Asymmetric Synthesis Using Chiral Acetals: Highly Diastereoselective Addition of Organocerium Reagents to Chiral α-Aldoxime–Ether Acetal

Hiromichi FUJIOKA,* Masahiro FUJI, Yoshihiko OKAICHI, Takayuki YOSHIDA, Hirokazu ANNOURA, Yasuyuki KITA, and Yasumitsu TAMURA*

Faculty of Pharmaceutical Sciences, Osaka University, 1–6, Yamada-oka, Suita, Osaka 565, Japan. *Received August 1, 1988*

Nucleophilic addition of organometallic reagents [organocerium reagents ($RMgX–CeCl_3$, $RLi–CeCl_3$), Grignard reagent, and organolithium reagents] to the chiral α-aldoxime–ether acetal (1) was studied. Among the reagents, organocerium reagents showed higher reactivity and stereoselectivity, giving the *N*-oxygenated chiral amine derivatives (6Aa—c) in a highly diastereoselective manner, whereas Grignard and organolithium reagents afforded no 6. As an application of the reaction, the synthesis of (−)-*N*-acetylamphetamine (11) was achieved.

Keywords asymmetric synthesis; diastereoselective nucleophilic addition; chiral aldoxime–ether acetal; (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol; organocerium reagent; *N*-oxygenated chiral amine; (−)-*N*-acetylamphetamine

Chiral amine moieties are found in many natural products and methods for constructing them in a stereoselective manner are highly desirable. One of the most direct methods for getting chiral amines is the nucleophilic addition of organometallic reagents to the chiral imine function and its derivatives (oximes, hydrazones), and much effort has been devoted to this.[1] As a part of our studies to develop a new asymmetric C–C bond-forming reactions by using the chiral acetals derived from C_2-symmetric diols, we have recently reported that nucleophilic addition of Grignard reagents to the chiral α-keto acetals derived from (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol proceeds in a highly diastereoselective manner to give chiral alcohol moieties.[2] As an extension of the chiral acetal method, we now present a highly stereoselective nucleophilic addition of organocerium reagents ($RMgX–CeCl_3$, $RLi–CeCl_3$) to the chiral aldoxime–ether acetal (**1**), leading to the *N*-oxygenated chiral amines (**6**), and its application to the synthesis of (−)-*N*-acetylamphetamine (**11**).[3]

Results and Discussion

Synthesis of the Chiral Aldoxime–Ether Acetal (1) The aldoxime–ether acetal (**1**) was readily prepared as depicted in Chart 2. Acetophenone (**2**) was transformed into the chiral α-acetoxy acetal (**3**) in 60% yield in a three-step sequence: i) formation of α-hydroxydimethylacetal by Moriarty's procedure,[4] ii) acetylation of the primary alcohol, and iii) transacetalization with (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol[5] in the presence of a catalytic amount of camphorsulphonic acid (CSA) under reduced pressure (1 mmHg) without any solvent. Without prior acetylation of the primary alcohol, the subsequent transacetalization resulted in a poor yield. All procedures were carried out without any purification. Alkaline hydrolysis of **3** afforded the chiral α-hydroxyacetal (**4**) in 98% yield. Oxidation of **4** was achieved by Swern's procedure[6] to give the aldehyde acetal (**5**), which was coupled with *O*-benzylhydroxylamine to give the α-aldoxime–ether acetal (**1**) in 75% yield from **4**. Since the compound **1** was obtained as a single product, the stereochemistry of the C–N double

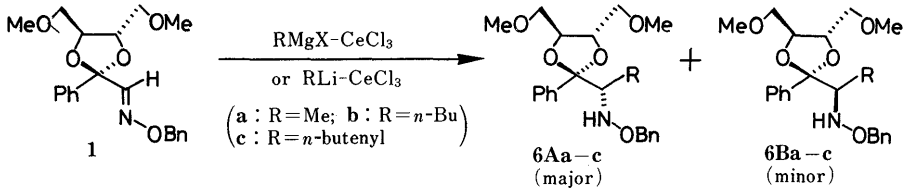


Chart 1

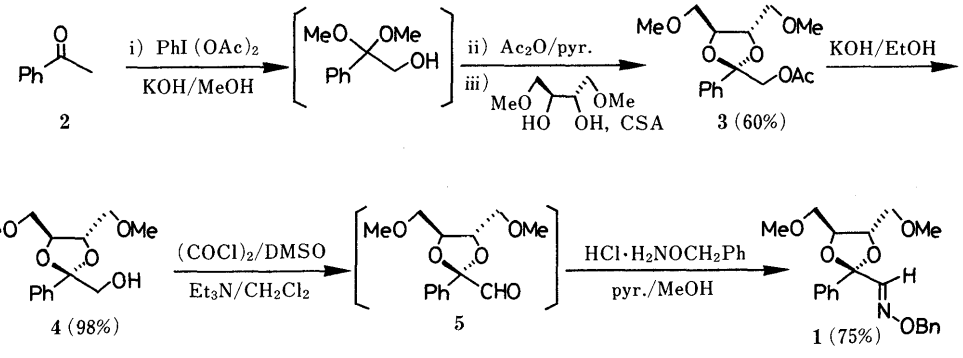


Chart 2

bond was assumed to be *E*.

