Novel synthesis of enantiomerically enriched 5-hydroxycyclohex-2-enone by enantioselective deprotonation strategy: application to the synthesis of inositol phosphatase inhibitor

Toshio Honda * and Katsunori Endo

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

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A novel synthetic path to enantiomerically enriched 5-hydroxycyclohex-2-enone, a versatile chiral building block, is developed by a two-step sequence, where an enantioselective deprotonation of a 3,5-dihydroxycyclohexanone derivative with lithium (*S,S′*)-α,α′-dimethyldibenzylamide in the presence of TMSCl, and subsequent treatment of the silyl enol ether with TBAF in THF at room temperature are employed as the key reactions.

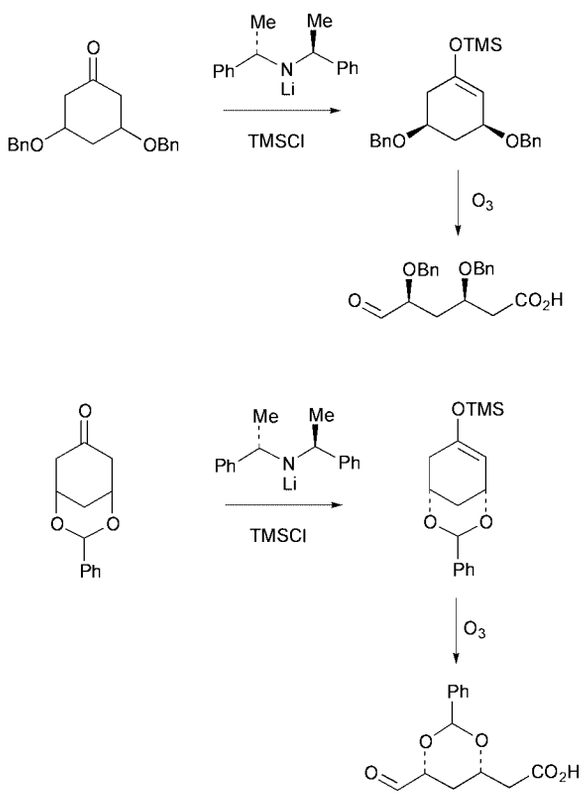
Syntheses of chiral cyclohex-2-enone derivatives have been of continuing interest in organic chemistry, since these compounds have often been employed as convenient building blocks for the preparation of a variety of biologically important compounds including natural products.[1] Consequently, a number of synthetic methods for chiral cyclohex-2-enones have been developed during the last few years by elaboration of a chiral starting substrate such as sugars,[2] pinene,[3] quinic acid,[4] and quebrachitol,[5] by chemoenzymatic process,[6] and by enantioselective syntheses.[7] Among the various types of cyclohex-2-enone derivatives, 5-alkoxy- or 5-hydroxycyclohex-2-enones seem to be the most attractive and versatile chiral building blocks, because of their wide applicability as chiral synthons to a variety of structurally and biologically interesting compounds in optically active forms. Hence, the synthesis of 5-(benzyloxy)-cyclohex-2-enone was achieved by using asymmetric hydrolysis of *meso*-1,3-diacetoxy-5-benzyloxycyclohexane with porcine liver esterase, as a key reaction.[8] Moreover, an efficient and practical method for both enantiomers of 5-(*tert*-butyldimethylsiloxy)cyclohex-2-enone was recently developed by Sato and co-workers starting from optically active ethyl 3-(*tert*-butyldimethylsiloxy)hex-5-enoate,[9] and they also utilized such chiral building blocks successfully in the syntheses of naturally occurring compounds.[10]

As part of our continuing effort in the synthesis of biologically active compounds by application of an enantioselective deprotonation strategy,[11] we are also interested in the preparation of chiral cyclohex-2-enone derivatives.

Our own interest grew out of a desire to find a new route to optically active 5-hydroxycyclohex-2-enone itself, since its chiral synthesis has not been reported to date, to the best of our knowledge.

