CN	reflux	7	16	32	13
4	BCl ₃	CH ₂ Cl ₂	reflux	3	21	----	13
5	BCl ₃	CH ₃ CN	reflux	7	29	11	12
6	BBr ₃	CH ₂ Cl ₂	reflux	7	46	4	9
7	BBr ₃	CH ₃ CN	rt	7	10	4	13
8	BBr ₃	CH ₃ CN	reflux	7	57	19	16
9	BBr ₃	toluene	reflux	7	49	2	15
10	BBr ₃	CH ₃ CN-xylene(1:1)	reflux	7	54	8	12

a) Isolated yield.

Table 3. Reaction of 4-Hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinolines (**1b**, **d-k**) with BBr₃ in CH₃CN under Reflux.

Starting material 1	Reaction time	Product (%) ^{a)}			
		2	3	4	12
	10	35	6	7	---
	7	28	4	12	---
	10	25 ^{b)}	---	---	---
	10	45	4	10	---
	10	48	3	11	---
	10	54	6	6	---
	10	50	---	3	---
	7	---	77	---	15
	10	20	---	---	53

a) Isolated yield. b) Yield of 7-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**13**).

The new reduction reaction of the benzylic hydroxy groups of 4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**1**) to the corresponding alkanes (**2**) was found to proceed by use of both of mineral and Lewis acids described above. On the basis of these results and the following facts, the reaction of **1** to **2** was suggested to proceed through the olefins (**3**) as an intermediates. In general, benzyl alcohols are easily dehydrated with acid to the corresponding olefins.⁴ In fact, TLC behavior of the reaction mixture of **1a** with 10N HCl-C₂H₅OH at room temperature for 30 min showed a presence of the olefin (**3a**) as a sole product. This mixture was successively refluxed for 3 h to give **2a** in 33% yield, indicating the intermediate from **1a** to **2a** to be **3a**. On the other hand, the amide (**4a**) was thought to be formed by the oxidation of 2-methyl-4-phenylisoquinolinium chloride derived from the intermediate (**3a**) since *N*-substituted isoquinolinium salt are known⁹ to be oxidized to the corresponding amides.

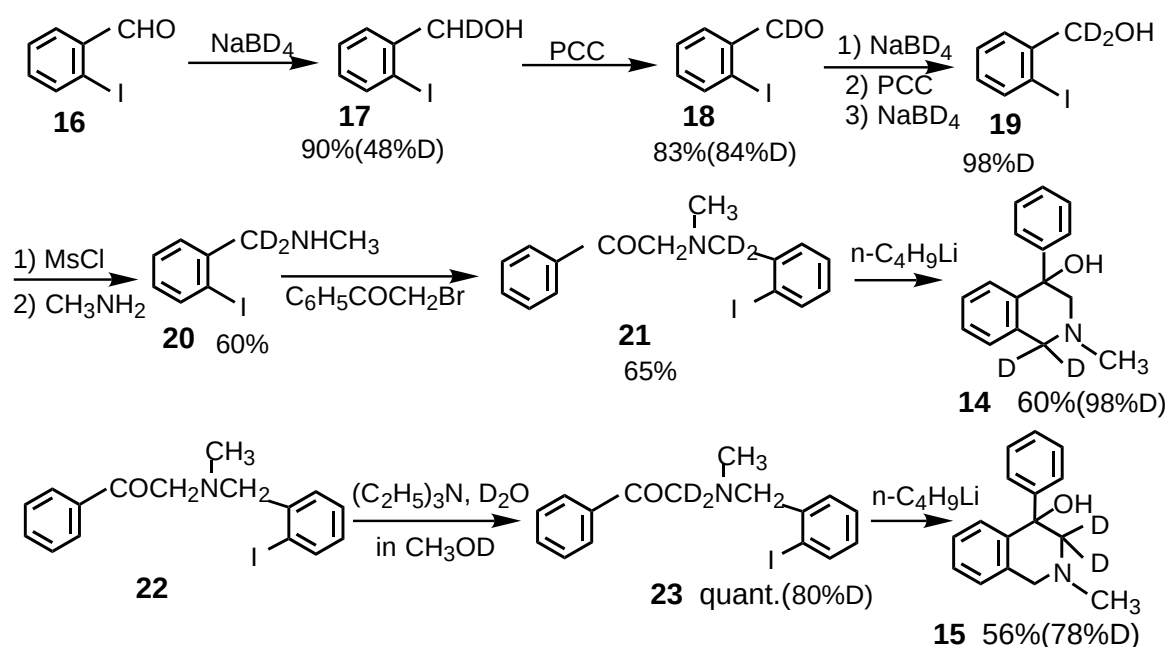
Furthermore, the reaction of **1k** with BBr₃ in CH₃CN (Table 3) also suggests the olefin (**3k**) to be intermediate from **1k** to **2k** as follows. The secondary amine (**1k**) gave 4-phenylisoquinoline (**12**) in 53% yield without an amide (**4k**). The compound (**12**) should be formed by oxidation of the 1,2-dihydroisoquinoline (**3k**) since *N*-unsubstituted 1,2,3,4-tetrahydroisoquinolines are known¹⁰ to be oxidized easily to 3,4-dihydroisoquinolines. The reaction of **1k** also afforded the reduced product (**2k**) (20%). On the other hand, the reaction of *N*-formyl compound (**1j**) with BBr₃ gave a good yield of the dehydrated product (**3j**), which may be unable to give reduced compound (**2j**) because of the high stability of **3j** due to its amide structure.

Since the reduction process from the intermediates (**3**) to **2** described above can be regarded as a formal hydrogen addition to the double bond at C-3 and C-4, it is important to clarify the hydrogen source for this reaction. We expected that the hydrogens at C-1 or C-3 of the substrate (**1**) may be a possible hydrogen source. In order to confirm this possibility, we undertook the synthesis of 1- and 3-deuterated compounds (**14** and **15**) to examine the reaction with 10N HCl-C₂H₅OH and BBr₃ in CH₃CN.