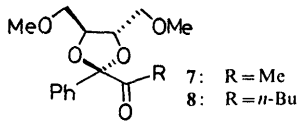
Nucleophilic Addition of Organometallics to the α-Aldoxime–Ether Acetal (1) The reactions of **1** with 5—8 mol eq of organometallic reagents are summarized in Table I. In the reaction of **1** with Grignard reagent [methylmagnesium bromide (MeMgBr)], nucleophilic addition reaction did not proceed and **1** was recovered (run 7). In the case of organolithium reagents, the ketones **7** (run 8) and **8** (run 9) were formed. Presumably, these products might arise *via* nitrile intermediates. Similar results were recently reported in the reactions of simple aldoxime ethers with organolithium reagents by Itsuno *et al.*[7] However, with organocerium reagents,[8] which were generated by the reaction of $CeCl_3$ respectively with RMgX and RLi according to the known procedure, nucleophilic addition reaction proceeded in high yields with a high diastereoselectivity to afford *N*-oxygenated amines (**6Aa—c**). Furthermore, interestingly, a difference of stereoselectivity between the organocerium reagents prepared from RMgX–$CeCl_3$ and RLi–$CeCl_3$ was observed. Namely, extremely high diastereoselectivity (86—100% diastereomeric excess (de)) was realized in the reactions of the reagent from RMgX–$CeCl_3$ (runs 1, 3, 5, 6), while the reagent from RLi–$CeCl_3$ showed slightly lower selectivity (50—80% de) (runs 2, 4).

The stereochemistries of the products were determined as follows. The absolute configuration of the α-carbon of the amino function of the product **6Aa** (R=Me; 99% de) formed in run 1 was determined as *S* by conversion to (−)-*N*-acetylamphetamine (**11**) (Chart 3). Thus, N–O bond fission of **6Aa** was achieved by $LiAlH_4$–$NiCl_2$ reduction[9] to give **9**. Acetylation of **9** afforded **10**, which was reductively deacetalized to give **11**, showing a good agreement of the specific rotation ($[\alpha]_D$ −42.9°) with the reported value (−43.5°).[10] Since the predominant product (**6Aa**) in runs 1 and 2 was proved to be formed by the attack of the reagent on the *si*-face of the C–N double bond, the stereochemistries of the products in runs 3—6 were tentatively assigned by assuming the same sense of diastereoselection as observed for **6Aa**.

TABLE I. Nucleophilic Addition of Organometallic Reagents (RM) to **1**

Run	RM	Solvent	Temp. (°C)	Yield (%)	Product	Ratio (A : B)
1	MeMgBr–$CeCl_3$	THF	0	84	**6Aa**+**6Ba**	>99 : <1[c]
2	MeLi–$CeCl_3$	THF–ether (5:1)	−78	70	**6Aa**+**6Ba**	90 : 10[c]
3	*n*-BuMgCl–$CeCl_3$	THF	0	81	**6Ab**+**6Bb**[b]	97 : 3[d]
4	*n*-BuLi–$CeCl_3$	THF–hexane (10:1)	−78	75	**6Ab**+**6Bb**[b]	75 : 25[d]
5	 MgBr–$CeCl_3$	THF	−23	67	**6Ac**+**6Bc**[b]	95 : 5[c]
6	*n*-BuMgCl–$CeCl_3$	THF–hexane (10:1)	−23	86	**6Ab**+**6Bb**[b]	93 : 7[d]
7	MeMgBr	THF	r.t.	0[a]	—	—
8	MeLi	THF–ether (4:1)	−78	90	**7**	—
9	*n*-BuLi	THF–hexane (5:2)	−78	90	**8**	—

a) The starting material was recovered unchanged. *b*) Tentatively assigned. *c*) Determined by ^{1}H-NMR. *d*) Determined by HPLC analysis.