We recently established the synthesis of a 1,3-*syn*-dihydroxy system by using an enantioselective deprotonation, as a key reaction,[12] where a *meso*-3,5-dialkoxycyclohexanone was employed as a starting material (Scheme 1). In these reactions, it was shown that the enantioselective deprotonation of the bicyclo compound afforded the silyl enol ether with a higher enantiomeric excess (>99% and 95%, at a reaction temperature of −100 °C and −78 °C, respectively) than that for 3,5-di-(benzyloxy)cyclohexanone (74% and 70% ee, at a reaction temperature of −100 °C and −78 °C, respectively), due to the rigidity of its conformation.

We, therefore, thought that careful desilylation of the chiral silyl enol ether of the bicyclo compound **1** prior to ozonolysis



Scheme 1

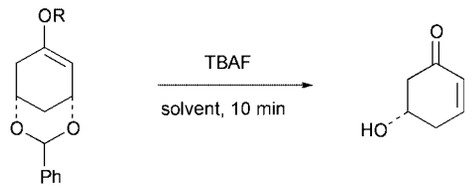
in these reaction sequences would give the desired cyclohex-2-enone **2** with reasonable enantiomeric excess by elimination of the 3-alkoxy group, as shown in Scheme 2.

Based on this consideration, we searched for the optimal conditions for the elimination reaction using the silyl enol ether **1** (95% ee), prepared from 3,5-(benzylidenedioxy)-cyclohexanone with lithium (*S,S′*)-α,α′-dimethyldibenzylamide at −78 °C, as the starting material.[11b,c]

Results and discussion

We first screened the effectiveness of the fluoride ion species for this reaction. When the silyl enol ether **1** was treated with 0.1

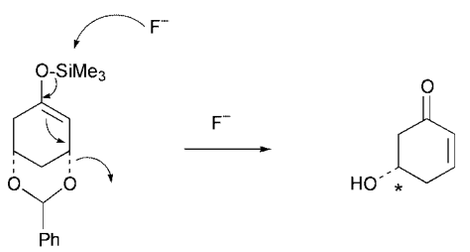
Table 1 Conversion of silyl enol ether **1** to enone **2** with TBAF



1 (95% ee) **2**

Entry	R	Equiv.	Solv.	Temp. (T/°C)	Yield (%)[c]	Ee(%)[d]
1	TMS	1.0[a]	THF	rt	77	89.0
2	TMS	0.1[a]	THF	rt	71	82.8
3	TES	1.2[a]	THF	rt	63	86.2
4	TMS	1.0[a]	THF	−78	57	78.5
5	TMS	1.2[a]	CH_3CN	rt	64	83.1
6	TMS	1.2[a]	Toluene	rt	67	89.1
7	TMS	0.1[b]	THF	−78	33	69.1
8	TMS	0.1[b]	THF	rt	25	77.2

[a] 1.0 M THF solution was used. [b] Dry TBAF was prepared and used according to the literature.[10a] [c] Isolated yield. [d] The ees were determined by HPLC analysis with the chiral column Chiralcel AD.



