Pergamon

Tetrahedron 54 (1998) 11011–11026

TETRAHEDRON

Formal Total Synthesis of Nikkomycin B Based on a Lipase-catalysed Hydrolysis of an Acetate Possessing Two Stereogenic Centers

Hiroyuki Akita,* Cheng Yu Chen and Keisuke Kato

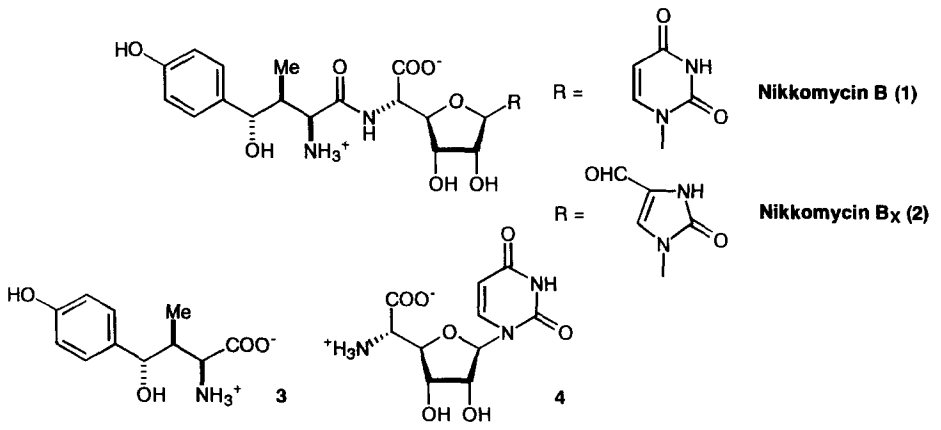
School of Pharmaceutical Science, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan

Received 8 June 1998; accepted 1 July 1998

Abstract: A stereoselective synthesis of the versatile chiral synthon possessing two stereogenic centers, (2*S*,3*S*)-**11** (>99% ee) was achieved by using chemo-enzymatic method. The conversion of (2*S*,3*S*)-**11** into the homochiral intermediates (2*S*,3*S*,4*S*)-**25** and (2*S*,3*S*,4*S*)-**27** corresponding to the N-terminal amino acid moiety of nikkomycin B (**1**) and their application to the formal total synthesis of nikkomycin B (**1**) are described.

Introduction

Nikkomycins are peptidyl nucleoside antibiotics which have been isolated from the culture broths of *Streptomyces tendae* and *Streptomyces cacaoi* subsp. *asoensis*.[1,2] These antibiotics are potent competitive inhibitors of chitin synthetase and exhibit antifungal, insecticidal and acaricidal activities. From the point view of fungal infections, chitin synthetase inhibition seems to be a useful approach for the sake of safer antifungal agents and much efforts has been devoted to the total synthesis of nikkomycins B (**1**)[3] and Bx (**2**).[4] Synthesis of nikkomycin B (**1**) can be achieved by the coupling of two structural units, the N-terminal amino acid **3** and the C-terminal nucleoside amino acid, uracil polyoxin C (**4**). The presence of three consecutive stereogenic centers in **3** is the greater synthetic challenge, and several approaches to this amino acid and its congener in either racemic[5] or optically active form,[6] have been recently reported. We now report a stereoselective synthesis of Barrett's intermediate (2*S*,3*S*,4*S*)-**25**, a potential precursor of the N-terminal amino acid (**3**) based on the chemo-enzymatic method and its application to the formal total synthesis of **1** by the coupling of uracil polyoxin C congener (**35**).

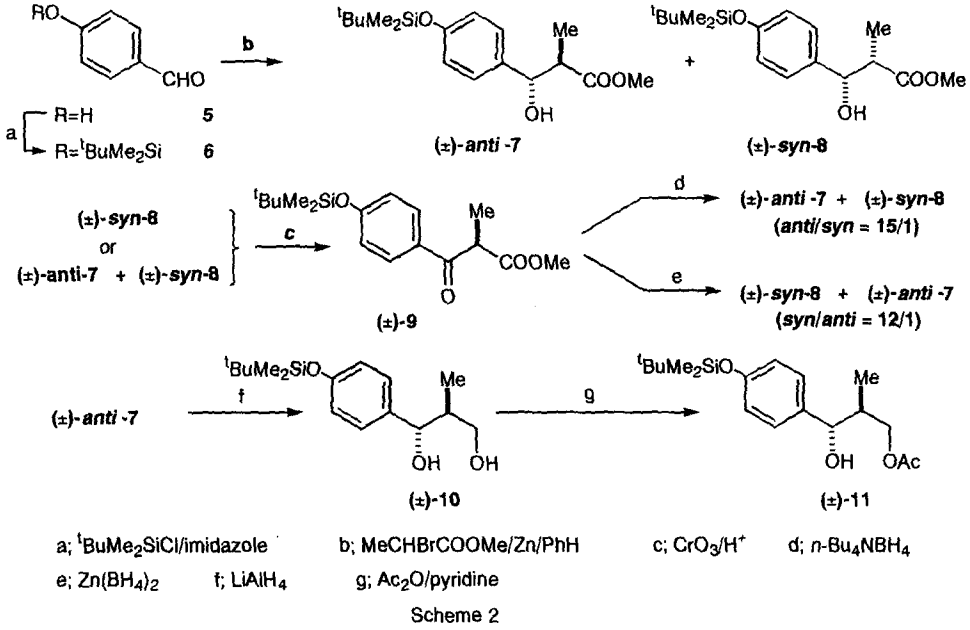


Scheme 1

PII: S0040-4020(98)00647-4

Results and discussion

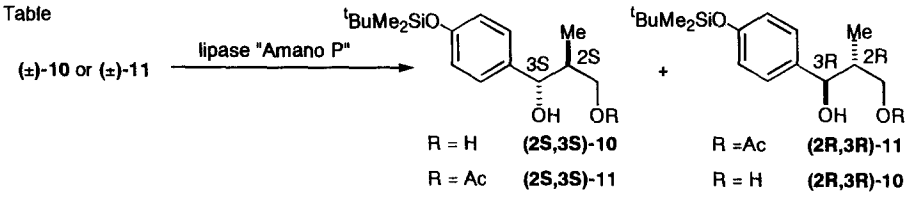
Reformatsky reaction of *p*-silyloxybenzaldehyde **6** (85%) obtained by the silylation of *p*-hydroxybenzaldehyde **5** and α-bromopropionate gave (±)-*anti*-**7** (36%) and (±)-*syn*-**8** (54%). The major (±)-*syn*-**8** was oxidized with Jones reagent to afford the β-keto ester (±)-**9** (86%). Jones oxidation of a mixture of (±)-*anti*-**7** and (±)-*syn*-**8** gave also (±)-**9** in 86% yield. Reduction of (±)-**9** with *n*-Bu_4NBH_4[7] gave the (±)-*anti*-**7** (71.3%) along with a small amount of the (±)-*syn*-**8** (4.8%) with high *anti*-diastereoselectivity (*anti*/*syn* =15/1). In order to confirm the reaction products, (±)-*syn*-**8** was also obtained in 81.2% yield by the $Zn(BH_4)_2$ reduction of (±)-**9** with high *syn*-diastereoselectivity (*syn*/*anti* = 12/1), because $Zn(BH_4)_2$ reduction of α-methyl-β-keto esters has been reported to give predominantly the *syn*-α-methyl-β-hydroxy ester **8**.[8] Reduction of (±)-**7** with $LiAlH_4$ provided (±)-*anti* diol **10** in 76% yield, which was treated with one equivalent of Ac_2O in pyridine to afford (±)-mono acetate **11** in 43% yield.