7: R=Me
8: R=*n*-Bu

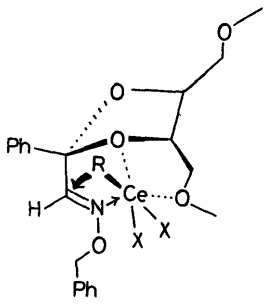


Fig. 1

The *si*-face selectivity in the reactions of organocerium reagents with the chiral α-aldoxime–ether acetal (**1**) may be rationalized by assuming a chelation model developed before in the reactions of Grignard reagents with chiral α-keto acetals.[2] Namely, cerium metal is fixed by chelation between the nitrogen atom, the methoxy oxygen atom, and one of the acetal oxygen atoms leading to a rigid structure (Fig. 1) in the transition state of the reaction, then the alkyl groups of the reagents attack the *si*-face of the C–N double bond. The reason for the difference of stereoselectivity between RMgX–$CeCl_3$ and RLi–$CeCl_3$ is still not clear.[11]

In summary, a new method for constructing chiral amine moieties was attained through the nucleophilic addition of organocerium reagents to the chiral α-aldoxime–ether acetal. Since the chiral diol is available in both enantiomeric forms,[5] this work promises to provide a useful method for building chiral amine moieties in both enantiomeric forms.

Experimental

The following instruments were used to obtain physical data: specific rotation, Perkin-Elmer 241 polarimeter; infrared (IR) spectra, JASCO IRA-1 spectrometer; proton nuclear magnetic resonance (^{1}H-NMR) spectra, Hitachi R-22 (90 MHz), JEOL JNM-FX 90Q FT-NMR (90 MHz) or JEOL LNM-GX 500 FT-NMR (500 MHz) spectrometer (with trimethylsilane as an internal standard); low- and high-resolution mass spectra (MS), JEOL JMS D-300 mass spectrometer (with a direct inlet system). A JASCO TRIROTAR-II high-pressure liquid chromatography (ultraviolet (UV) detector) was used for high-performance liquid chromatographic (HPLC) analysis. E. Merck silica gel (0.063—0.200 mm, 70—230 mesh ASTM) for column chromatography and E. Merck TLC plates pre-coated with Silica gel $60F_{254}$ for preparative thin layer chromatography (TLC)

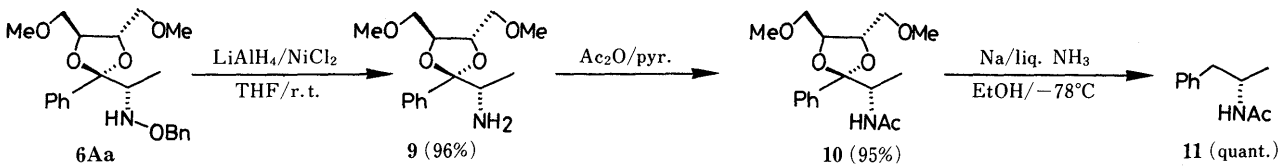


Chart 3

(0.5 mm) and TLC detection (0.2 mm) were used. Specific rotation was measured at 20 °C in $CHCl_3$, unless otherwise mentioned. All melting points are uncorrected.

α-Acetoxyacetophenone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (3) $PhI(OAc)_2$ (2.36 g, 7.32 mmol) was added to a stirred solution of **2** (800 mg, 6.66 mmol) and KOH (1.27 g, 22.6 mmol) in anhydrous MeOH at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 12 h at room temperature. Ice water (2 ml) was added to the mixture and MeOH was evaporated off. The residue was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure in the presence of one microspatula-full of K_2CO_3. The residue was dissolved in pyridine (10 ml) and Ac_2O (3.4 ml) was added dropwise to the solution at 0 °C. The resulting solution was stirred for 1 h at room temperature and then concentrated under reduced pressure. The completely dried residue was mixed with (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol (810 mg, 5.4 mmol) and CSA (one microspatula-full) and then stirred for 4 h at 40 °C under reduced pressure (1 mmHg). CH_2Cl_2 (15 ml) and K_2CO_3 (suitable amount), $MgSO_4$ (suitable amount) were added and the mixture was stirred for 10 min. The insoluble salt was removed by passage through a celite column with CH_2Cl_2 as an eluent. The filtrate was concentrated under reduced pressure to give a residue, which was subjected to column chromatography on silica gel with hexane–ether (2 : 1) as an eluent to give **3** (1.27 g, 62% yield). Colorless oil, $[\alpha]_D$ +12.8° (*c* = 1.85). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1065. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s, $-OCOCH_3$), 3.31, 3.43 (3H each, both s, $-OCH_3 \times 2$), 3.1—3.5 (2H, m, $-CH_2OCH_3$), 3.61 (2H, d, *J* = 4.8 Hz, $-CH_2OCH_3$), 3.8—4.4 (2H, m, $-OCH- \times 2$), 4.25 (2H, d, *J* = 1.7 Hz, $-CH_2OAc$), 7.2—7.6 (5H, m, aromatic protons). *Anal.* Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 62.08; H, 7.14.