Compound (**14**) was prepared from the deuterated 2-iodobenzyl alcohol (**19**) as a key intermediate shown in Scheme 5. PCC oxidation of **17** (48% D) obtained by reduction of 2-iodobenzaldehyde (**16**) with NaBD₄ gave a deuterated benzaldehyde (**18**) (84% D). This high deuterated ratio should be due to the

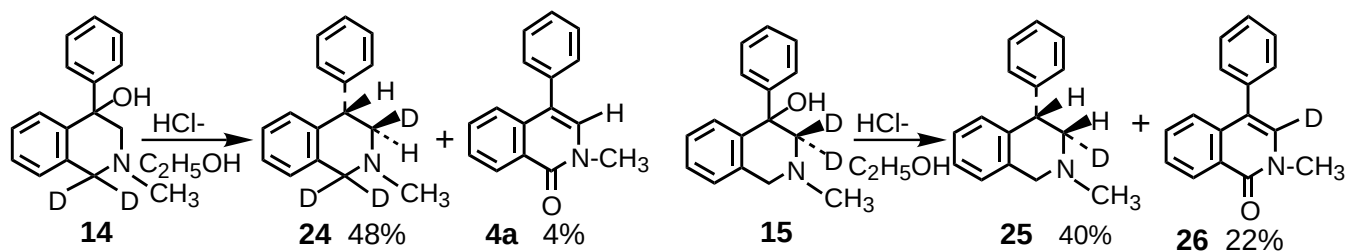
isotope effect¹¹ of the deuterium of **17** for the oxidation with PCC. The successive NaBD₄ reduction, PCC oxidation, and NaBD₄ reduction of **18** resulted in 98% D of 2-iodobenzyl alcohol (**19**). Mesylation of **19**, followed by amination of the product with methylamine gave a benzylamine (**20**). Intramolecular Barbier reaction^{5b} of the phenacylamine (**21**) obtained from **20** gave the deuterated compound (**14**). The structure of **14** was determined by its MS spectrum and the similarity of ¹H-NMR spectrum of **14** to that of **1a** except for the absence of the methylene protons at C-1. The 3-deuterated compound (**15**) (78% D) was prepared by intramolecular Barbier reaction of phenacylamine (**23**) (80% D), which was obtained by treatment of phenacylamine (**22**)^{5b} with Et₃N and D₂O in CH₃OD.¹² The deuterated ratio and the structure of **15** were determined by its ¹H-NMR and MS spectra.

Scheme 5



The reaction of compound (**15**) thus obtained with boiling 10N HCl-C₂H₅OH gave the reduced product (**25**) in 40% yield with oxygenated⁹ compound (**26**) having a deuterium (80% D) (Scheme 6). The molecular ion peak [*m/z* 224.1432(M⁺); C₁₆H₁₆DN] of **25** showed that the reduced compound had one deuterium. The deuterium was found to be located at C-3α by comparison of the ¹H-NMR spectrum with that of non-deuterated compound (**2a**) (Table 4). These facts indicate that the reaction did not proceed by direct reduction of the hydroxy group but proceeded through a dehydrated compound as an intermediate in a stereoselective manner. On the other hand, the reaction of 1,1-dideuterated compound (**14**) with boiling 10N HCl-C₂H₅OH gave reduced product (**24**) bearing three deuteriums [FAB-MS *m/z* 227.1631(M+1); C₁₆H₁₅D₃N] with non-deuterated amide (**4a**) in 48% and 4% yields, respectively. The ¹H-NMR spectral data (Table 4) of **24** reveal that the deuteriums are at C-1 and C-3β. The deuterated ratio at C-3β was found to be 81%, while the presence of deuterium was not observed at C-3α. Furthermore, the deuteriums (90% D) at C-1 of **24** were retained on the reaction of **14** (98% D). These findings indicate that the deuterium at C-3β of reduced compound (**24**) is not generated from C-1 of the same molecule but

Scheme 6



Scheme 7

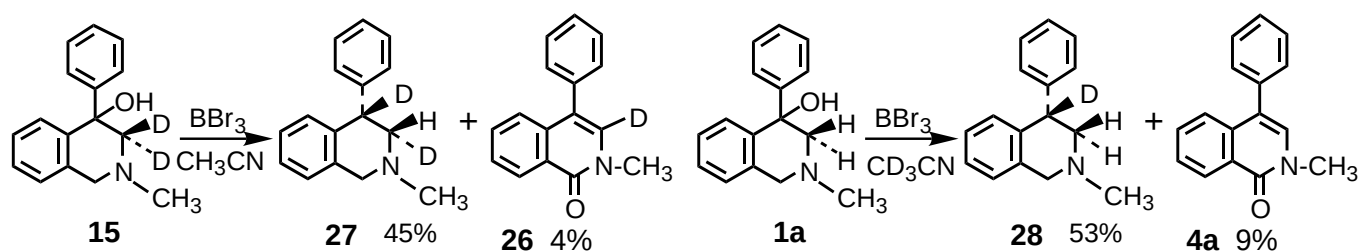


Table 4. ^1H -NMR Spectral Data of **2a**, **24**, **25**, **27**, and **28**.

	C_1		C_3		C_4
	H_β	H_α	H_β	H_α	
2a	3.77 (d, J=14.7 Hz)	3.61 (d, J=14.7 Hz)	3.04 (ddd, J=11.5, 5.6, 1.2 Hz)	2.56 (dd, J=11.5, 8.5 Hz)	4.29 (dd, J=8.5, 5.6 Hz)
24	-----	-----	-----	2.54 (d, J=8.5 Hz)	4.27 (d, J=8.5 Hz)
25	3.76 (d, J=14.9 Hz)	3.62 (d, J=14.9 Hz)	3.00 (d, J=5.6 Hz)	-----	4.27 (d, J=5.6 Hz)
27	3.75 (d, J=14.9 Hz)	3.62 (d, J=14.9 Hz)	3.00(s)	-----	-----
28	3.76 (d, J=14.9 Hz)	3.61 (d, J=14.9 Hz)	3.02 (d, J=12.0 Hz)	2.56 (d, J=12.0 Hz)	-----

from that of another molecule. Namely, this reduction includes a stereoselective and intermolecular shift of a deuterium from C-1 of one molecule to C-3 of another molecule.