1 **2**

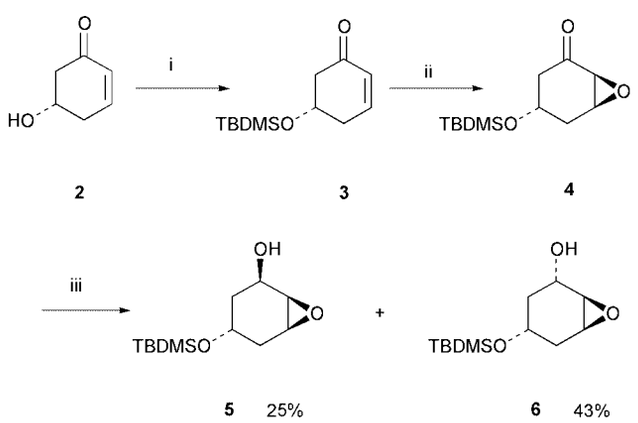
Scheme 2

equiv. of hydrogen fluoride–pyridine complex in THF at 0 °C for 10 min, only the starting prochiral 3,5-(benzylidenedioxy)cyclohexanone was isolated quantitatively. Other fluoride species, such as CsF and KF, gave unsatisfactory results in terms of yields and enantioselectivity. Among the various fluoride species investigated, TBAF seemed to be the most effective reagent for this eliminative enone formation. The results using TBAF as the desilylating agent are summarized in Table 1. As can been seen in Table 1, the amount of TBAF does not seem to affect the results (entries 1 and 2). Obviously, the trimethylsilyl group is superior to the triethylsilyl (TES) group in this reaction (entry 3). When the reaction was carried out at −78 °C, both the yield and ee were decreased (entry 4). Regarding the solvent, the reaction in THF gave the desired compound in better yield than those in acetonitrile or toluene; however, a similar degree of enantioselectivity was obtained in these solvent systems (entries 5 and 6). Since Sato and coworkers reported a similar elimination reaction by using dry TBAF in THF in the presence of 4 Å molecular sieves at −30 °C, we also attempted the reaction by adopting their reaction conditions.[10a] Treatment of the silyl enol ether **1** with 0.1 equiv. of dry TBAF in THF at −78 °C for 10 min, however, gave enone **2** in 33.1% yield with 69.1% ee (entry 7). When this reaction was carried out at room temperature for 10 min, the yield was much decreased with slightly better ee (entry 8). In the above enone formation, partial racemization was observed, unexpectedly. This fact can be rationalized by assuming that partial desilylation of silyl enol ether to ketone might occur prior to elimination of the alkoxy group during this conversion.

Although the mechanistic details for this elimination are still obscure at present, the absolute stereochemistry of the synthesized 5-hydroxycyclohex-2-enone was unambiguously determined by its conversion to the corresponding *tert*-butyldimethylsilyl ether, whose sign of optical rotation was equal to the sign of the reported literature value.[10]

Since we had succeeded in developing a simple preparation of a versatile chiral building block, 5-hydroxycyclohex-2-enone, our attention was focused on its utilization in the synthesis of a biologically active compound, an inositol phosphatase inhibitor.[13]

Silylation of 5-hydroxycyclohex-2-enone **2** with *tert*-butyldimethylsilyl chloride in DMF in the presence of imidazole gave silyl ether **3**, which on treatment with alkaline hydrogen peroxide provided epoxide **4**, stereoselectively (Scheme 3).

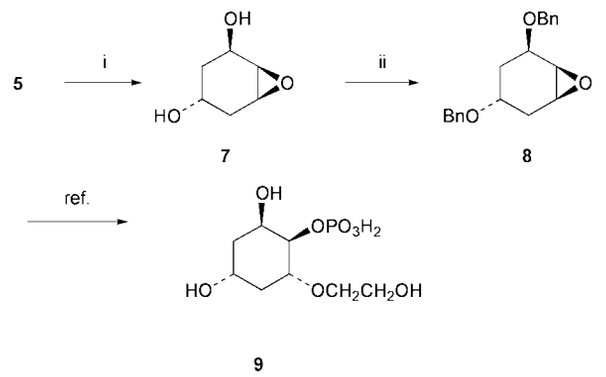


Scheme 3 *Reagents and conditions*: i, TBDMSCl, imidazole, DMF, rt (86%): ii, 30% H_2O_2, 1 M NaOH, MeOH rt (56%); iii; $NaBH_4$, MeOH, 0 °C (**5** : 25%; **6** : 43%).

Reduction of epoxy ketone **4** with $NaBH_4$ in MeOH gave a diastereoisomeric mixture of alcohols **5** and **6**, in a ratio of *ca.* 1 : 2, respectively. Although the stereoselective reductions of α,β-epoxy ketone to the corresponding *syn*-alcohol were attempted according to the literature methods,[14] no satisfactory results were obtained, probably due to the instability of the product under the reaction conditions employed.