α-Hydroxyacetophenone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (4) A 5% KOH–MeOH solution (2 ml) was added to **3** (60 mg, 0.19 mmol) and the mixture was stirred for 10 min at room temperature under a nitrogen atmosphere. MeOH was evaporated off. Water (10 ml) was added to the residue and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–AcOEt (1 : 1) as an eluent to give **4** (48 mg, 95% yield). Colorless oil, $[\alpha]_D$ +16.2° (*c* = 1.14). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1070. ^{1}H-NMR ($CDCl_3$) δ: 3.1—3.6 (2H, m, $-CH_2OCH_3$), 3.29, 3.44 (3H each, both s, $-OCH_3 \times 2$), 3.6—3.8 (4H, m, $-CH_2OCH_3$ and $-CH_2OH$), 3.8—4.1 (1H, m, $-OCH-$), 4.2—4.5 (1H, m, $-OCH-$), 7.2—7.6 (5H, m, aromatic protons). Exact MS Calcd for $C_{13}H_{17}O_4$ ($M^+ - OMe$): 237.1124. Found: 237.1123.

α-Benzyloxyiminoacetophenone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (1) Dimethyl sulfoxide (DMSO) (0.51 ml, 7.2 mmol) was added to a stirred solution of oxalyl chloride $(COCl)_2$ (0.26 ml, 3 mmol) in anhydrous CH_2Cl_2 (9 ml) at −78 °C. The resulting mixture was stirred for 5 min and then **4** (306 mg, 1.14 mmol) in anhydrous CH_2Cl_2 (2 ml) was added. After further stirring for 45 min, Et_3N (2.2 ml, 16 mmol) was added to the reaction mixture. The resulting solution was stirred for 15 min and then treated with water. (The reaction was carried out at −60——70 °C under a nitrogen atmosphere.) The mixture was extracted with CH_2Cl_2. The organic layer was washed with aqueous 5% HCl, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$. The solution was concentrated under reduced pressure. The residue (**5**) was dissolved in anhydrous MeOH (3 ml). *O*-Benzylhydroxylamine hydrochloride ($HCl \cdot H_2NOCH_2Ph$) (176 mg, 1.1 mmol) and pyridine (0.3 ml, 3.3 mmol) were added to the above solution and the mixture was refluxed for 15 min. MeOH was evaporated off. Water (5 ml) was added to the residue. The mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel with hexane–ether (5 : 1) as an eluent to give **1** (319 mg, 75% yield). Colorless oil, $[\alpha]_D$ +15.2° (*c* = 1.2). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1075. ^{1}H-NMR ($CDCl_3$) δ: 3.32, 3.35 (3H each, both s, $-OCH_3 \times 2$), 3.39—3.58 (4H, m, $-CH_2OCH_3 \times 2$), 4.0—4.3 (2H, m, $-OCH- \times 2$), 5.03 (2H, s, $-OCH_2Ph$), 7.2—7.6 (10H, m, aromatic protons), 7.52 (1H, s, $HC=N-$). *Anal.* Calcd for $C_{21}H_{25}O_5N$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.90; H, 6.68; N, 3.75.

Nucleophilic Addition of Organometallic Reagents to the α-Aldoxime–Ether Acetal (1) All runs were carried out under a nitrogen atmosphere.

General Procedure for Runs 1—5: Organocerium reagents ($RMgX–CeCl_3$, $RLi–CeCl_3$) were prepared according to the reported procedure.[8] Organocerium reagent (5—8 mol eq) was added dropwise to a stirred solution of **1** (1 mmol) in dry tetrahydrofuran (THF) (10 ml) at −78 °C. The reaction mixture was stirred for 1—3 h (TLC check) at −23—0 °C in the case of $RMgX–CeCl_3$ and at −78 °C in the case of $RLi–CeCl_3$ then treated with water (5 ml). The resulting mixture was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give 2*S*-2-benzyloxyamino-1-phenyl-1-propanone (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6Aa**), 2*S*-2-benzyloxyamino-1-phenyl-1-hexanone (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6Ab**), 2*S*-2-benzyloxyamino-1-phenyl-5-hexene-1-one (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6Ac**), 2*R*-2-benzyloxyamino-1-phenyl-1-propanone (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6Ba**), 2*R*-2-benzyloxyamino-1-phenyl-1-hexanone (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6Bb**), and 2*R*-2-benzyloxyamino-1-phenyl-5-hexene-1-one (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6Bc**).