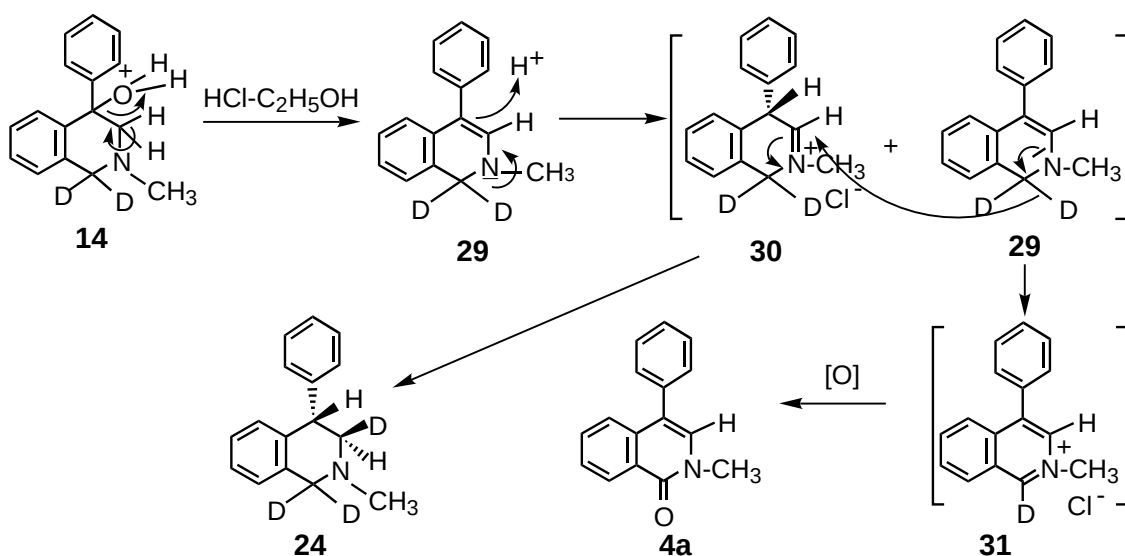
Next, we carried out the reaction of 3,3-dideuterated compound (**15**) with boiling BBr_3 in CH_3CN . The reduced compound (**27**) was obtained in 45 % yield with the amide (**26**) (Scheme 7). The ^1H -NMR spectrum (Table 4) of **27** showed the presence of deuteriums at C4 (26% D) and C3 α (82% D), indicating the deuterium source at C4 to be from C3. The deuterated ratio (26%) at C4 of **27** suggests that the hydrogen source at C4 may be one from CH_3CN as a solvent. In order to confirm this suggestion, compound (**1a**) was treated with BBr_3 in deuterated acetonitrile (CD_3CN). The reduced product (**28**) was found to possess a deuterium (76% D) at C4 (Table 4) according to our expectation, whereas the reaction of **1a** with BBr_3 in deuterated benzene (C_6D_6) gave no deuterated product. From these findings, the reduction reaction of 4-hydroxy-tetrahydroisoquinolines (**1**) with BBr_3 in CH_3CN should proceed in stereoselective

manner as well as with 10N HCl-C₂H₅OH and the hydrogen sources at C4 are those from C3 of **1** and solvent (CH₃CN).

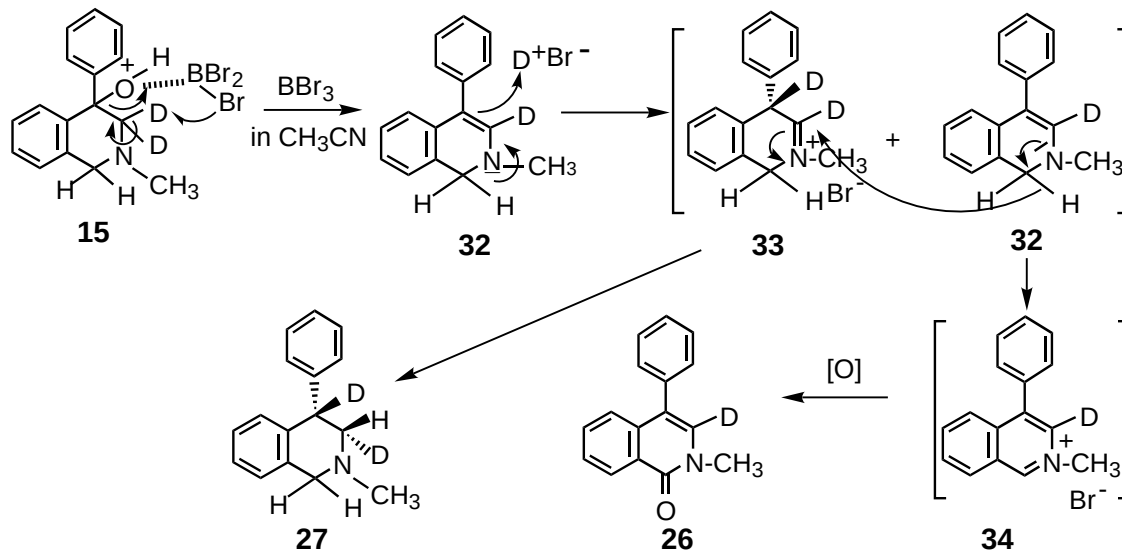
On the basis of these results, in the reaction of 1,1-deuterated compound (**14**) with 10N HCl-C₂H₅OH, the reduction was concluded to proceed by a novel intermolecular deuteride(D⁻) shift mechanism as shown in Scheme 8. The benzylic alcohol (**14**) is dehydrated to give the olefin (**29**), to which adds acid(HCl) to form a quaternary iminium salt (**30**). The deuteride leaved from C-1 of another molecule of **29** attacks to C-3 of **30** from the opposite side of the 4-phenyl group because of a steric hindrance and thus produces the reduced compound (**24**) having *cis* configuration between H-4 and D-3. On the other hand, the isoquinolinium salt (**31**) formed by leaving the deuteride from C-1 of **29** is oxidized⁹ to the amide (**4a**). The reason for this stereoselective reaction is not clear but may be explained in term of intermolecular stacking¹³ between **29** and **30** in the deuteride shift process. Knabe¹⁴ and Dyke *et al.*¹⁵ reported the rearrangement of 1-benzyl-1,2-dihydroisoquinolines with mineral acid into 3-benzyl-3,4-dihydroisoquinolines. Their proposed bimolecular exchange mechanism¹⁵ for the rearrangement also supports the intermolecular hydride shift mechanism of the reaction of **14** to **24** found in this study. In the reaction of 3,3-dideuterated compound (**15**) with 10N HCl-C₂H₅OH, the *cis* configuration between H-3 and H-4 of the product (**25**) and the yield of the amide (**26**) having a deuterium at C3 support the mechanism similar to that shown in Scheme 8.

In the case of reaction of 3,3-dideuterated compound (**15**) with BBr₃ in CH₃CN, the stereoselective and intermolecular hydride shift mechanism as shown in Scheme 9 is also supported by the formation of the reduced compound (**27**) having deuteriums at C3 α and C4 and the amide (**26**). The deuterium bromide (DBr) formed by the reaction of **15** with BBr₃ should be deuterium source at C4 in the dehydrated

Scheme 8



Scheme 9



compound (32), giving 4-deuterated compound (27). In the same way, the reaction of compounds (1) and the related compound (8) with 10N HCl-EtOH and BBr₃ in CH₃CN should also proceed by the intermolecular hydride shift mechanism depicted in Schemes 8 and 9.