Scheme 2

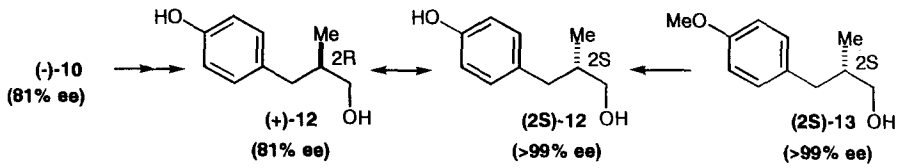
Initially, (±)-**10** was subjected to screening experiments using several kinds of commercially available lipases. Among them, lipase "Amano P" from *Pseudomonas* sp. was found to give the (2*R*,3*R*)-mono acetate **11** (53%, 75% ee, $[\alpha]_D$ +11.0 (c=1.88, $CHCl_3$) and the unchanged (2*S*,3*S*)-**10** (36%, 81% ee, $[\alpha]_D$ -20.0 (c=1.29, $CHCl_3$) in the presence of isopropenyl acetate as an acyl donor in isopropyl ether as shown in table. On the other hand, stereoselective hydrolysis of (±)-**11** using "Amano P" in water saturated isopropyl ether gave (2*S*,3*S*)-**11** (49%, 77% ee) and (2*R*,3*R*)-**10** (44%, 70% ee). The recovered (2*S*,3*S*)-**11** having 77% enantiomeric excess was again subjected to the enzymatic hydrolysis using "Amano P" for 18 hour to give (2*S*,3*S*)-**11** (84%, $[\alpha]_D$ -14.1 (c=0.93, $CHCl_3$); corresponds to >99% ee) and (2*R*,3*R*)-**10** (13%, 37% ee). The enantiomeric purity of the enzymatic reaction products was determined by HPLC on a CHIRALCEL OD (250 X 4.6 mm) column. In order to confirm the absolute configuration of the present (-)-**10**, (-)-**10** was

Table



Entry	Substrate (g)	Products %(% ee)	%(% ee)
1	(±)-**10** (1.66)	**(2S,3S)-10** 36(81)	**(2R,3R)-11** 53(75)
2	(±)-**11** (3.06)	**(2S,3S)-11** 49(77)	**(2R,3R)-10** 44(70)
3*	**(2S,3S)-11** (1.43)	**(2S,3S)-11** 84(>99)	**(2R,3R)-10** 13(37)

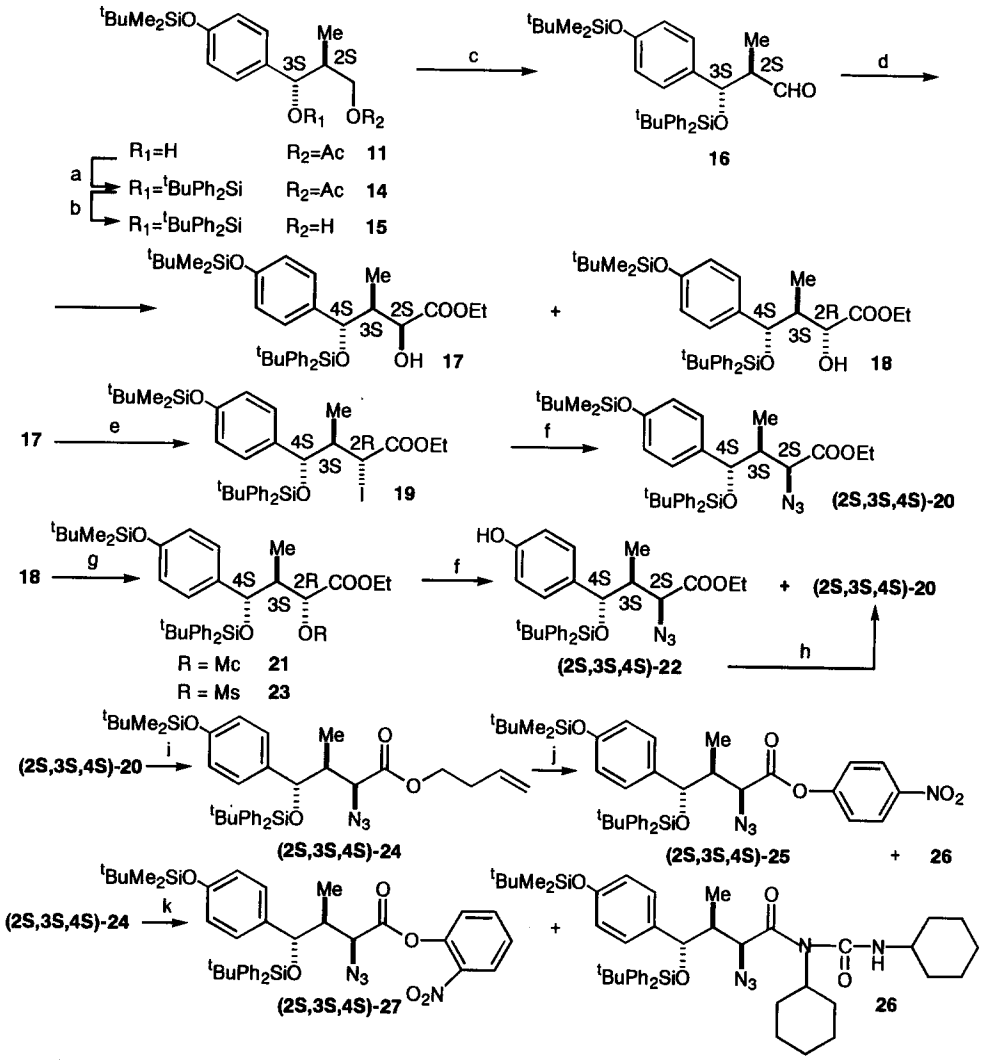
* Optically active **(2S,3S)-11** (77% ee) was employed.



Scheme 3

successfully converted to the mono alcohol (+)-**12** ([α]$_D$ +7.41 (c=1.39, $CHCl_3$); corresponds to 81% ee), whose sign of [α]$_D$ was opposite in comparison with that ([α]$_D$ -9.72 (c=1.08, $CHCl_3$); corresponds to >99% ee) of (2*S*)-mono alcohol **12** derived from (2*S*)-**13** previously reported by us.[9] Consequently, absolute configuration of (+)-**12** was determined to be 2*R*, and thence absolute configurations of (-)-**10** and (+)-**11** were confirmed to be 2*S*,3*S* and 2*R*,3*R*, respectively.

Silylation (**14**, 97%) of the optically pure (2*S*,3*S*)-**11** followed by reductive deacetylation gave mono alcohol (2*S*,3*S*)-**15** ([α]$_D$ -90.4 (c=1.81, $CHCl_3$), which was subjected to the Swern oxidation provided the aldehyde **16**. By applying Barrett's procedure,[3] **16** was subjected to the Felkin Ahn controlled addition of lithiated ethyl vinyl ether under dry-ice acetone cooling. The generated vinyl ether was directly ozonolyzed and subsequently treated with dimethyl sulfide to yield a 4.3:1 mixture of α-hydroxy ethyl esters **17** and **18**. Chromatographic separation of a mixture gave **17** ([α]$_D$ -61.7 (c=0.92, $CHCl_3$), 47% overall yield from **15**) and **18** ([α]$_D$ +74.4 (c=0.81, $CHCl_3$), 11% overall yield from **15**). Conversion of **17** to the iodide **19** ([α]$_D$ -10.6 (c=1.05, $CHCl_3$), 77%) followed by nucleophilic displacement with NaN_3 provided the desired (2*S*)-α-azido ethyl ester **20** ([α]$_D$ -45.4 (c=1.21, $CHCl_3$), 88%) as a single diastereoisomer. For the purpose of useful utilization of the minor **18**, treatment of **18** with chloromethylsulfonyl chloride (MeCl)[10] afforded the chloromethyl sulfonate **21** (91%), which was treated with NaN_3 to provide (2*S*,3*S*,4*S*)-**20** (50%) and desilylated compound (2*S*,3*S*,4*S*)-**22** ([α]$_D$ -40.5 (c=2.04, $CHCl_3$), 35%) along with recovery starting material **21** (5%). Silylation of (2*S*,3*S*,4*S*)-**22** gave also the desired (2*S*,3*S*,4*S*)-**20** (84%). Total conversion yield of **20** from **18** was found to be 72%. Instead of using chloromethyl sulfonate **21**, the reaction of the corresponding mesylate **23** and NaN_3 provided the desilylated compound (2*S*,3*S*,4*S*)-**22** in 49% yield. Formation of the activated ester **25** was carried out by the same way for Barrett's procedure.[3] Transesterification of **20** in the presence of 3-buten-1-ol and Ti(O-*i*-Pr)$_4$ gave the corresponding ester **24** ([α]$_D$ -40.7 (c=1.38, $CHCl_3$), 90%),