Run 1: The product **6Aa** (R = Me, 99% de, 44 mg) was obtained from **1** (50 mg, 0.135 mmol) and $MeMgBr–CeCl_3$ in 84% yield (eluent, hexane : ether = 3 : 1). Colorless oil, $[\alpha]_D$ +27.8° (*c* = 1.04). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1090. ^{1}H-NMR (C_6D_6) δ: 1.27 (3H, d, *J* = 6.1 Hz, $-CHCH_3$), 2.94 (3H, s, $-OCH_3$), 3.04 (1H, dd, *J* = 5.5, 9.8 Hz, $-HCHOCH_3$), 3.09 (3H, s, $-OCH_3$), 3.23 (1H, dd, *J* = 6.1, 9.8 Hz, $-HCHOCH_3$), 3.39 (1H, A part in ABX, *J* = 5.5, 10.4 Hz, $-HCHOCH_3$), 3.42 (1H, B part in ABX, *J* = 4.3, 10.4 Hz, $-HCHOCH_3$), 3.60 (1H, q, *J* = 6.1 Hz, $-CHCH_3$), 3.83 (1H, ddd, *J* = 4.3, 5.5, 7.9 Hz, $-OCH-$), 4.17 (1H, ddd, *J* = 5.5, 6.1, 7.9 Hz, $-OCH-$), 4.65 (2H, s, $-OCH_2Ph$), 7.05—7.7 (10H, m, aromatic protons). Exact MS Calcd for $C_{22}H_{30}O_5N$ ($M^+ + H$): 388.2121. Found: 388.2110.

Run 2: The product [**6Aa**(R = Me) : **6Ba**(R = Me) = 90 : 10, 20.5 mg] was prepared from **1** (28 mg, 0.08 mmol) and $MeLi–CeCl_3$ in 70% yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1090. ^{1}H-NMR (C_6D_6) δ: 1.27, 1.31 (total 3H, each d, *J* = 6.1 Hz, ratio 9 : 1, $-CHCH_3$), 2.94, 2.95 (total 3H, both s, ratio 9 : 1, $-OCH_3$), 3.04 (1H, dd, *J* = 5.5, 9.8 Hz, $-HCHOCH_3$), 3.06, 3.09 (total 3H, both s, ratio 1 : 9, $-OCH_3$), 3.23 (1H, dd, *J* = 6.1, 9.8 Hz, $-HCHOCH_3$), 3.39 (1H, A part in ABX, *J* = 5.5, 10.4 Hz, $-HCHOCH_3$), 3.42 (1H, B part in ABX, *J* = 4.3, 10.4 Hz, $-HCHOCH_3$), 3.60 (1H, q, *J* = 6.1 Hz, $-CHCH_3$), 3.83 (1H, ddd, *J* = 4.3, 5.5, 7.9 Hz, $-OCH-$), 4.17 (1H, ddd, *J* = 5.5, 6.1, 7.9 Hz, $-OCH-$), 4.65 (2H, s, $-OCH_2Ph$), 7.05—7.7 (10H, m, aromatic protons). Exact MS Calcd for $C_{22}H_{29}O_5N$: 387.2043. Found: 387.2040.

Run 3: **6Ab** (R = *n*-Bu, 94% de, 17.4 mg) was prepared from **1** (18.6 mg, 0.05 mmol) and *n*-$BuMgCl–CeCl_3$ in 81% yield (eluent, benzene : ether = 3 : 1). The ratio of the products was determined by HPLC analysis [Nucleosil 50-5 column; eluent, hexane : AcOEt = 1 : 2, flow rate 1 ml/min; retention time (t_R): **6Ab** (R = *n*-Bu), 13.82 min, **6Bb** (R = *n*-Bu), 13.26 min]. Colorless oil, $[\alpha]_D$ +10.7° (*c* = 0.41). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1095. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, *J* = 7.3 Hz, $-CH_2CH_3$), 1.15—1.55 (6H, m, $-CH_2- \times 3$), 3.12 (1H, dd, *J* = 5.5, 9.8 Hz, $-HCHOCH_3$), 3.15 (1H, dd, *J* = 3.7, 9.8 Hz, $-CHN-$), 3.26, 3.37 (3H each, both s, $-OCH_3 \times 2$), 3.33 (1H, dd, *J* = 6.1, 9.8 Hz, $-HCHOCH_3$), 3.56 (2H, d, *J* = 4.9 Hz, $-CH_2OCH_3$), 3.73—3.82 (1H, m, $-OCH-$), 4.06—4.12 (1H, m, $-OCH-$), 4.59 (2H, s, $-OCH_2Ph$), 7.2—7.55 (10H, m, aromatic protons). Exact MS Calcd for $C_{25}H_{36}O_5N$ ($M^+ + H$): 430.2594. Found: 430.2611.