In conclusion, we have found a new reduction reaction of benzylic hydroxy groups of 4-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinolines without using a reducing agent under acidic conditions. The reduction mechanism presented in this study is a novel example of intermolecular hydride shift under acidic conditions, although the reaction proceeded by intermolecular hydride shift mechanism with strong base is well known as Cannizzaro reaction.¹⁶

EXPERIMENTAL

High-resolution mass spectra (HRMS) were recorded on JELO SX-102A and JEOL JMS-D 300 spectrometers. ¹H-NMR spectra were recorded on a JEOL JNM-FX 200 spectrometer in CDCl₃ with tetramethylsilane as a standard and are given in δ values.

General Procedure for the Reaction of 4-Hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolines (1) with 10N HCl-C₂H₅OH This is exemplified by the reaction of **1a** with 10N HCl-C₂H₅OH. The hydrochloride (73.5 mg, 0.267 mmol) of **1a** was refluxed with 10N HCl-C₂H₅OH (3.0 mL) for 10 h. The reaction mixture was evaporated *in vacuo*. Water (20 mL) was added to the residue. The mixture was basified with 28% NH₄OH and extracted with CH₂Cl₂ (50 mL x 5). The extract was washed with water, dried over MgSO₄, and evaporated *in vacuo* to give an oily product. This was subjected to preparative TLC on Al₂O₃ with hexane-CH₂Cl₂ (3 : 2). The fraction of *R_f* 0.22-0.41 gave **2a** as a yellow oil (28.0 mg, 48%). ¹H-NMR (CDCl₃) δ : 7.20 (1H, dd, *J*=8.0, 2.2 Hz), 7.03 (1H, dd, *J*=7.4, 2.4 Hz), 6.85 (1H, d, *J*=7.1 Hz), 4.29 (1H, dd, *J*=8.5, 5.6 Hz), 3.77 (1H, d, *J*=14.7 Hz), 3.61 (1H, d, *J*=14.7 Hz), 3.04 (1H, ddd, *J*=11.5, 5.6, 1.2 Hz), 2.56 (1H, dd, *J*=11.5, 8.5 Hz), 2.43 (3H, s).

HRMS (m/z) M^+ : Calcd for $C_{16}H_{17}N$: 223.1360. Found: 223.1341. The fraction of R_f 0.04-0.11 gave **4a** as a powder (10.3 mg, 17%) (mp 178-181.5°C). 1H -NMR ($CDCl_3$) δ : 8.53 (1H, dd, $J=7.3, 1.7$ Hz), 7.36-7.64 (8H, m), 7.04 (1H, s), 3.65 (3H, s). HRMS (m/z) M^+ : Calcd for $C_{16}H_{13}NO$: 235.0997. Found: 235.0998. *Anal.* Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.54; H, 5.57; N, 5.91. The fraction of R_f 0.69-0.78 gave **3a** as an oil (4.0 mg, 7%). 1H -NMR ($CDCl_3$) δ : 7.30-7.38 (5H m), 7.00-7.10 (4H, m), 6.22 (1H, s), 4.19 (2H, s), 2.82 (3H, s). HRMS (m/z) M^+ : Calcd for $C_{16}H_{15}N$: 221.1206. Found: 221.1200.

The reaction of other tetrahydroisoquinolines (**1b-e**) with 10N HCl- C_2H_5OH was carried out in the same way as **1a** (Table 1).

Reaction of 4-Cyclohexyl-4-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (8) with 10N HCl- C_2H_5OH Compound (**8**) (61.9 mg, 0.253 mmol) was refluxed with 10N HCl- C_2H_5OH (7.0 mL). The reaction mixture was treated in the same way as **1a** to give a pale brown oil. This crude product was subjected to preparative TLC on Al_2O_3 with hexane- CH_2Cl_2 (3 : 2). The fraction of R_f 0.21-0.40 gave **9** as an oil (23.0 mg, 40%). 1H -NMR ($CDCl_3$) δ : 7.07-7.25 (3H, m), 7.01 (1H, d, $J=6.4$ Hz), 3.57 (1H, d, $J=14.8$ Hz), 3.44 (1H, d, $J=14.8$ Hz), 2.80 (1H, m), 2.66 (2H, m), 2.41 (3H, s). HRMS (m/z) M^+ : Calcd for $C_{16}H_{23}N$: 229.1831. Found: 229.1834. The fraction of R_f 0.04-0.06 gave **11** as an oil (3.3 mg, 5 %). 1H -NMR ($CDCl_3$) δ : 8.50 (1H, d, $J=8.3$ Hz), 7.55-7.75 (2H, m), 7.38-7.52 (1H, m), 6.85 (1H, s), 3.61 (3H, s). HRMS (m/z) M^+ : Calcd for $C_{16}H_{19}NO$: 241.1467. Found: 241.1473. The fraction of R_f 0.78-0.86 gave **10** as an oil (2.8 mg, 5%). 1H -NMR ($CDCl_3$) δ : 7.00-7.20 (4H, m), 5.89 (1H, s), 3.96 (2H, s), 2.72 (3H, s).

General Procedure for the Reaction of 4-Hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolines (1) with BBr_3 in CH_3CN This is exemplified by the reaction of **1a** with BBr_3 in CH_3CN . BBr_3 (1.0 M sol. in CH_2Cl_2 , 0.025 mL, 1.47 mmol) was added to a solution of **1a** (76 mg, 0.32 mmol) in CH_2Cl_2 (2.5 mL) at 0°C under N_2 . The mixture was stirred for 20 min at rt and then refluxed for 7 h. Water (20 mL) was added and the mixture was basified with 28% NH_4OH , extracted with CH_2Cl_2 (50 mL x 3). The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to give an oil. The crude product was subjected to preparative TLC on Al_2O_3 with hexane- CH_2Cl_2 (3 : 2). The fractions of R_f 0.20-0.37, R_f 0.66-0.76, and R_f 0.04-0.10 gave **2a** (oil, 40.7 mg, 57%), **3a** (oil, 13.2 mg, 19 %), and **4a** (white powder, 11.8 mg, 16%), respectively. The structures of **2a**, **3a**, and **4a** obtained with BBr_3 were confirmed by comparisons of their 1H -NMR spectra with those of **2a**, **3a**, and **4a** obtained with 10N HCl- C_2H_5OH .