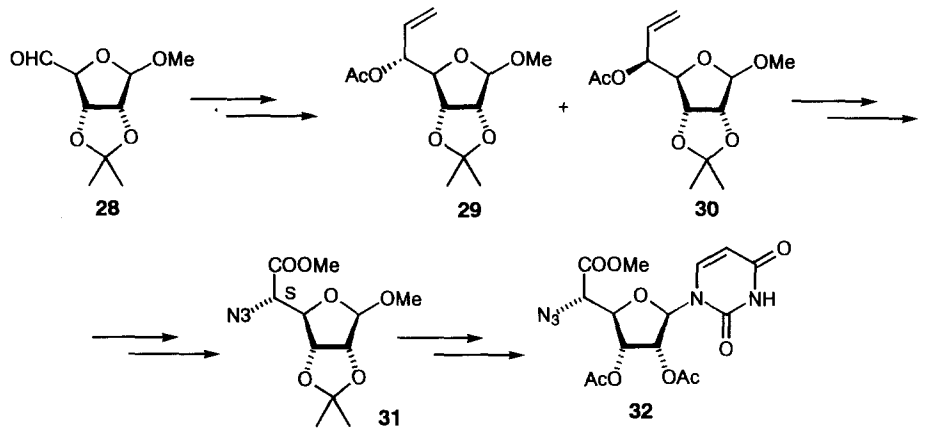


Scheme 4

whose spectral data ([α]$_D$, ^{1}H-NMR, IR and FAB-MS) were good agreement with those ([α]$_D$ -25 (c=0.44, $CHCl_3$) reported by Barrett.[3] Ozonolysis of the butene moiety followed by treatment with DBU *in situ* afforded the α-azido acid. Without further purification, treatment of the α-azido acid with *p*-nitrophenol in the presence of dicyclohexylcarbodiimide (DCC) gave the activated ester **25** ([α]$_D$ -33.8 (c=1.24, $CHCl_3$), 43%)

and the unknown acyl urea **26** ([α]$_D$ -25.3 (c=0.93, $CHCl_3$), 27%). Attempted conversion of **26** into **25** was carried out and no exchange was observed. The formation of acyl urea **26** is considered to result from migration of the unstable intermediary acyl isourea obtained by the reaction of the above mentioned α-azido acid and DCC.[11] In order to improve the yield of activated ester, the reaction of the above mentioned α-azido acid and *o*-nitrophenol in stead of *p*-nitrophenol was carried out. In this case, the activated ester **27** ([α]$_D$ -24.6 (c=0.67, $CHCl_3$), 44%) and the acyl urea **26** (53%) were obtained.

On the other hand, uracil polyoxin C congener **35** corresponding to the C-terminal nucleoside amino acid part of nikkomycin B (**1**) was synthesized from the reported 1-(methyl 2',3'-di-*O*-acetyl-5'-azido-5'-deoxy-β-D-alloruranosyluronate)uracil **32**.[12] We reported the synthesis of **32** from 2,3-*O*-isopropylidene-β-ribo-pentodialdo-1,4-furanoside **28** as shown in scheme 5.[12] Vinylation of **28** followed by acetylation gave a mixture of acetates **29** and **30** which was converted to the (5*S*)-azido ester **31** (55% overall yield from **28**). Conversion of **31** to the β-nucleoside **32** was achieved in 61% overall yield. Total overall yield of **32** from the starting aldehyde **28** was 34%.

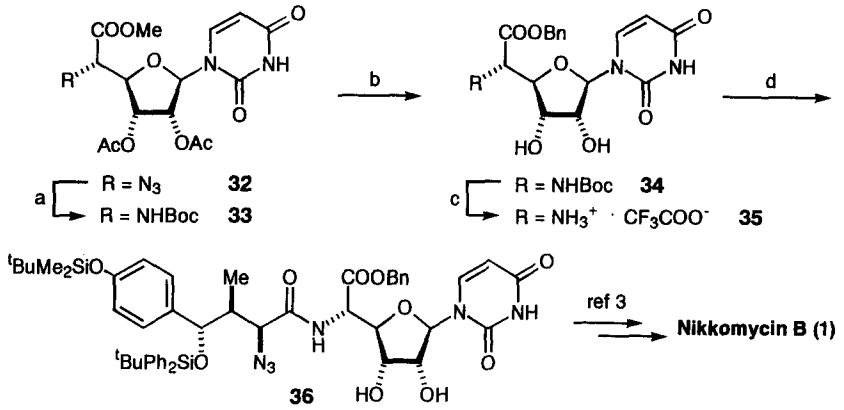


Scheme 5

Hydrogenation of the azide **32** in the presence of 10% Pd-C afforded α-amino acid ester which was treated with di-*tert*-butyldicarbonate (Boc_2O) in the presence of Et_3N to provide the N-protected amino acid ester **33** ([α]$_D$ +29.7 (c=1.095, $CHCl_3$), 65%). Transesterification of **33** in the presence of benzyl alcohol and Ti(O-*i*-Pr)$_4$ provided the corresponding benzyl ester **34** ([α]$_D$ +4.3 (c=1.04, $CHCl_3$), 47%) along with the selective deacetylation. Treatment of **34** with trifluoroacetic acid (TFA) gave the corresponding ammonium trifluoroacetate **35** which was directly subjected to the amide formation reaction using N-methylmorpholine in DMF to afford an amide **36** ([α]$_D$ -10.9 (c=1.26, $CHCl_3$), 53%). The spectral data ([α]$_D$, ^{1}H-NMR, ^{13}C-NMR and FAB-MS) of **36** were identical with those ([α]$_D$ -10.2 (c=0.98, $CHCl_3$)) of authentic **36** reported by Barrett.[3] The total synthesis of nikkomycin B (**1**) from **36** has already been achieved by Barrett.[3] Attempted reaction of **35** and **27** under the same condition as for **25** gave 10% yield of **36** along with recovery starting material **27** (66%).

In conclusion, synthetic route to the (2*S*,3*S*,4*S*)-γ-hydroxy-β-methyl-α-amino butonoic acid moiety, a common feature of the nikkomycin N-terminal acid part based on a combination of both chemical

diastereoselectivity and enzymatic enantioselectivity has been achieved. The coupling reaction of uracil polyoxin C congener **35** with the activated ester **25** gave an important Barrett's intermediate **36** for the synthesis of nikkomycin B (**1**).



a; 1) H_2/10% Pd-C 2) Boc_2O/Et_3N b; $PhCH_2OH/Ti(O\text{-}i\text{-}Pr)_4$ c; CF_3COOH (TFA) in EtOAc
d; **(2S,3S,4S)-25** or **(2S,3S,4S)-27**/N-Methylmorpholine in DMF

Scheme 6

Experimental

General. All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL EX 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS-DX 303 spectrometer. IR spectra were recorded a JASCO FT/IR-300 spectrometer. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

4-*tert*-Butyldimethylsilyloxy-benzaldehyde 6 To a well stirred solution of *p*-hydroxy- benzaldehyde **5** (20.1 g, 164 mmol) in CH_2Cl_2 (200 ml) at 0 °C, imidazole (24.5 g, 360 mmol) and *tert*-butyldimethylsilyl chloride (27.2 g, 180 mmol) was added and the whole mixture was stirred for 40 min. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was chromatographed on silica gel (300 g, *n*-hexane/EtOAc=50:1) to give **6** (32.97 g, 85%) as a colorless oil. **6**: IR (neat):1699 cm^{-1}. NMR: δ 0.25 (6H, s), 1.00 (9H, s), 6.95 (2H, d, *J*=8 Hz), 7.79 (2H, d, *J*=8 Hz), 9.89 (1H, s). HRMS (EI) Calcd. for $C_{13}H_{20}O_4Si$ (M^+; m/z) 236.1222. Found 236.1257.