The stereochemistries of the reduction products could not be determined at this stage; however, the minor product seemed to have the desired configuration based upon examination of molecular models in this reduction. Therefore, the minor product **5** was employed for further transformation into the key intermediate for the synthesis of an inositol phosphatase inhibitor **9**.[13b]

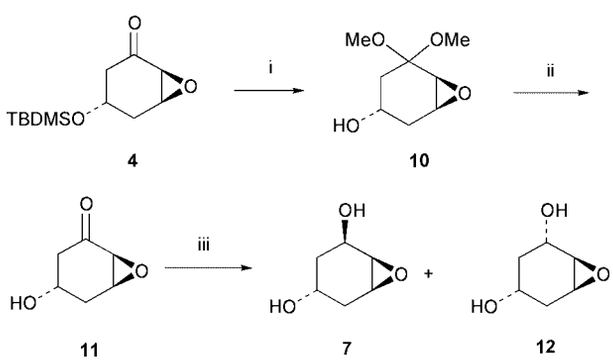
Desilylation of **5** with TBAF in THF in the usual manner gave diol **7**, which on dibenzylation with benzyl bromide and sodium hydride in THF in the presence of a phase-transfer catalyst provided the desired di(benzyl ether) **8**. The spectroscopic data including the specific optical rotation of the synthetic compound were in good accordance with those reported.[13] Thus, the stereochemistry of the newly generated hydroxy group in **5** was unambiguously determined as depicted in Scheme 4.



Scheme 4 *Reagents and conditions*: i, TBAF, THF, rt (98%); ii, BnBr, NaH, TBAI, THF, rt (69%).

In this synthesis, however, low stereoselectivity in the reduction of **4** was observed; we therefore investigated an alternative synthetic path to **7**, where removal of the silyl group of **4** was carried out prior to the reduction of the carbonyl group.

Although difficulties were initially encountered even in the simple conversion of **4** to **11**, *e.g.*, attempted desilylation by treatment with hydrochloric acid in MeOH or THF, and TBAF in THF, treatment of **4** with iodine in MeOH,[15] followed by acid hydrolysis of the resulting ketal **10**, afforded the desired hydroxy ketone **11** (Scheme 5). Again, the overall yield of



Scheme 5 *Reagents and conditions*: i, I_2, MeOH, rt (48%); ii, 1% HCl, rt (71%); iii; $NaBH_4$, MeOH, 0 °C (**7** : 54%; **12** : 18%).

this conversion was not high enough; however, reduction of hydroxy ketone **11** with $NaBH_4$ in MeOH provided the desired diol **7** as a major product together with **12** in a ratio of *ca.* 3 : 1, respectively.

Thus, we have disclosed a novel synthetic procedure for enantiomerically enriched 5-hydroxycyclohex-2-enone, a useful chiral building block, and its utilization in the synthesis of a biologically active compound.

Experimental

General experimental procedures

IR spectra were recorded for samples as thin films. ^{1}H NMR and ^{13}C NMR spectra were obtained for a solution in $CDCl_3$, and chemical shifts are reported on the δ-scale from TMS as internal standard. The signals for carbonyl carbons were sometimes missing in ^{13}C NMR spectra of the synthesized compounds. Optical rotations were measured on a JASCO DIP-360 polarimeter.

(5*S*)-5-Hydroxycyclohex-2-enone 2

To a stirred solution of silyl enol ether **1** (263 mg, 0.91 mmol, 95% ee) in THF (3 mL) was added TBAF (3 mL, 0.91 mmol) at ambient temperature, and the resulting solution was stirred for a further 10 min. After quenching of the reaction by adding saturated aq. ammonium chloride, the organic solvent was removed by evaporation, and the residue was extracted with ethyl acetate. The extract was dried (Na_2SO_4), and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (1 : 1, v/v) as eluent to afford enone **2** (78 mg, 77%) as a colorless oil. Its enantiomeric excess was determined to be 89% by HPLC analysis with the chiral column CHIRALCEL AD; IR 3400, 1678 cm^{-1}; ^{1}H NMR δ 2.38–2.61 (2H, m), 2.66–2.81 (2H, m), 4.33 (1H, ddd, J = 4.4, 8.8, and 13.2 Hz), 6.10 (1H, dt, J = 2.0 and 10.1 Hz), 6.91 (1H, ddd, J = 3.6, 4.4, and 10.1 Hz); ^{13}C NMR δ 34.2, 46.7, 66.2, 129.5, 147.7, 199.0; HRMS (EI) [Calc. for $C_6H_8O_2$: (*M*) 112.0524. Found: M$^+$, 112.0517] (Calc. for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.48; H, 7.26%). Since this compound seemed to be relatively unstable, a subsequent conversion to the silyl ether was attempted as follows.