The reaction of **1a** with other Lewis acids was carried out in the same way as with BBr_3 (Table 2) and the reaction of other tetrahydroisoquinolines (**1b, d-i**) with BBr_3 was performed in the same way as **1a** (Table 3).

Reaction of 2-Formyl-4-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinolines (1j) with BBr_3 in CH_3CN BBr_3 (1.0 M sol. in CH_2Cl_2 , 0.033 mL, 1.96 mmol) was added to a solution of **1j** (80 mg, 0.316 mmol) in CH_2Cl_2 (2.75 mL) at 0°C under N_2 . The mixture was stirred for 20 min at rt and then refluxed for 7 h. The reaction mixture was treated in the same way as **1a** to give an oil. The crude product was subjected to preparative TLC on Al_2O_3 with hexane- CH_2Cl_2 (3 : 2). The fractions of R_f 0.22-

0.38 gave **3j** as an oil (58.0 mg, 77%). ¹H-NMR (CDCl₃) δ: 8.37 and 8.23 (1H, each s), 7.01-7.52 (9H m), 6.62 (1H, s), 4.49 and 4.78 (2H, each s). HRMS (m/z) M⁺: Calcd for C₁₆H₁₃NO: 235.0997. Found: 235.0999. The fraction of *R_f* 0.16-0.22 gave **12** as an oil (9.8 mg, 15%). ¹H-NMR (CDCl₃) δ: 9.26 (1H, s), 8.49 (1H, s), 7.89-8.06 (2H, m), 7.68-7.26 (7H m). HRMS (m/z) M⁺: Calcd for C₁₅H₁₁N: 205.0891. Found: 205.0892.

Reaction of 4-Hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (1k) with BBr₃ in CH₃CN BBr₃ (1.0 M sol. in CH₂Cl₂, 0.020 mL, 1.18 mmol) was added to a solution of the hydrochloride (77 mg, 0.30 mmol) of **1k** in CH₂Cl₂ (5 mL) at 0°C under N₂. The mixture was stirred for 2 min at rt and then refluxed for 10 h. The reaction mixture was treated in the same way as **1a** to give an oil. The crude product was subjected to preparative TLC on Al₂O₃ with hexane-CH₂Cl₂ (3 : 2). The fraction of *R_f* 0.03-0.08 gave **2k** as an oil (12.5 mg, 20%). ¹H-NMR (CDCl₃) δ: 7.07-7.41 (8H, m), 6.90 (1H, d, *J*=7.8 Hz), 3.92-4.20 (3H, m), 3.40 (1H, m), 3.09 (1H, m). HRMS (m/z) M⁺: Calcd for C₁₅H₁₅N: 209.1205. Found: 209.1195. The fraction of *R_f* 0.13-0.33 gave **12** as an oil (32 mg, 53%). The structure of this product was confirmed by comparison of its ¹H-NMR spectrum with that of **12** obtained from **1j**.

¹H-NMR and MS Spectral Data of Tetrahydroisoquinolines (2b-i), 1,2-Dihydroisoquinolines (3b,d, f-h), Amides (4b-i), and Phenolic Tetrahydroisoquinoline (13) **2b**: ¹H-NMR (CDCl₃) δ: 7.23 (2H, d, *J*=6.6 Hz), 7.11 (2H, d, *J*=6.6 Hz), 6.86 (1H, d, *J*=7.6 Hz), 4.17 (1H, m), 3.72 (2H, s), 3.65 (2H, s), 3.00 (1H, dd, *J*=11.5, 5.1 Hz), 2.66 (1H, dd, *J*=11.5, 6.8 Hz). HRMS (m/z) M⁺: Calcd for C₂₂H₂₀NCl: 333.1284. Found: 333.1274. **3b**: ¹H-NMR (CDCl₃) δ: 7.26-7.35 (14H, s), 6.38 (1H, s), 4.22 (4H, s). **4b**: ¹H-NMR (CDCl₃) δ: 8.56 (1H, dd, *J*=7.6, 2.0 Hz), 7.42 and 7.30 (each 2H, d, *J*=8.3 Hz), 7.04 (1H, s), 5.27 (2H, s). HRMS (m/z) M⁺: Calcd for C₂₂H₁₆NOCl: 345.0921. Found: 345.0915. **2c**: ¹H-NMR (CDCl₃) δ: 7.11 (2H, d, *J*=8.5 Hz), 6.83 (2H, d, *J*=8.5 Hz), 4.23 (1H, m), 3.72-3.78 (3H, m), 3.59 (1H, d, *J*=14.9 Hz), 3.01 (1H, dd, *J*=11.3, 5.5 Hz), 2.53 (1H, dd, *J*=11.3, 8.8 Hz), 2.42 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₇H₁₉NO: 253.1467. Found: 253.1464. **4c**: ¹H-NMR (CDCl₃) δ: 8.52 (1H, dd, *J*=7.3, 1.2 Hz), 7.33 (2H, d, *J*=8.7 Hz), 7.00 (2H, d, *J*=8.7 Hz), 3.88 (3H, s), 3.65 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₇H₁₅NO₂: 265.1102. Found: 265.1098. **2d**: ¹H-NMR (CDCl₃) δ: 7.54 (2H, d, *J*=8.1 Hz), 7.31 (2H, d, *J*=8.1 Hz), 7.09-7.17 (3H, m), 6.83 (1H, d, *J*=7.3 Hz), 4.32 (1H, m), 3.69 (2H, s), 2.99 (1H, dd, *J*=11.5, 5.4 Hz), 2.42 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₇H₁₆NF₃: 291.1235. Found: 291.1238. **3d**: ¹H-NMR (CDCl₃) δ: 6.29 (1H, s), 4.25 (2H, s), 2.87 (3H, s). **4d**: ¹H-NMR (CDCl₃) δ: 8.55 (1H, dd, *J*=7.6, 1.5 Hz), 7.74 (2H, d, *J*=8.1 Hz), 7.56 (2H, d, *J*=8.1 Hz), 7.07 (1H, s), 3.68 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₇H₁₂NOF₃: 303.0871. Found: 303.0888. **2e**: ¹H-NMR (CDCl₃) δ: 6.70 (1H, dd, *J*=6.6, 2.6 Hz), 6.61 (1H, d, *J*=2.6 Hz), 4.20 (1H, dd, *J*=6.2, 5.7 Hz), 3.76 (3H, s), 3.65 (2H, m), 3.00 (1H, ddd, *J*=11.4, 5.7, 0.9 Hz), 2.58 (1H, dd, *J*=11.4, 6.2 Hz), 2.41 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₇H₁₉NO: 253.1468. Found: 253.1467. **4e**: ¹H-NMR (CDCl₃) δ: 7.93 (1H, d, *J*=3.0 Hz), 6.94 (1H, s), 3.94 (3H, s), 3.77 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₇H₁₅NO₂: 265.1103. Found: 265.1099. **2f**: ¹H-NMR (CDCl₃) δ: 7.24 (2H, d, *J*=8.5 Hz), 7.12 (2H, d, *J*=8.5 Hz), 6.83 (1H, d, *J*=7.1 Hz), 4.23 (1H, m), 3.70 (1H, d, *J*=15.1 Hz), 3.62 (1H, d, *J*=15.1 Hz), 2.97 (1H, dd, *J*=11.5, 5.6 Hz), 2.55 (1H, dd, *J*=11.5, 5.8 Hz), 2.41 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₇H₁₆NCl: 257.0971. Found: 257.0989. **3f**: ¹H-NMR (CDCl₃) δ: 6.21 (1H, s),