(±)-Methyl (2,3-*anti*)-3-Hydroxy-3-(4-*tert*-butyldimethylsilyloxyphenyl)-2-methylpropanoate 7 and (±)-Methyl (2,3-*syn*)-3-Hydroxy-3-(4-*tert*-butyldimethylsilyloxyphenyl)-2-methylpropanoate 8 A stirred mixture of **3** (20.18 g, 85.5 mmol), methyl α-bromopropanoate (15.71 g, 94.1 mmol) and activated Zn dust [prepared from Zn (9 g)] in dry benzene (100 ml) was refluxed for 90 min. The reaction mixture was diluted with H_2O and 1M aqueous HCl, and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent provided a crude oily product, which was chromatographed on silica gel (300 g, *n*-hexane/EtOAc=20:1) to afford (±)-*syn*-**8** (14.96, 54%) as a colorless oil and (±)-*anti*-**7** (9.98g, 36%) as a colorless oil. (±)-*syn*-**8**: IR (neat):3444, 1739 cm^{-1}. NMR: δ 0.19 (6H, s), 0.98 (9H, s), 1.14 (3H, d, *J*=7 Hz), 2.75 (1H, dq, *J*=5, 7 Hz), 2.88 (1H, d, *J*=3 Hz), 3.64 (3H, s), 4.99 (1H, br. s), 6.80 (2H, d, *J*=8 Hz), 7.19 (2H, d, *J*=8 Hz). HRMS (EI) Calcd. for $C_{17}H_{28}O_4Si$ (M^+; m/z) 324.1757. Found 324.1820. (±)-*anti*-**7**: IR (neat):3464, 1739 cm^{-1}. NMR: δ 0.20 (6H, s), 0.97 (3H, d, *J*=7 Hz), 0.98 (9H, s), 2.78 (1H, dq, *J*=7, 9 Hz), 2.90 (1H, d, *J*=4 Hz), 3.73 (3H, s), 4.69 (1H, dd. J=4, 9 Hz), 6.82 (2H, d, *J*=8 Hz), 7.20 (2H, d, *J*=8 Hz). HRMS (EI) Calcd. for $C_{17}H_{28}O_4Si$ (M^+; m/z) 324.1757. Found 324.1827.

(±)-Methyl 3-(4-*tert*-Butyldimethylsilyloxyphenyl)-2-methyl-3-oxopropanoate 9 1) To a stirred solution of (±)-**8** (871 mg, 2.68 mmol) in acetone (5 ml) cooled in ice-water was added Jone's reagent (2 ml). After the reaction mixture had been stirred for 30 min at the same temperature, isopropyl alcohol (2 ml) was added and the whole mixture was stirred for 10 min. The reaction mixture was concentrated, diluted with H_2O and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane/EtOAc=100:1) to afford (±)-**9** (752 mg, 86%) as a colorless oil. (±)-**9**: IR (neat):1747,1681 cm^{-1}. NMR: δ 0.25 (6H, s), 1.00 (9H, s), 1.48 (3H, d, *J*=7 Hz), 3.68 (3H, s), 4.38 (1H, q, *J*= 7 Hz), 6.88 (2H, d, *J*=9 Hz), 7.90 (2H, d, *J*=9 Hz). HRMS (EI) Calcd. for $C_{17}H_{26}O_4Si$ (M^+; m/z) 322.1601. Found 322.1628. *Anal.* Found: C, 63.37; H, 8.35. Calcd. for $C_{17}H_{26}O_4Si$: C, 63.35; H, 8.07 %. 2) To a stirred solution of a mixture (13.33 g, 41 mmol) of (±)-**7** and (±)-**8** in acetone (60 ml) cooled in ice-water was added Jone's reagent (24 ml). After the reaction mixture had been stirred for 100 min at the same temperature, isopropyl alcohol (17.4 ml) was added and the whole mixture was stirred for 10 min. The reaction mixture was worked up by the same way as for 1) to provide (±)-**9** (11.43 g, 86%) as a colorless oil.

***n*-Bu_4NBH_4 reduction of (±)-9** To a solution of (±)-**9** (2.003 g, 6.2 mmol) in MeOH (40 ml) was added *n*-Bu_4NBH_4 (1.95 g, 7.6 mmol) under argon atmosphere at -78 °C and the reaction mixture was stirred for 24 h at the same temperature. After the addition of 1M aqueous HCl, the whole was extracted with EtOAc. The organic layer was worked up and purified by the same way as for the preparation of (±)-**7** and (±)-**8** to give (±)-**8** (97 mg, 4.8%) and (±)-**7** (1.437 g, 71.3%).

$Zn(BH_4)_2$ reduction of (±)-9 A $Zn(BH_4)_2$-Et_2O solution (6 ml) [prepared from 0.9 mol solution of $ZnCl_2$ in Et_2O (80 ml) and $NaBH_4$ (4 g) in Et_2O (300 ml)] was added to solution of (±)-**6** (109 mg, 0.34 mmol) in dry Et_2O (3 ml) under argon atmosphere at -20 °C and the reaction mixture was stirred for 4 h at the same temperature. After the addition of 1M aqueous HCl, the whole was extracted with Et_2O. The organic layer was worked up and purified by the same way as for the preparation of (±)-**7** and (±)-**8** to yield (±)-**8** (82.2 mg, 75%) and (±)-**7**

(6.9 mg, 6.2%).

(±)-3-(4-*tert*-Butyldimethylsilyloxyphenyl)-2-methyl-1,3-propane diol 10 To a suspension of $LiAlH_4$ (0.2 g, 5.2 mmol) in dry THF (10 ml) was added a solution of (±)-**7** (1.709 g, 5.2 mmol) in dry THF (35 ml) under argon atmosphere at 0 °C and the reaction mixture was stirred for 90 min at the same temperature. After the addition of H_2O (4 ml), the whole mixture was filtered with the aid of Celite and the precipitate was washed with EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (30 g, *n*-hexane/EtOAc=4:1) to give crystals (±)-**10** which was recrystallized from *n*-hexane-EtOAc to provide (±)-**10** (1.187 g, 76%) as a colorless needless. (±)-**7**: mp 78~79 °C; IR (nujol):3359, 1608 cm^{-1}. NMR (D_6-acetone): δ 0.21 (6H, s), 0.67 (3H, d, *J*= 7 Hz), 1.00 (9H, s), 1.87~1.95 (1H, m), 3.62 (2H, dt, *J*=5 Hz), 3.96 (1H, t, *J*=5 Hz), 4.49 (1H, dd, *J*=3, 8 Hz), 4.56 (1H, d, *J*=3 Hz), 6.83 (2H, d, *J*=8 Hz), 7.23 (2H, d, *J*=8 Hz). HRMS (EI) Calcd. for $C_{16}H_{28}O_3Si$ (M^+; m/z) 296.1808. Found 296.1821. *Anal.* Found: C, 65.01; H, 9.66. Calcd. for $C_{16}H_{28}O_3Si$: C, 64.86; H, 9.46 %.