(5*S*)-5-(*tert*-Butyldimethylsiloxy)cyclohex-2-enone 3

A solution of hydroxy enone **2** (29.2 mg, 0.23 mmol) and TBDMSCl (58.9 mg, 0.39 mmol) in DMF (1 mL) in the presence of imidazole (35.5 mg, 0.52 mmol) was stirred at room temperature for 1 h. The mixture was treated with saturated aq. ammonium chloride, and extracted with ethyl acetate. The extract was dried (Na_2SO_4), and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (3 : 2, v/v) as eluent to afford silyl ether **3** (50.7 mg, 86%) as a colorless oil, $[\alpha]_D$ +8.8 (*c* 1.1, $CHCl_3$) {lit.,[10c] $[\alpha]_D$ +9.82 (*c* 1.0, $CHCl_3$)}; IR 1684 cm^{-1}; ^{1}H NMR δ 0.07 (6H, s), 0.88 (9H, s), 2.31–2.71 (4H, m), 4.18–4.28 (1H, m), 6.06 (1H, dt, J = 1.8, and 10.1 Hz), 6.88 (1H, ddd, J = 3.3, 5.1, and 10.1 Hz); ^{13}C NMR δ −4.9, −4.8, 18.0, 25.7, 35.6, 48.0, 67.6, 130.1, 146.9, 198.7; HRMS (EI) [Calc. for $C_{12}H_{23}O_2Si$: (*M* + 1) 227.1467. Found: *m*/*z*, 227.1478]. These spectroscopic data were identical with those reported.[10c]

(2*S*,3*S*,5*S*)-5-(*tert*-Butyldimethylsiloxy)-2,3-epoxycyclohexanone 4

To a stirred solution of enone **3** (265 mg, 1.17 mmol) in MeOH (9 mL) was added dropwise a mixed solution of 30% H_2O_2 (0.37 mL, 3.28 mmol) and 1 M NaOH (0.37 mL, 0.37 mmol) at room temperature, and the resulting solution was stirred for a further 10 min. 5% aq. KI was added to the solution and the mixture was concentrated by evaporation of the organic solvent to give a residue, which was extracted with ethyl acetate. The extract was dried (Na_2SO_4), and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (3 : 2, v/v) as eluent to afford epoxide **4** (160 mg, 56%) as a colorless oil, $[\alpha]_D$ −12.9 (*c* 1.5, $CHCl_3$); IR 1726 cm^{-1}; ^{1}H NMR δ 0.05 (6H, s), 0.86 (9H, s), 2.01 (1H, dddd, J = 1.5, 3.5, 6.3, and 15.3 Hz), 2.19 (1H, ddd, J = 1.8, 6.3, and 15.3 Hz), 2.39 (1H, ddd, J = 1.5, 4.3, and 15.3 Hz), 2.78 (1H, dd, J = 3.1 and 15.3 Hz), 3.27 (1H, d, J = 3.8 Hz), 3.53–3.58 (1H, m), 4.23–4.31 (1H, m); ^{13}C NMR δ −4.94, −4.88, 17.9, 25.6, 29.7, 33.0, 45.0, 54.7, 55.5, 67.3; HRMS (EI) [Calc. for $C_{12}H_{22}O_3Si$: (*M*) 242.1338. Found: M$^+$, 242.1357].

(1*R*,2*R*,3*S*,5*R*)-5-(*tert*-Butyldimethylsiloxy)-2,3-epoxycyclohexanol 5 and (1*S*,2*R*,3*S*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2,3-epoxycyclohexanol 6