Run 4: The product [**6Ab** (R = *n*-Bu) : **6Bb** (R = *n*-Bu) = 75 : 25, 19 mg] was prepared from **1** (22 mg, 0.06 mmol) and *n*-$BuLi–CeCl_3$ in 75% yield. The ratio of the product was determined by HPLC analysis (see run 3). Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1095. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, *J* = 7.3 Hz, $-CH_2CH_3$), 1.15—1.55 (6H, m, $-CH_2- \times 3$), 3.12 (1H, dd, *J* = 5.5, 9.8 Hz, $-HCHOCH_3$), 3.15, 3.20 (total 1H, each dd, *J* = 3.7, 9.8 Hz and 4.9, 9.8 Hz, ratio 3 : 1, $-CHN-$), 3.26, 3.29, 3.37,3.38 (total 6H, all s, ratio 3 : 1 : 3 : 1, $-OCH_3 \times 2$), 3.33 (1H, dd, *J* = 6.1, 9.8 Hz, $-HCHOCH_3$), 3.56 (2H, d, *J* = 4.9 Hz, $-CH_2OCH_3$), 3.73—3.82 (1H, m, $-OCH-$), 4.06—4.12 (1H, m, $-OCH-$), 4.59 (2H, s, $-OCH_2Ph$), 7.2—7.55 (10H, m, aromatic protons). Exact MS Calcd for $C_{25}H_{36}O_5N$ ($M^+ + H$): 430.2593. Found: 430.2608.

Run 5: The product **6Ac** ($R = -CH_2CH_2CH=CH_2$, 90% de, 23 mg) was prepared from **1** (30 mg, 0.08 mmol) and $CH_2=CHCH_2CH_2MgBr–CeCl_3$ in 67% yield (eluent, hexane : ether = 4 : 1). Colorless oil, $[\alpha]_D$ +10.6° (*c* = 0.50). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1095. ^{1}H-NMR ($CDCl_3$) δ: 1.47—1.65 (2H, m, $-CH_2-$), 1.97—2.06, 2.15—2.25 (2H, m, $-CH_2-$), 3.12 (1H, dd, *J* = 5.5, 9.8 Hz, $-HCHOCH_3$), 3.18 (1H, dd, *J* = 3.7, 9.2 Hz, $-CHN-$), 3.26, 3.29, 3.366, 3.374 (total 6H, all s, ratio 19 : 1 : 19 : 1, $-OCH_3 \times 2$), 3.33 (1H, dd, *J* = 6.1, 9.8 Hz, $-HCHOCH_3$), 3.56 (2H, d, *J* = 4.3 Hz, $-CH_2OCH_3$), 3.79 (1H, dt, *J* = 8.0, 4.3 Hz, $-OCH-$), 4.10 (1H, ddd, *J* = 5.5, 6.1, 8.0 Hz, $-OCH-$), 4.60 (2H, s, $-OCH_2Ph$), 4.88 (1H, dd, *J* = 1.8, 10.4 Hz, $^{H}\!>\!C=C\!<^{H}_{H}$), 4.92 (1H, dd, *J* = 1.8, 17.1 Hz, $^{H}\!>\!C=C\!<^{H}_{H}$), 5.66—5.75 (1H, m, $-CH=CH_2$), 7.2—7.55 (10H, m, aromatic protons). Exact MS Calcd for $C_{25}H_{34}O_5N$ ($M^+ + H$): 428.2434. Found: 428.2433.

Run 6: The product **6Ab** (R = *n*-Bu, 86% de, 27 mg) was prepared from **1**

(27 mg, 0.073 mmol) and *n*-BuMgCl–$CeCl_3$ in THF–hexane (10 : 1) in 86% yield. The ratio of the product was determined by HPLC analysis (see run 3). Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1095. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, J=7.3 Hz, $-CH_2CH_3$), 1.15—1.55 (6H, m, $-CH_2-\times3$), 3.12 (1H, dd, J=5.5, 9.8 Hz, $-HCHOCH_3$), 3.15 (1H, dd, J=3.7, 9.8 Hz, $-CHN-$), 3.26, 3.37 (3H each, both s, $-OCH_3\times2$), 3.33 (1H, dd, J=6.1, 9.8 Hz, $-HCHOCH_3$), 3.56 (2H, d, J=4.9 Hz, $-CH_2OCH_3$), 3.73—3.82 (1H, m, $-OCH-$), 4.06—4.12 (1H, m, $-OCH-$), 4.59 (2H, s, $-OCH_2Ph$), 7.2—7.55 (10H, m, aromatic protons). Exact MS Calcd for $C_{25}H_{36}O_5N$ (M^++H): 430.2593. Found: 430.2607.