(±)-1-Acetoxy-3-(4-*tert*-butyldimethylsilyloxyphenyl)-2-methyl-3-propanol 11 A mixture of (±)-**10** (2.79 g, 9.4 mmol), Ac_2O (0.96 g, 9.4 mmol) and pyridine (3 ml) was stirred for 1 h at 0 °C. The reaction mixture was diluted with 1M aqueous HCl and extracted with Et_2O. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (100 g, *n*-hexane/EtOAc=15:1~4:1) to afford (±)-**11** (1.37 g, 43%) as a colorless oil and recovered (±)-**10** (1.395 g, 50% recovery). (±)-**11**: IR (neat):3460, 1739 cm^{-1}. NMR: δ 0.20 (6H, s), 0.76 (3H, d, *J*= 7 Hz), 0.99 (9H, s), 2.08 (3H, s), 2.19~2.20 (1H, m), 2.32 (1H, br.s), 4.17 (1H, dd, *J*=5, 11 Hz), 4.27 (1H, dd, *J*=5, 11 Hz), 4.43 (1H, d, *J*=8 Hz), 6.82 (2H, d, *J*=8 Hz), 7.18 (2H, d, *J*=8 Hz). HRMS (EI) Calcd. for $C_{16}H_{30}O_4Si$ (M^+; m/z) 338.1912. Found 338.1948. *Anal.* Found: C, 64.06; H, 9.05. Calcd. for $C_{18}H_{30}O_4Si$: C, 63.91; H, 8.88.%.

HPLC analysis of the racemic alcohol (±)-10 and acetate (±)-11 by using a chiral column Two racemates (±)-**10** and (±)-**11** gave individually two well separated peaks (±)-**10**; 34 and 37 min, (±)-**11**; 16 and 18 min corresponding to each enantiomer under the following analytical conditions (column, CHIRALCEL OD (250 X 4.6 mm); eluent, *n*-hexane/EtOH=100:1; detection, UV at 254 nm; flow rate, 1 ml/min).

Enzymatic Resolution 1) A mixture of (±)-**10** (1.66 g, 5.6 mmol), isopropenyl acetate (1.6 g, 16 mmol) and lipase "Amano P" (800 mg) in isopropyl ether (100 ml) was stirred at 33 °C for 7 h. The reaction mixture was filtered with the aid of Celite and the precipitate was washed with EtOAc. The combined organic solvent was evaporated to give a residue, which was chromatographed on silica gel (60 g, *n*-hexane/EtOAc=10:1~4:1) to afford (2*R*,3*R*)-**11** (1.005 g, 53%, $[\alpha]_D^{30}$ +11.0 (c=1.88, $CHCl_3$); corresponds to 75% ee) and (2*S*,3*S*)-**10** (598 mg, 36%, $[\alpha]_D^{30}$ -20.0 (c=1.29, $CHCl_3$); corresponds to 81% ee). Enantiomeric excess (ee) of (2*R*,3*R*)-**11** and (2*S*,3*S*)-**10** was analysed by HPLC. 2) A mixture of (±)-**11** (3.06 g, 9 mmol) and lipase "Amano P" (1.5 g) in water-saturated isopropyl ether (300 ml) was stirred at 33 °C for 18 h. The reaction mixture was filtered with the aid of Celite and the precipitate was washed with EtOAc. The combined organic solvent was worked up in the same way as for the case 1) to provide a residue, which was chromatographed on silica gel (60

g, n-hexane/EtOAc=10:1~4:1) to afford (2*S*,3*S*)-**11** (1.5 g, 49%) and (2*R*,3*R*)-**10** (1.18 g, 44%). Enantiomeric excess (ee) of (2*S*,3*S*)-**11** and (2*R*,3*R*)-**10** was analysed by HPLC. 3) A mixture of (2*S*,3*S*)-**11** (77% ee, 1.43 g, 4.2 mmol) and lipase "Amano P" (0.7 g) in water-saturated isopropyl ether (150 ml) was stirred at 33 °C for 17 h. The reaction mixture was worked up in the same way as for case 1) to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane/EtOAc=10:1~4:1) to afford (2*S*,3*S*)-**11** (1.2 g, 84%, $[\alpha]_D^{31}$ -14.1 (c=0.93, $CHCl_3$); corresponds to >99% ee) and (2*R*,3*R*)-**10** (163 mg, 13%, $[\alpha]_D^{30}$ +9.81 (c=0.74, $CHCl_3$); corresponds to 37% ee). Enantiomeric excess (ee) of (2S,3*S*)-**11** and (2*R*,3*R*)-**10** was analysed by HPLC.

(2*R*)-3-(4-Hydroxyphenyl)-2-methyl-propanol 12 A solution of (2*S*,3*S*)-**10** (461 mg, 1.5 mmol) in EtOAc (6 ml) was subjected to hydrogenation at ordinary temperature and pressure in the presence of 20% $Pd(OH)_2$-C (100 mg) and 60% aqueous perchloric acid (1 drop). After hydrogenation absorption had ceased, the catalyst was filtered off and the filtrate was washed with saturated aqueous $NaHCO_3$ and saturated brine, then dried over $MgSO_4$. The organic layer was evaporated to give an oily product, which was chromatographed on silica gel (30 g, *n*-hexane/EtOAc=20:1) to afford the (2*R*)-3-(4-*tert*-butyldimethylsilyloxyphenyl)-2-methylpropanol (105 mg, 24%) as a colorless oil. To a solution of the above compound (105 mg, 0.38 mmol) in THF (5 ml) was added *n*-$Bu_4N^+F^-\cdot 3\ H_2O$ (110 mg, 0.3 mmol) and the whole mixture was stirred at rt for 30 min. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (10 g, *n*-hexane/EtOAc=5:1) to afford (2*R*)-**12** (57 mg, 91%) as a colorless oil. (2*R*)-**12**: $[\alpha]_D^{27}$ +7.41 (c=1.39, $CHCl_3$) corresponding to 81% ee; IR (neat):3350 cm^{-1}. NMR: δ 0.91 (3H, d, *J*= 7 Hz), 1.20~1.25 (1H, m), 1.86~1.94 (1H, m), 2.38 (1H, dd, *J*=7, 14 Hz), 2.65 (1H, dd, *J*=7, 14 Hz), 3.47 (1H, dd, *J*=6, 11 Hz), 3.52 (1H, dd, *J*=6, 11 Hz), 5.39 (1H, s), 6.75 (2H, d, *J*=8 Hz), 7.02 (2H, d, *J*=8 Hz). FAB MS *m/z*: 167 (M^++1).

(2*S*)-3-(4-Hydroxyphenyl)-2-methylpropanol 12 To a solution of (2*S*)-**13** (52 mg, 0.28 mmol) in EtSH (1 ml) was added to a solution of $AlCl_3$ (0.2 g, 1.5 mmol) in EtSH (1 ml) at 0 °C and the whole mixture was stirred at 0 °C for 15 min. The reaction mixture was diluted with 1M aqueous HCl and extracted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/EtOAc=5:1) to give (2*S*)-**12** (43 mg, 91%) as a colorless oil. (2*S*)-**12**: $[\alpha]_D^{22}$ -9.72 (c=1.08, $CHCl_3$) corresponding to >99% ee; MS(EI) m/z: 166 (M^+); *Anal.* Found: C, 71.66; H, 8.60. Calcd. for $C_{10}H_{14}O_2$1/10 H_2O: C, 71.48; H, 8.52 %. Other spectral data (NMR and IR) were identical with those of (2*R*)-**12**.