To a stirred solution of ketone **4** (100 mg, 0.42 mmol) in MeOH (3 mL) was added portionwise $NaBH_4$ (19 mg, 0.50 mmol) at 0 °C, and the resulting mixture was stirred for a further 10 min at the same temperature. After treatment with brine, the mixture was extracted with ethyl acetate, and the extract was dried (Na_2SO_4), and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (5 : 1, v/v) as eluent to afford alcohol **5** (26 mg, 25%) as a colorless oil, $[\alpha]_D$ +41.3 (*c* 0.5, $CHCl_3$); IR 3460 cm^{-1}; ^1H NMR δ 0.04 (6H, s), 0.68 (9H, s), 1.48 (1H, ddd, *J* = 1.5, 10.6, and 12.1 Hz), 1.74–1.85 (2H, m), 2.00 (2H, dd, *J* = 5.8 and 10.6 Hz), 3.37 (2H, m), 3.98 (1H, m), 4.32 (1H, br t, *J* = 5.8 Hz); ^{13}C NMR δ −5.1, −5.0, 17.9, 25.6, 32.6, 36.2, 54.0, 55.3, 65.0, 65.3; HRMS (EI) [Calc. for $C_8H_{15}O_3Si$: (*M* − Bu) 187.0790. Found: *m*/*z*, 187.0787]. Further elution with the same solvent system gave a diastereoisomeric alcohol **6** (43.0 mg, 43%) as a colorless oil, $[\alpha]_D$ −17.3 (*c* 0.4, $CHCl_3$); IR 3500 cm^{-1}; ^1H NMR δ 0.10 (6H, s), 0.91 (9H, s), 1.68 (2H, ddd, *J* = 1.8, 4.0, and 14.5 Hz), 1.76–1.87 (1H, m), 2.03–2.09 (1H, m), 3.18–3.24 (1H, m), 3.29–3.34 (1H, m), 4.00–4.06 (1H, m), 4.15–4.24 (1H, m); ^{13}C NMR δ −5.2, −5.0, 17.8, 25.7, 32.0, 32.9, 49.6, 54.4, 65.2, 65.3; HRMS (EI) [Calc. for $C_8H_{15}O_3Si$: (*M* − Bu) 187.0790. Found: *m*/*z*, 187.0778].

(1*R*,3*R*,4*R*,5*S*)-4,5-Epoxycyclohexane-1,3-diol 7

To a stirred solution of silyl ether **5** (44 mg, 0.18 mmol) in THF (1 mL) was added TBAF (0.54 mL, 0.54 mmol) at ambient temperature and the resulting mixture was stirred for a further 1 h at the same temperature. The mixture was treated with saturated aq. NH_4Cl and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (1 : 3, v/v) as eluent to give diol **7** (23 mg, 98%) as a colorless oil, $[\alpha]_D$ +20.8 (*c* 0.4, $CHCl_3$); IR 3345 cm^{-1}; ^1H NMR δ 1.52–1.88 (4H, m), 2.04 (1H, d, *J* = 2.8 Hz), 2.19 (1H, dd, *J* = 4.8 and 15.8 Hz), 3.41 (2H, br s), 4.07 (1H, m), 4.36 (1H, br t, *J* = 6.3 Hz); ^{13}C NMR δ 32.1, 36.3, 54.2, 55.0, 64.5, 64.7; HRMS (EI) [Calc. for $C_6H_{11}O_3$: (M + 1) 131.0708. Found: *m*/*z*, 131.0685].

(1*R*,2*R*,3*S*,5*R*)-1,5-Dibenzyloxy-2,3-epoxycyclohexane 8

To a stirred suspension of diol **7** (4.5 mg, 0.035 mmol), sodium hydride (60% in mineral oil; 2.9 mg, 0.073 mmol), and tetrabutylammonium iodide (TBAI) (2.6 mg, 6.9 μmol) in THF (0.5 mL) was added benzyl bromide (12.3 μL, 0.10 mmol) at 0 °C, and the resulting mixture was stirred for a further 24 h at room temperature. The mixture was treated with saturated aq. NH_4Cl and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (10 : 1, v/v) as eluent to give di(benzyl ether) **8** (7.4 mg, 69%) as a colorless oil, $[\alpha]_D$ +65.6 (*c* 0.2, MeOH) {lit.,[13b] $[\alpha]_D$ +72.6 (*c* 0.208, MeOH)}; ^1H NMR δ 1.60–1.71 (1H, m), 2.04–2.18 (3H, m), 3.26–3.32 (1H, m), 3.40–3.44 (1H, m), 3.68–3.75 (1H, m), 4.13–4.20 (1H, m), 4.41 (2H, s), 4.67 (1H, d, *J* = 12.4 Hz), 4.72 (1H, d, *J* = 12.4 Hz), 7.22–7.53 (10H, m); HRMS (EI) (Calc. for $C_{20}H_{22}O_3$: *M*, 310.1569. Found: M^+, 310.1561). These spectroscopic data were identical with those reported.[13b]