4.21 (2H, s), 2.84 (3H, s). **4f**: $^1\text{H-NMR}$ (CDCl_3) δ : 8.53 (1H, m), 7.50 (2H, d, $J=8.3$ Hz), 7.34 (2H, d, $J=8.3$ Hz), 7.03 (1H, s), 3.66 (3H, s). HRMS (m/z) M^+ : Calcd for $\text{C}_{16}\text{H}_{12}\text{NOCl}$: 269.0608. Found: 269.0608. **2g**: $^1\text{H-NMR}$ (CDCl_3) δ : 7.04 (1H, dd, $J=7.9, 2.9$ Hz), 6.88 (1H, d, $J=7.6$ Hz), 4.25 (1H, dd, $J=7.8, 5.4$ Hz), 3.74 (2H, s), 3.07 (1H, dd, $J=11.5, 5.4$ Hz), 2.67 (1H, dd, $J=11.5, 7.8$ Hz). HRMS (m/z) M^+ : Calcd for $\text{C}_{22}\text{H}_{21}\text{N}$: 299.1675. Found: 299.1672. **3g**: $^1\text{H-NMR}$ (CDCl_3) δ : 7.14-7.29 (11H, m), 6.87-7.00 (3H, m), 6.32 (1H, s), 4.12 (4H, s). HRMS (m/z) M^+ : Calcd for $\text{C}_{22}\text{H}_{19}\text{N}$: 297.1519. Found: 297.1497. **4g**: $^1\text{H-NMR}$ (CDCl_3) δ : 8.56 (1H, d, $J=7.8$ Hz), 7.07 (1H, s), 5.27 (2H, s). HRMS (m/z) M^+ : Calcd for $\text{C}_{22}\text{H}_{17}\text{NO}$: 311.1310. Found: 311.1314. **2h**: $^1\text{H-NMR}$ (CDCl_3) δ : 7.00-7.34 (8H, m), 6.84 (1H, d, $J=8.1$ Hz), 4.27 (1H, dd, $J=8.6, 5.8$ Hz), 3.88 (1H, d, $J=14.8$ Hz), 3.61 (1H, d, $J=14.8$ Hz), 3.14 (1H, ddd, $J=11.5, 5.8, 1.5$ Hz), 2.50-2.63 (3H, m), 1.16 (3H, t, $J=7.2$ Hz). HRMS (m/z) M^+ : Calcd for $\text{C}_{17}\text{H}_{19}\text{N}$: 237.1517. Found: 237.1513. **3h**: $^1\text{H-NMR}$ (CDCl_3) δ : 6.32 (1H, s), 4.26 (2H, s), 3.15 (2H, m), 1.42 (3H, t, $J=7.2$ Hz). **4h**: $^1\text{H-NMR}$ (CDCl_3) δ : 8.54 (1H, d, $J=7.6$ Hz), 7.40-7.60 (8H, m), 7.05 (1H, s), 4.12 (2H, q, $J=7.3$ Hz), 1.42 (3H, t, $J=7.3$ Hz). HRMS (m/z) M^+ : Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}$: 249.1153. Found: 249.1163. **2i**: $^1\text{H-NMR}$ (CDCl_3) δ : 7.19-7.34 (5H, m), 7.02-7.13 (3H, m), 6.84 (1H, d, $J=7.3$ Hz), 4.23 (1H, m), 3.84 (2H, s), 3.12 (1H, dd, $J=11.5, 5.6$ Hz), 2.90 (1H, m), 2.62 (1H, dd, $J=11.5, 9.0$ Hz), 1.09 (6H, m). HRMS (m/z) M^+ : Calcd for $\text{C}_{18}\text{H}_{21}\text{N}$: 251.1674. Found: 251.1664. **4i**: 8.55 (1H, d, $J=6.8$ Hz), 7.09 (1H, s), 5.47 (1H, m), 1.42 (6H, d, $J=6.8$ Hz). HRMS (m/z) M^+ : Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}$: 263.1310. Found: 262.1316. **13**: $^1\text{H-NMR}$ (CDCl_3) δ : 7.14-7.29 (5H, m), 6.67 (1H, d, $J=8.5$ Hz), 6.55 (1H, dd, $J=8.5, 2.4$ Hz), 6.12 (1H, d, $J=2.4$ Hz), 4.25 (1H, m), 3.49 (1H, d, $J=14.9$ Hz), 3.33 (1H, d, $J=14.9$ Hz), 3.11 (1H, dd, $J=11.8, 6.0$ Hz), 2.46 (1H, m), 2.42 (3H, s). HRMS (m/z) M^+ : Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}$: 239.1311. Found: 239.1321.

α -Deutero-2-iodobenzyl Alcohol (17) A solution of NaBD_4 (98% atom D, 0.568 g, 14.0 mmol) in CH_3OD (10 mL) was added to a solution of 2-iodobenzaldehyde (**16**) (2.50 g, 10.8 mmol) in CH_3OD (15 mL) and the mixture was stirred for 30 min at 0°C under N_2 . The reaction mixture was evaporated *in vacuo*. Water (50 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 , and evaporated to give **17** as a colorless powder (2.289 g, 90%). $^1\text{H-NMR}$ (CDCl_3) δ : 7.82 (1H, d, $J=7.8$ Hz), 7.20-7.50 (2H, m), 7.03 (1H, ddd, $J=7.8, 7.6, 1.7$ Hz), 4.63 (0.96H, s), 2.17 (1H, s). This product was used for PPC oxidation without further purification.