(2*S*,3*S*)-1-Acetoxy-3-(4-*tert*-butyldimethylsilyloxyphenyl)-3-*tert*-butyldiphenylsilyloxy-2-methylpropane 14 To a well stirred solution of (2*S*,3*S*)-**11** (2.97 g, 8.7 mmol) in CH_2Cl_2 (30 ml) at rt, imidazole (1.73 g, 25.4 mmol), *tert*-butyldiphenylsilyl chloride (5.39 g, 19.6 mmol) and 4-dimethylaminopyridine (100 mg, 0.8 mmol) was added and the whole mixture was stirred for 44 h at rt. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (100 g, *n*-hexane/EtOAc=80:1) to give **14** (4.93 g, 97%) as a colorless oil. **14**: $[\alpha]_D^{31}$ -69.6 (c=0.84, $CHCl_3$); IR (neat):1743 cm^{-1}; NMR: δ 0.18 (6H,

s), 0.68 (3H, d, *J*= 7 Hz), 0.98 (9H, s), 1.01 (9H, s), 1.88 (3H, s), 2.12~2.17 (1H, m), 3.85 (1H, dd, *J*=6, 11 Hz), 3.92 (1H, dd, *J*=6, 11 Hz), 4.60 (1H, d, *J*=6 Hz), 6.69 (2H, d, *J*=8 Hz), 7.00 (2H, d, *J*=8 Hz), 7.18~7.75 (10H, m). FAB MS *m/z*: 519 (M^+-C_4H_9). *Anal.* Found: C, 70.85; H, 8.60. Calcd. for $C_{34}H_{48}O_4Si_2$: C, 70.78; H, 8.39 %.

(2*S*,3*S*)-3-(4-*tert*-Butyldimethylsilyloxyphenyl)-3-*tert*-butyldiphenylsilyloxy-2-methylpropanol 15 To a well stirred solution of **14** (4.66 g, 8.1 mmol) in toluene (40 ml) was added 1.5M HAl(*i*-Bu)$_2$/toluene (24 ml, 36 mmol) at -78 °C under argon atmosphere and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was treated with a trace amount of H_2O and filtered. The precipitate was washed with EtOAc. The combined organic filtrate was dried over $MgSO_4$ and evaporated to afford a residue, which was chromatographed on silica gel (100 g, *n*-hexane/EtOAc=40:1) to give **15** (4.27 g, 99%) as a colorless oil. **15**: $[\alpha]_D^{31}$ -90.4 (c=1.81, $CHCl_3$); IR (neat):3419 cm^{-1}; NMR: δ 0.17 (3H, s), 0.18 (3H, s), 0.64 (3H, d, *J*= 7 Hz), 0.98 (9H, s), 1.01 (9H, s), 1.78 (1H, br. s), 1.90~2.00 (1H, m), 3.48~3.53 (2H, m), 4.56 (1H, d, *J*=7 Hz), 6.66 (2H, d, *J*=8 Hz), 6.98 (2H, d, *J*=8 Hz), 7.18~7.71 (10H, m). FAB MS *m/z*: 534 (M^+). *Anal.* Found: C, 71.98; H, 8.68. Calcd. for $C_{32}H_{46}O_3Si_2$: C, 71.91; H, 8.61 %.

Ethyl (2*S*,3*S*,4*S*)-4-(4-*tert*-Butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-3-methylbutanoate 17 and Ethyl (2*R*,3*S*,4*S*)-4-(4-*tert*-Butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-3-methylbutanoate 18 1) To a well stirred solution of oxalylchloride (1.4 ml, 16 mmol) in CH_2Cl_2 (6 ml) was added a solution of DMSO (2.4 ml, 34 mmol) in CH_2Cl_2 (3 ml) at -78 °C and the whole mixture was stirred for 15 min at the same temperature. A solution of **15** (3.724 g, 7 mmol) in CH_2Cl_2 (12 ml) was added to the above reaction mixture at -78 °C and the whole mixture was stirred at -78 °C for 40 min. Triethylamine (8.5 ml, 61 mmol) was added to the above reaction mixture at -78 °C and the reaction mixture was stirred at -78 °C for 1 h and at -20 °C for 10 min. The reaction mixture was diluted with saturated brine and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The residue was dissolved in n-hexane and filtered. The precipitate was washed with *n*-hexane and the combined filtrate was evaporated to give a crude aldehyde **16**, which was used without further purification. 2) To a solution of ethyl vinyl ether (4 ml, 41.8 mmol) in THF (8 ml) at -78 °C was added *tert*-BuLi (1.5 M in pentane, 13 ml (20.4 mmol)). The reaction mixture was stirred at -78 °C for 20 min and at -20 °C for 1 h. The generated carbanion solution (18 ml, 17.4 mmol) was added to a solution of crude aldehyde **16** in THF (10 ml) at -78 °C and the whole mixture was stirred at -78 °C for 2 h. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated. The residue was dissolved in CH_2Cl_2 (20 ml) and ozone was passed through the above solution at -78 °C for 90 min followed by adding dimethyl sulfide (6 ml). The whole reaction mixture was stirred at rt for 10 min and diluted with H_2O, extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (100 g, *n*-hexane/EtOAc=50:1) to afford (2*S*,3*S*,4*S*)-**17** (1.975 g, 47%) as a colorless oil and (2*R*,3*S*,4*S*)-**18** (462 mg, 11%) as a colorless oil. (2*S*,3*S*,4*S*)-**17**: $[\alpha]_D^{30}$ -61.7 (c=0.92, $CHCl_3$); IR (neat):3527, 1730 cm^{-1}; NMR: δ 0.14 (3H, s), 0.15 (3H, s), 0.41 (3H, d, *J*= 7 Hz), 0.96 (9H, s), 0.98 (9H, s), 1.31 (3H, t, *J*=7 Hz), 2.25~2.32 (1H, m), 2.53 (1H, d, *J*=5 Hz), 4.24 (2H, q, *J*=7 Hz), 4.54 (1H, d, *J*=9 Hz), 4.80 (1H, dd, *J*=2, 5 Hz), 6.59 (2H, d, *J*=8 Hz), 6.91

(2H, d, *J*=8 Hz), 7.18~7.63 (10H, m). FAB MS *m/z*: 549 (M^+-C_4H_9); *Anal.* Found: C, 69.26; H, 8.02. Calcd. for $C_{35}H_{50}O_5Si_2$: C, 69.26; H, 8.30 %. (2*R*,3*S*,4*S*)-**18**: $[\alpha]_D^{29}$ -74.4 (c=0.81, $CHCl_3$); IR (neat):3525, 1730 cm^{-1}; NMR: δ 0.17 (6H, s), 0.62 (3H, d, *J*= 7 Hz), 0.97 (9H, s), 1.00 (9H, s), 1.18 (3H, t, *J*=7 Hz), 2.09~2.20 (1H, m), 2.61 (1H, d, *J*=7 Hz), 3.85~4.00 (3H, m), 4.87 (1H, q, *J*=7 Hz), 6.65 (2H, d, *J*=8 Hz), 6.99 (2H, d, *J*=8 Hz), 7.20~7.72 (10H, m). FAB MS *m/z*: 549 (M^+-C_4H_9); *Anal.* Found: C, 69.17; H, 8.62. Calcd. for $C_{35}H_{50}O_5Si_2$: C, 69.26; H, 8.30 %.

Ethyl (2*R*,3*S*,4*S*)-4-(4-*tert*-Butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-2-iodo-3-methylbutanoate 19 Triphenylphosphine (3.3 g, 12.6 mmol) and imidazole (700 mg, 10.2 mmol) were added to a solution of **17** (999 mg, 1.6 mmol) in a mixed solvent (Et_2O (10 ml) and CH_3CN (10 ml)) at rt. Iodine (2.1 g, 8.3 mmol) was added to the above reaction mixture at 0 °C without light and the whole mixture was stirred at 0 °C for 30 min and at rt for 12 h. The reaction mixture was diluted with *n*-hexane and the organic layer was washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $CuSO_4$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (40 g, *n*-hexane/EtOAc=200:1) to afford (2*R*,3*S*,4*S*)-**19** (909 mg, 77%) as a colorless oil. (2*R*,3*S*,4*S*)-**19**: $[\alpha]_D^{30}$ -10.6 (c=1.05, $CHCl_3$); IR (neat):1738 cm^{-1}; NMR: δ 0.19 (6H, s), 0.92 (3H, d, *J*= 7 Hz), 0.99 (9H, s), 1.05 (9H, s), 1.19 (3H, t, *J*=7 Hz), 2.27~2.36 (1H, m), 3.63 (1H, d, *J*=11 Hz), 4.07~4.11 (2H, m), 5.06 (1H, d, *J*=4 Hz), 6.70 (2H, d, *J*=8 Hz), 6.97 (2H, d, *J*=8 Hz), 7.20~7.66 (10H, m). FAB MS *m/z*: 659 (M^+-C_4H_9).