Run 7: A mixture of **1** (14.5 mg, 0.04 mmol) and MeMgBr (0.235 mmol) in dry THF (0.4 ml) was stirred for 1.5 h at −78 °C, for 1 h at −23 °C, overnight at 0 °C, and for 2 h at room temperature. Usual work-up resulted in the recovery of **1**.

Run 8: An ether solution of MeLi (0.9 N in ether, 0.29 ml, 0.26 mmol) was added dropwise to a stirred solution of **1** (12.3 mg, 0.033 mmol) in anhydrous THF (1.2 ml) at −78 °C. The resulting mixture was stirred for 0.5 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by preparative TLC (benzene : ether = 5 : 1) to give 2-keto-1-phenyl-1-propanone (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**7**) (8.3 mg, 90% yield), which was identical with the authentic sample prepared earlier by us.[2b]

Run 9: A solution of *n*-BuLi (1.6 N in hexane, 0.27 ml, 0.43 mmol) was added dropwise to a stirred solution of **1** (19.7 mg, 0.053 mmol) in dry THF (0.65 ml). The reaction mixture was stirred for 1 h at the same temperature. Usual work-up afforded the crude product, which was purified by preparative TLC (benzene : ether = 5 : 1) to give 2-keto-1-phenyl-1-hexanone (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**8**) (15.4 mg, 90% yield). Colorless oil, $[\alpha]_D$ +24.4° (c=0.31). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735, 1105. ^{1}H-NMR ($CDCl_3$): 0.81 (3H, t, J=6.3 Hz, $-CH_3$), 0.96—1.7 (4H, m, $-CH_2-\times2$), 2.4—2.64 (2H, m, $-COCH_2-$), 3.34, 3.40 (3H each, both s, $-OCH_3\times2$), 3.4—3.6 (4H, m, $-CH_2O-\times2$), 3.9—4.3 (2H, m, $-CHO-\times2$), 7.2—7.6 (5H, m, aromatic protons). *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.07; H, 8.16.

2*S*-2-Amino-1-phenyl-1-propanone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (9) A solution of **6Aa** (99% de, 42 mg, 0.11 mmol) in dry THF (0.6 ml) was added to a stirred solution of $NiCl_2$ (42 mg, 0.33 mmol) in dry THF (1.2 ml) at room temperature under a nitrogen atmosphere. The resulting solution was cooled to −78 °C and a suspension of $LiAlH_4$ (1.5 mg, 0.33 mmol) in dry THF (0.6 ml) was added dropwise. The reaction mixture was allowed to warm to −35 °C over 30 min and then stirred for 2.5 h at room temperature. The reaction was quenched with saturated aqueous K_2CO_3 (5 ml) and the solution was extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$: MeOH = 10 : 1) to give **9** (30 mg, 97% yield). Colorless oil, $[\alpha]_D$ +30.7° (c=0.86). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3375, 1590, 1090. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J=6.2 Hz, $-CHCH_3$), 3.0—3.4 (3H, m, $-CH_2O-$ and $-CHNH-$), 3.27, 3.43 (3H each, both s, $-OCH_3\times2$), 3.61 (2H, d, J=4.4 Hz, $-CH_2O-$), 3.7—4.25 (2H, m, $-OCH-\times2$), 7.2—7.6 (5H, m, aromatic protons). Exact MS Calcd for $C_{15}H_{24}O_4N$ (M^++H): 282.1704. Found: 282.1729.

2*S*-2-Acetamido-1-phenyl-1-propanone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (10) Ac_2O (1.7 ml) was added to a solution of **9** (22 mg, 0.08 mmol) in pyridine (3.5 ml) and the reaction mixture was stirred for 14 h at room temperature. At the end of this time, Ac_2O and pyridine were evaporated off. The residue was subjected to column chromatography on silica gel with benzene–AcOEt (1 : 2) as an eluent to give **10** (24 mg, 95% yield). Colorless oil, $[\alpha]_D$ +3.2° (c=0.8). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1660. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=6.8 Hz, $-CHCH_3$), 1.94 (3H, s, $-COCH_3$), 3.01 (1H, dd, J=6.2, 9.9 Hz, $-HCHOCH_3$), 3.22, 3.49 (3H each, both s, $-OCH_3\times2$), 3.3—3.6 (1H, m, $-HCHOCH_3$), 3.8—4.5 (4H, m, $-CH_2O-$ and $-OCH-\times2$), 4.42 (1H, q, J=6.8 Hz, $-NCH-$), 7.2—7.6 (5H, m, aromatic protons). Exact MS Calcd for $C_{17}H_{26}O_5N$ (M^++H): 324.1811. Found: 324.1811.