(1*S*,3*S*,4*S*)-4,5-Epoxy-3,3-dimethoxycyclohexanol 10

A solution of ketone **4** (43.2 mg, 0.18 mmol) in 1 wt % I_2–MeOH was stirred at room temperature for 24 h. The mixture was treated with 5% aq. $Na_2S_2O_3$, and then concentrated *in vacuo*. The residual aqueous layer was extracted with ethyl acetate, and the extract was dried (Na_2SO_4) and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (1 : 1, v/v) as eluent to give ketal **10** (15 mg, 48%) as a colorless oil, $[\alpha]_D$ +20.8 (*c* 0.4, $CHCl_3$); IR 3400 cm^{-1}; ^1H NMR δ 1.72 (1H, dd, *J* = 7.9 and 13.3 Hz), 1.85–1.95 (2H, m), 2.31 (1H, dd, *J* = 4.9 and 15.0 Hz), 2.64 (1H, br d, *J* = 5.9 Hz), 3.24 (1H, d, *J* = 4.9 Hz), 3.35–3.38 (1H, m), 3.35 (3H, s), 3.38 (3H, s), 3.90 (1H, br s); ^{13}C NMR δ 33.4, 36.7, 48.4, 49.0, 53.1, 53.5, 63.7, 98.8. The ketal **10** was used in the next step without further purification.

(2*S*,3*S*,5*S*)-2,3-Epoxy-5-hydroxycyclohexanone 11

A solution of ketal **10** (82 mg, 0.47 mmol) in 1% hydrochloric acid (10 mL) and MeOH (2 mL) was stirred at room temperature for 3 h. After treatment with saturated aq. $NaHCO_3$, the mixture was extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (1 : 1, v/v) as eluent to give ketone **11** (43 mg, 71%) as a colorless oil, $[\alpha]_D$ −31.3 (*c* 0.3, $CHCl_3$); IR 3420, 1718 cm^{-1}; ^1H NMR δ 1.90 (1H, br s), 2.02–2.13 (1H, m), 2.24 (1H, dd, *J* = 6.2 and 15.2 Hz), 2.51 (1H, dd, *J* = 3.4 and 15.2 Hz), 2.92 (1H, d, *J* = 3.4 and 15.2 Hz), 3.30 (1H, d, *J* = 3.4 Hz), 3.60 (1H, br s), 4.36 (1H, br s); ^{13}C NMR δ 31.8, 35.5, 54.8, 55.7, 66.8, 205.3; HRMS (EI) (Calc. for $C_6H_8O_3$: *M*, 128.0473. Found: M^+, 128.0491).

(1*R*,3*R*,4*R*,5*S*)-4,5-Epoxycyclohexane-1,3-diol 7 and (1*R*,3*S*,-4*R*,5*S*)-4,5-epoxycyclohexane-1,3-diol 12

To a stirred solution of ketone **11** (14.8 mg, 0.116 mmol) in MeOH (1 mL) was added portionwise $NaBH_4$ (5.2 mg, 0.139 mmol) at 0 °C, and the resulting mixture was stirred for a further 10 min at the same temperature. After addition of acetone (1 mL), the mixture was concentrated, and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (1 : 3, v/v) as eluent to give diol **12** (2.7 mg, 18%) as the first eluant as a colorless oil, IR 3345 cm^{-1}; ^1H NMR δ 1.70–1.92 (2H, m), 2.02–2.23 (2H, m), 2.54 (1H, br s), 4.04 (1H, br s), 4.25 (1H, br s); ^{13}C NMR δ 32.0, 33.0, 49.9, 54.4, 64.0, 65.3; HRMS (EI) [Calc. for $C_6H_{11}O_3$: (*M* + 1) 131.0708. Found: *m*/*z*, 131.0685]. Further elution with the same solvent system gave **7** (8.1 mg, 54%), which was identical with the sample obtained above.

Acknowledgements

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