Ethyl (2*S*,3*S*,4*S*)-2-Azido-4-(4-*tert*-butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-3-methylbutanoate 20 A mixture of (2*R*,3*S*,4*S*)-**19** (95.4 mg, 0.13 mmol), NaN_3 (40 mg, 0.6 mmol) in DMF (1 ml) was stirred at 60 °C for 1 h. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g, *n*-hexane/EtOAc=200:1) to provide (2*S*,3*S*,4*S*)-**20** (74 mg, 88%) as a colorless oil. (2*R*,3*S*,4*S*)-**20**: $[\alpha]_D^{30}$ -45.4 (c=1.21, $CHCl_3$); IR (nujol):2108, 1747 cm^{-1}; NMR: δ 0.15 (3H, s), 0.16 (3H, s), 0.41 (3H, d, *J*= 7 Hz), 0.96 (9H, s), 0.97 (9H, s), 1.32 (3H, t, *J*=7 Hz), 2.42~2.51 (1H, m), 4.22~4.30 (2H, m), 4.35 (1H, d, *J*=9 Hz), 4.70 (1H, d, *J*=2 Hz), 6.64 (2H, d, *J*=8 Hz), 6.77 (2H, d, *J*=8 Hz), 7.22~7.64 (10H, m). *Anal.* Found: C, 66.95; H, 7.78; N, 6.53. Calcd. for $C_{35}H_{49}O_4Si_2N_3$: C, 66.56; H, 7.77, N, 6.66 %.

Ethyl (2*R*,3*S*,4*S*)-4-(4-*tert*-Butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-2-chloromethylsulfonyloxy-3-methylbutanoate 21 Chloromethylsulfonyl chloride (McCl, 20 μ l, 0.22 mmol) was added to a solution of (2*R*,3*S*,4*S*)-**18** (69 mg, 0.11 mmol) in pyridine (1 ml) at 0 °C and the whole mixture was stirred at 0 °C for 10 min and at rt for 12 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with 1M aqueous HCl, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (10 g, *n*-hexane/EtOAc=20:1) to afford (2*R*,3*S*,4*S*)-**21** (75 mg, 91%) as a colorless oil. (2*R*,3*S*,4*S*)-**21**: NMR: δ 0.15 (3H, s), 0.16 (3H, s), 0.66 (3H, d, *J*=7 Hz), 0.96 (9H, s), 0.99 (9H, s), 1.19 (3H, d, *J*=7 Hz), 2.53~2.57 (1H, m), 4.06~4.20 (2H, m), 4.66 (2H, s), 4.74 (1H, d, *J*=8 Hz), 5.37 (1H, d, *J*=4 Hz), 6.61 (2H, d, *J*=8 Hz), 6.90 (2H, d, *J*=8 Hz), 7.21~7.62 (10H, m).

Ethyl (2*R*,3*S*,4*S*)-4-(4-*tert*-Butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-2-methanesulfonyloxy-3-methylbutanoate 23 Methanesulfonyl chloride (MsCl, 11 μl, 0.14 mmol) was added to a solution of (2*R*,3*S*,4*S*)-**18** (42 mg, 0.069 mmol) in pyridine (0.5 ml) at 0 °C and the whole mixture was stirred at 0 °C for 30 min and at rt for 12 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with 1M aqueous HCl, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (10 g, *n*-hexane/EtOAc=20:1) to afford (2*R*,3*S*,4*S*)-**23** (42 mg, 89%) as a colorless oil. (2*R*,3*S*,4*S*)-**23**: NMR: δ 0.16 (6H, s), 0.70 (3H, d, *J*=7 Hz), 0.97 (9H, s), 1.00 (9H, s), 1.19 (3H, d, *J*=7 Hz), 2.45~2.53 (1H, m), 3.04 (3H, s), 4.04~4.20 (2H, m), 4.77 (1H, d, *J*=7 Hz), 5.08 (1H, d, *J*=5 Hz), 6.93 (2H, d, *J*=8 Hz), 6.95 (2H, d, *J*=8 Hz), 7.20~7.63 (10H, m).

Ethyl (2*S*,3*S*,4*S*)-2-Azido-4-*tert*-butyldiphenylsilyloxy-4-(4-hydroxyphenyl)-3-methylbutanoate 22 and (2*S*,3*S*,4*S*)-20 1) A mixture of (2*R*,3*S*,4*S*)-**21** (156 mg, 0.21 mmol), NaN_3 (82 mg, 1.26 mmol) in DMF (2 ml) was stirred at 60 °C for 20 h. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (12 g, *n*-hexane/EtOAc=200:1) to provide (2*S*,3*S*,4*S*)-**20** (69 mg, 50%) from *n*-hexane/EtOAc=100:1 eluate, starting material **21** (9 mg, 5% recovery) from *n*-hexane/EtOAc=20:1 eluate and (2*S*,3*S*,4*S*)-**22** (39 mg, 35%) as a colorless oil from *n*-hexane/EtOAc=10:1 eluate. (2*R*,3*S*,4*S*)-**22**: $[\alpha]_D^{25}$ -40.5 (c=2.04, $CHCl_3$); IR (neat):3416, 1740 cm^{-1}; NMR: δ 0.43 (3H, d, *J*= 7 Hz), 0.97 (9H, s), 1.32 (3H, t, *J*=7 Hz), 2.42~2.51 (1H, m), 4.22~4.30 (2H, m), 4.37 (1H, d, *J*=9 Hz), 4.69 (1H, d, *J*=3 Hz), 6.61 (2H, d, *J*=8 Hz), 6.92 (2H, d, *J*=8 Hz), 7.21~7.62 (10H, m). FAB MS *m/z*: 516 (M^+-1), 460 (M^+-C_4H_9). *Anal.* Found: C, 66.77; H, 7.25; N, 7.51. Calcd. for $C_{29}H_{35}O_4SiN_3$.1/2H_2O: C, 66.13; H, 6.89, N, 7.98 %. 2) A mixture of (2*R*,3*S*,4*S*)-**23** (42 mg, 0.061 mmol), NaN_3 (20 mg, 0.3 mmol) in DMF (1 ml) was stirred at 60 °C for 2 h and at 80 °C for 16 h. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g, *n*-hexane/EtOAc=10:1) to provide (2*S*,3*S*,4*S*)-**22** (16 mg, 49%) as a colorless oil.

Silylation of (2*S*,3*S*,4*S*)-22 To a well stirred solution of (2*R*,3*S*,4*S*)-**22** (135 mg, 0.26 mmol) in DMF (2 ml) was added *tert*-butyldimethyl chloride (48 mg, 0.7 mmol) and imidazole (61 mg, 0.4 mmol) and the whole mixture was stirred at 40 °C for 5 h. The reaction mixture was worked up in the same way as for the preparation of **6** to afford (2*S*,3*S*,4*S*)-**20** (139 mg, 84%) as a colorless oil.