α -Deutero-2-iodobenzaldehyde (18) PCC (3.15 g, 14.6 mmol) was added to a solution of **17** (2.289 g, 9.74 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred for 30 min at rt. The reaction mixture was subjected to flash chromatography on Florisil (5.0 g) with ether. The eluent was evaporated *in vacuo*. The residue was purified by flash chromatography on SiO_2 with hexane-benzene (1:5) to give **18** as an oil (1.88 g, 83%). $^1\text{H-NMR}$ (CDCl_3) δ : 10.03 (0.16H, s), 7.15-7.95 (4H, m). FAB-HRMS (m/z) $\text{M}+1$: Calcd for $\text{C}_7\text{H}_5\text{DIO}$: 233.9526. Found: 233.9525.

α,α -Dideutero-2-iodobenzyl Alcohol (19) Compound (**18**) (1.88 g, 8.10 mmol) was treated with NaBD_4 (440 mg, 10.7 mmol) in CH_3OD (15 mL) in the same way as **17** to give α,α -dideutero-2-iodobenzyl alcohol (1.91 g, 99% yield, 91% D). This product (1.89 g, 8.00 mmol) was oxidized with PCC (3.00 g, 14 mmol) in the same way as **18** to give α -deutero-2-iodobenzaldehyde (1.67 g, 90%). Usual treatment of this product (1.67 g, 7.16 mmol) with NaBD_4 (390 mg, 9.31 mmol) in CH_3OD (15 mL) gave

19 as colorless needles (1.60 g, 95%). ¹H-NMR (CDCl₃) δ: 7.80 (1H, d, J=8.1 Hz), 7.20-7.50 (2H, m), 6.98 (1H, ddd, J=8.1, 7.8, 1.7 Hz), 2.49 (1H, br s). HRMS (m/z) M⁺: Calcd for C₇H₅D₂OI: 235.9667. Found: 235.9672.

α,α-Dideutero-2-iodo-N-methylbenzylamine (20) CH₃SO₂Cl (1.70 mL, 22.0 mmol) and triethylamine (3.07 mL, 22.0 mmol) were added to a solution of **19** (2.60 g, 11.0 mmol) in CH₂Cl₂ (30 mL) at 0°C under N₂. The mixture was stirred for 30 min at 0°C and 5% HCl (15 mL) was added. The mixture was extracted with CH₂Cl₂ (50 mL x 5). The extract was washed with water, dried over MgSO₄, and evaporated *in vacuo* to give the mesylate of **19** as an oil (3.44 g, 99%). ¹H-NMR (CDCl₃) δ: 7.89 (1H, d, J=7.8 Hz), 7.36-7.50 (2H, m), 7.09 (1H, d, J=7.4 Hz), 3.03 (3H, m). FAB-HRMS (m/z) M+NaI: Calcd for C₈H₇D₂O₃INaS: 336.9340. Found: 336.9367.

A solution of methylamine in CH₃OH (40%, 23.68 mL, 240 mmol) was added to a solution of the mesylate (3.40 g, 10.8 mmol) of **19** obtained above in dry ether (22 mL) at 0°C under N₂. The mixture was stirred for 45 min at 0°C and evaporated *in vacuo*. 5% HCl (12 mL) and water (20 mL) were added and the residue was washed with ether (80 mL x 3). The aqueous layer was basified with 28% NH₄OH and extracted with CH₂Cl₂ (100 mL x 3). The extract was washed with water, dried over MgSO₄, and evaporated *in vacuo* to give an oil. This crude product was converted to the hydrochloride of **20** as colorless needles (1.85 g, 69%). FAB-HRMS (m/z) M-Cl: Calcd for C₈H₉D₂NI: 250.0062. Found: 250.0055. ¹H-NMR (free base, CDCl₃) δ: 7.82 (1H, d J=7.8 Hz), 7.35 (2H, m), 6.95 (1H, m), 2.81 (1H, br s), 2.45 (3H, s).

α,α-Dideutero-N-benzoylmethyl-N-methylbenzylamine (21) A solution of phenacyl bromide (2.05 g, 10.5 mmol) and propylene oxide (7.78 mL, 134.0 mmol) in dioxane (10 mL) was added to a solution of **20** (free base, 2.57 g, 10.3 mmol) in dioxane (20 mL). The mixture was stirred for 12 h at rt and filtered. The filtrate was evaporated *in vacuo*. The residue was subjected to flash chromatography on SiO₂ with hexane-benzene-ethyl acetate (25:10:1) to give **21** as an oil (2.47 g, 65%). ¹H-NMR (CDCl₃) δ: 7.96 (2H, dd, J=7.1, 1.5 Hz), 7.84 (1H, d, J=7.8 Hz), 7.26-7.56 (5H, m), 6.96 (1H, ddd, J=7.8, 7.7, 1.7 Hz), 3.90 (2H, s), 2.43 (3H, s). FAB-HRMS (m/z) M+1: Calcd for C₁₆H₁₅D₂NOI: 368.0481. Found: 368.0464.

1,1-Dideutero-4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (14)

n-C₄H₉Li (1.6 M sol. in hexane, 7.7 mL, 12.3 mmol) was added to a solution of **21** (2.26 g, 6.15 mmol) in dry THF (25 mL) at -78°C under N₂ and the mixture was stirred for 30 min at -78°C. Water (20 mL) was added and the mixture was extracted with ether (100 mL x 3). The extract was washed with water, dried over MgSO₄, and evaporated *in vacuo* to give an oil. This was subjected to flash chromatography on SiO₂ with hexane-ethyl acetate (3:2) to give **14** as colorless prisms (830 mg, 60%). ¹H-NMR (CDCl₃) δ: 6.94-7.46 (9H, m), 4.49 (1H, br s), 2.94 (1H, d, J=11.7 Hz), 2.63 (1H, d, J=11.7 Hz), 2.38 (1H, d, J=11.7 Hz). FAB-HRMS (m/z) M+1: Calcd for C₁₆H₁₆D₂NO: 242.1514. Found: 242.1528.

α,α-Dideutero-N-(2-iodobenzyl)-N-methylphenacylamine (23) Triethylamine (230 μL, 1.65 mmol) and D₂O (45 μL, 2.49 mmol) were added to a solution of compound (**22**)⁵ (298 mg, 0.82 mmol) in CH₃OD (5 mL) at 0°C under N₂. The mixture was stirred for 2 h at 50°C and evaporated *in vacuo* to give **23** as an oil (299 mg, 99%). ¹H-NMR (CDCl₃) δ: 7.96 (2H, dd, J=7.9, 1.7 Hz), 7.84 (1H, d, J=8.1 Hz), 7.26-7.58 (5H, m), 6.96 (1H, ddd, J=8.1, 7.6, 1.7 Hz), 3.75 (2H, s), 2.42 (3H, s). HRMS (m/z) M⁺:

Calcd for C₁₆H₁₄D₂NOI: 367.0403. Found: 367.0410. This product was used for the cyclization with *n*-C₄H₉Li without further purification.