Amide 11 (*N*-Acetyl Amphetamine) A solution of **10** (24 mg, 0.074 mmol) and EtOH (40 μl) in dry THF (1.5 ml) was added to a solution of Na metal (14 mg) in liquid NH_3 (6 ml) at −78 °C. The mixture was stirred for 3 min, then the reaction was quenched by the addition of saturated aqueous NH_4Cl and allowed to warm to room temperature to remove NH_3. The residue was dissolved in water and extracted with ether. The ether layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by preparative TLC (benzene : AcOEt = 1 : 5) to give **11** (11 mg, quantitative yield), which was identical with the authentic sample in melting point, 124—124.5 °C (lit.,[10] 121—124 °C), and $[\alpha]_D$ −42.9° (c=0.35) [lit.,[10] −43.5° (c=2.0)]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=6.6 Hz, $-CH_3$), 1.93 (3H, s, $-COCH_3$), 2.75 (2H, m, $-CH_2Ph$), 4.26 (1H, m, $-HCN-$), 6.9—7.4 (5H, m, aromatic protons).

References and Notes

1) For example: Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu, and W. Ito, *J. Am. Chem. Soc.*, **108**, 7778 (1986) and references cited therein; C. Fuganti, P. Grasselli, and G. P. Fantoni, *J. Org. Chem.*, **48**, 909 (1983); D. Enders, H. Schubert, and C. Nubling, *Angew. Chem. Int. Ed. Engl.*, **25**, 1109 (1986); S. E. Denmark, T. Weber, and D. W. Piotrowski, *J. Am. Chem. Soc.*, **109**, 2224 (1987); D. A. Claremon, P. K. Lumma, and B. T. Phillips, *ibid.*, **108**, 8265 (1986); T. Mukaiyama, Y. Goto, and S. Shoda, *Chem. Lett.*, **1983**, 671.

2) *a*) Y. Tamura, H. Kondo, H. Annoura, R. Takeuchi, and H. Fujioka, *Tetrahedron Lett.*, **27**, 81 (1986); Y. Tamura, H. Annoura, H. Kondo, M. Fuji, T. Yoshida, and H. Fujioka, *Chem. Pharm. Bull.*, **35**, 2305 (1987); *b*) Y. Tamura, T. Ko, H. Kondo, H. Annoura, M. Fuji, R. Takeuchi, and H. Fujioka, *Tetrahedron Lett.*, **27**, 2117 (1986); Y. Tamura, H. Annoura, M. Fuji, T. Yoshida, R. Takeuchi, and H. Fujioka, *Chem. Pharm. Bull.*, **35**, 4736 (1987).

3) Presented at the Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii, December 1987, Y. Tamura *et al.*, Abstracts, M03-Y-03.

4) R. M. Moriarty and K.-C. How, *Tetrahedron Lett.*, **25**, 691 (1984).

5) (−)-(2*S*,3*S*)-1,4-Dimethoxy-2,3-butanediol can be readily prepared from L-(+)-tartaric acid in four steps: (1) $Me_2C(OMe)_2$/MeOH/*p*-TsOH/cyclohexane/Δ [M. Carmack and C. J. Kely, *J. Org. Chem.*, **33**, 2171 (1968)]; (2) $LiAlH_4/Et_2O$/reflux; (3) MeI/KOH/DMSO; (4) 95% EtOH/*p*-TsOH/reflux. The (+)-enantiomer is available from D-mannitol (A. H. Haines and C. S. P. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 273.

6) A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).

7) S. Itsuno, K. Miyazaki, and K. Ito, *Tetrahedron Lett.*, **27**, 3033 (1986).

8) For preparation of RMgX–$CeCl_3$, see T. Imamoto, N. Takiyama, and K. Nakamura, *Tetrahedron Lett.*, **26**, 4763 (1985); for preparation of RLi–$CeCl_3$, see T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, *J. Org. Chem.*, **49**, 3904 (1984).

9) J. J. Tufarielo, H. Meckler, and K. P. A. Senarante, *Tetrahedron*, **41**, 3447 (1985).

10) N. J. Leonard, J. A. Adamick, C. Djerassi, and O. Halpern, *J. Am. Chem. Soc.*, **80**, 4858 (1958).

11) The difference of stereoselectivity might be caused by the inorganic salts (magnesium salt or lithium salt) formed *in situ*. The effect of inorganic salt on the stereoselectivity was reported previously. See E. L. Eliel and Kenso Soai, *Tetrahedron Lett.*, **22**, 2859 (1981).