3,3-Dideutero-4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (15)

Reaction of **23** (295 mg, 0.81 mmol) in dry THF (5 mL) with *n*-C₄H₉Li (1.6 M sol. in hexane, 760 mL, 1.22 mmol) at -78°C was carried out in the same way as **21** to give crude product. This was subjected to flash chromatography on SiO₂ with CHCl₃-acetone (6:1) to give **15** as colorless prisms (109 mg, 56%). ¹H-NMR (CDCl₃) δ: 7.07-7.47 (8H, m), 6.94 (1H, d, J=7.5 Hz), 3.80 (1H, d, J=14.9 Hz), 3.44 (1H, d, J=14.9 Hz), 2.45 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₆H₁₅D₂NO: 241.1436. Found: 241.1433.

Reaction of 14 with 10N HCl-C₂H₅OH Compound (**14**) (76.1 mg, 0.318 mmol) was refluxed with 10N HCl-C₂H₅OH (5.0 mL). The reaction mixture was evaporated *in vacuo*. Water (20 mL) was added to the residue. The mixture was basified with 28% NH₄OH and extracted with CH₂Cl₂ (60 mL x 3). The extract was washed with water, dried over MgSO₄, and evaporated *in vacuo* to give an oily product. This was subjected to preparative TLC on Al₂O₃ with hexane-CH₂Cl₂ (3 : 2). The fraction of *R_f* 0.23-0.42 gave **24** as a yellow oil (32.9 mg, 48%). ¹H-NMR (CDCl₃) δ: 7.02-7.29 (8H, m), 6.86 (1H, d, J=7.3 Hz), 4.27 (1H, d, J=8.5 Hz), 2.54 (1H, d, J=8.5 Hz), 2.43 (3H, s). FAB-HRMS (m/z) M+1: Calcd for C₁₆H₁₅D₃N: 227.1628. Found: 227.1631. The fraction of *R_f* 0.05-0.10 gave **4a** as a powder (2.3 mg, 4%). The structure of this product was confirmed by comparison of its ¹H-NMR spectrum with that of **4a** obtained from **1a**.

Reaction of 15 with 10N HCl-C₂H₅OH Compound (**15**) (76.7 mg, 0.317 mmol) was refluxed with 10N HCl-C₂H₅ (7.0 mL). The reaction mixture was treated in the same way as **14** to give crude product. This was subjected to preparative TLC on Al₂O₃ with hexane-CH₂Cl₂ (3 : 2). The fraction of *R_f* 0.20-0.40 gave **25** as an oil (28.6 mg, 40%). ¹H-NMR (CDCl₃) δ: 6.78 (1H, d, J=7.3 Hz), 4.27 (1H, d, J=5.6 Hz), 3.76 (1H, d, J=14.9 Hz), 3.62 (1H, d, J=14.9 Hz), 3.00 (1H, d, J=5.6 Hz), 2.43 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₆H₁₆DN: 224.1423. Found: 224.1432. The fraction of *R_f* 0.05-0.10 gave **26** as a powder (16.2 mg, 22%). ¹H-NMR (CDCl₃) δ: 8.53 (1H, d, J=7.8 Hz), 7.41-7.62 (8H, m), 3.49 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₆H₁₂DNO: 236.1060. Found: 236.1053.

Reaction of 15 with BBr₃ in CH₃CN BBr₃ (1.0 M sol. in CH₂Cl₂, 250 μL, 1.46 mmol) was added to a solution of **15** (76.1 mg, 0.32 mmol) in CH₃CN (2.5 mL) at 0°C under N₂. The mixture was stirred for 20 min at rt and then refluxed for 17 h. Water (20 mL) was added and the mixture was basified with 28% NH₄OH, extracted with CH₂Cl₂ (50 mL x 3). The extract was washed with water, dried over MgSO₄, and evaporated *in vacuo* to give an oil. This crude product was subjected to preparative TLC on Al₂O₃ with hexane-CH₂Cl₂ (3 : 2). The fraction of *R_f* 0.20-0.40 gave **27** as an oil (32 mg, 45%). ¹H-NMR (CDCl₃) δ: 6.78 (1H, d, J=7.3 Hz), 4.26 (0.74H, d, J=5.4 Hz), 3.75 (1H, d, J=14.9 Hz), 3.62 (1H, d, J=14.9 Hz), 3.00 (1H, d, J=5.4 Hz), 2.42 (3H, s). HRMS (m/z) M⁺: Calcd for C₁₆H₁₅D₂NO: 241.1436. Found: 241.1430. The fraction of *R_f* 0.05-0.10 gave **26** as a powder (2.5 mg, 4%). The structure of this product was confirmed by comparison of its ¹H-NMR spectrum with that of **26** obtained from **15** with 10N HCl-C₂H₅OH.

Reaction of 1a with BBr₃ in CD₃CN BBr₃ (1.0 M sol. in CH₂Cl₂, 249 μL, 1.46 mmol) was added to a solution of **1a** (76 mg, 0.32 mmol) in CD₃CN (3 mL) and the mixture was refluxed for 7 h.

The reaction mixture was treated in the same way as **15** in CH₃CN to give crude product. This was subjected to preparative TLC on Al₂O₃ with hexane-CH₂Cl₂ (3 : 2). The fraction of *R_f* 0.21-0.43 gave **28** as an oil (37.3 mg, 53%). ¹H-NMR (CDCl₃) δ: 7.09-7.30 (8H, m), 6.86 (1H, d, *J*=7.1 Hz), 4.27 (0.24H, m), 3.76 (1H, d, *J*=14.9 Hz), 3.61 (1H, d, *J*=14.9 Hz), 3.02 (1H, d, *J*=12 Hz), 2.56 (1H, m), 2.43 (3H, s). HRMS (*m/z*) *M*⁺: Calcd for C₁₆H₁₆DN: 224.1423. Found: 224.1415. The fraction of *R_f* 0.05-0.10 gave **4a** as a powder (6.4 mg, 9%). The structure of this product was confirmed by comparison of its ¹H-NMR spectrum with that of **4a** obtained from **1a**.

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