3-Buten-1-yl (2*S*,3*S*,4*S*)-2-Azido-4-(4-*tert*-butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-3-methylbutanoate 24 A mixture of (2*R*,3*S*,4*S*)-**20** (72 mg, 0.11 mmol), 3-buten-1-ol (0.22 ml, 2.6 mmol) and Ti(O-*i*-Pr)$_4$ (12 μl, 0.04 mmol) was refluxed for 2 h. The reaction mixture was diluted with 1M aqueous HCl and extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (8 g, *n*-hexane/EtOAc=200:1) to afford (2*S*,3*S*,4*S*)-**24** (68 mg,

90%) as a colorless oil. (2*S*,3*S*,4*S*)-**24**: $[\alpha]_D^{27}$ -40.7 (c=1.38, $CHCl_3$); IR (nujol):2108, 1743 cm^{-1}; NMR: δ 0.15 (3H, s), 0.16 (3H, s), 0.39 (3H, d, *J*= 7 Hz), 0.95 (9H, s), 0.97 (9H, s), 2.42~2.48 (3H, m), 4.22~4.30 (2H, m), 4.34 (1H, d, *J*=9 Hz), 4.70 (1H, d, *J*=3 Hz), 5.07~5.16 (2H, m), 6.63 (2H, d, *J*=8 Hz), 6.92 (2H, d, *J*=8 Hz), 7.23~7.62 (10H, m). FAB MS *m/z*: 656 (M^+-1). MS(EI) *m/z*: 600 (M^+-C_4H_9); *Anal.* Found: C, 66.90; H, 7.77; N, 6.13. Calcd. for $C_{37}H_{51}O_4Si_2N_3$. 1/2 H_2O: C, 66.62; H, 7.85, N, 6.30 %.

4-Nitrophenyl (2*S*,3*S*,4*S*)-2-Azido-4-(4-*tert*-butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-3-methylbutanoate 25 and Acyl urea 26 Ozone was passed through a solution of (2*S*,3*S*,4*S*)-**3** (237 mg, 0.36 mmol) in a mixed solvent (CH_2Cl_2 (5 ml) and MeOH (5 ml)) at -78 °C for 30 min, then Me_2S (2 ml) was added to the ozonolysed product and the reaction mixture was stirred for 4 h at rt. DBU (57 μ l, 0.38 mmol) was added to the above reaction mixture and it was acidified with 0.1M aqueous citric acid, extracted with CH_2Cl_2, dried over $MgSO_4$ and evaporated. To the crude acid in THF (5 ml) was added 4-nitrophenol (76 mg, 0.54 mmol) and DCC (89 mg, 0.43 mmol) and the reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with ether, filtered, and washed with saturated brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (50 g, *n*-hexane/EtOAc=100:1) to give (2*S*,3*S*,4*S*)-**25** (112 mg, 43%) as a pale yellow oil and acyl urea **26** (78 mg, 27%) as a colorless amorphous. (2*S*,3*S*,4*S*)-**25**: $[\alpha]_D^{27}$ -33.8 (c=1.24, $CHCl_3$); IR (neat):2109, 1768 cm^{-1}; NMR: δ 0.17 (6H, s), 0.55 (3H, d, *J*=7 Hz), 0.97 (9H, s), 0.98 (9H, s), 2.59~2.64 (1H, m), 4.43 (1H, d, *J*=9 Hz), 4.97 (1H, d, *J*=3 Hz), 6.67 (2H, d, *J*=8 Hz), 6.98 (2H, d, *J*=8 Hz), 7.24~7.68 (12H, m), 8.30 (2H, d, *J*=9 Hz). FAB MS *m/z*: 763 (M^++K), 747 (M^++Na), 667(M^+-C_4H_9). (2*S*,3*S*,4*S*)-**26**: mp 46~49 °C; $[\alpha]_D^{28}$ -25.3 (c=0.93, $CHCl_3$); IR (KBr):2932, 2857, 2105, 1708 cm^{-1}; NMR: δ 0.14 (3H, s), 0.15 (3H, s), 0.73 (3H, d, *J*=7 Hz), 0.96 (9H, s), 1.01 (9H, s), 1.12~1.95 (20H, m), 2.53 (1H, m), 3.60 (1H, m), 4.00 (1H, m), 4.24 (1H, m), 4.50 (1H, d, *J*=7 Hz), 6.61 (2H, d, *J*=8 Hz), 6.86 (2H, d, *J*=8 Hz), 7.21~7.61 (10H, m). *Anal.* Found: C, 68.04; H, 8.57; N, 8.33. Calcd. for $C_{46}H_{67}O_4Si_2N_5$: C, 68.19; H, 8.33, N, 8.64 %.

2-Nitrophenyl (2*S*,3*S*,4*S*)-2-Azido-4-(4-*tert*-butyldimethylsilyloxyphenyl)-4-*tert*-butyldiphenylsilyloxy-3-methylbutanoate 27 Ozone was passed through a solution of (2*S*,3*S*,4*S*)-**3** (40 mg, 0.06 mmol) in a mixed solvent (CH_2Cl_2 (1 ml) and MeOH (1 ml)) at -78 °C for 30 min, then Me_2S (0.5 ml) was added to the ozonolysed product and the reaction mixture was stirred for 4 h at rt. DBU (13 μ l, 0.087 mmol) was added to the above reaction mixture and it was acidified with 0.1M aqueous citric acid, extracted with CH_2Cl_2, dried over $MgSO_4$ and evaporated. To the crude acid in THF (1 ml) was added 2-nitrophenol (14 mg, 0.10 mmol) and DCC (20 mg, 0.097 mmol) and the reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with ether, filtered, and washed with saturated brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (20 g, *n*-hexane/EtOAc=50:1) to give (2*S*,3*S*,4*S*)-**27** (20 mg, 44%) as a pale yellow oil and acyl urea **26** (26 mg, 53%). (2*S*,3*S*,4*S*)-**27**: $[\alpha]_D^{27}$ -24.6 (c=0.67, $CHCl_3$); IR (neat):2109, 1777 cm^{-1}; NMR: δ 0.17 (6H, s), 0.56 (3H, d, *J*=7 Hz), 0.97 (9H, s), 0.98 (9H, s), 2.65~2.73 (1H, m), 4.40 (1H, d, *J*=9 Hz), 5.14 (1H, d, *J*=2 Hz), 6.67 (2H, d, *J*=8 Hz), 6.98 (2H, d, *J*=8 Hz), 7.23~7.71 (13H, m), 8.17 (1H, dd, *J*=2,8 Hz). FAB MS *m/z*: 763 (M^++K), 747 (M^++Na), 667(M^+-C_4H_9).

1-(Methyl 2',3'-di-O-acetyl-5'-N-*tert*-butoxycarbonylamino-D-allofuranosyluronate)uracil 33 A mixture of **32** (669 mg, 1.62 mmol) and 10% Pd-C (67 mg) in MeOH (20 ml) was subjected to catalytic hydrogenation at ordinary temperature and pressure and the reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give the residue. A mixture of the residue, di-*tert*-butyl-dicarbonate (0.4 ml, 1.7 mmol) and Et_3N (0.24 ml, 1.72 mmol) in dioxane (10 ml) was stirred at rt for 5 h. The reaction mixture was diluted with H_2O, extracted with EtOAc and the organic layer was washed with 10% aqueous citric acid, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (30 g, *n*-hexane/EtOAc=2:3) to afford **33** (518 mg, 65%) as a colorless amorphous. **33**: mp 90~93 °C; $[\alpha]_D^{26}$ +29.7 (c=1.095, $CHCl_3$); IR (KBr):3311, 1700 cm^{-1}; NMR: δ 1.45 (9H, s), 2.10 (3H, s), 2.11 (3H, s), 3.81 (3H, s), 4.41 (1H, t, *J*=4 Hz), 4.79 (19H, br. s), 5.27 (1H, t, *J*=6 Hz), 5.46 (1H, t, *J*=6 Hz), 5.66 (1H, d, *J*=8 Hz), 5.77 (1H, dd, *J*=2, 8 Hz), 6.01(1H, d, *J*=6 Hz), 7.35 (1H, d, *J*=8 Hz), 9.68 (1H, br, s); *Anal.* Found: C, 49.56; H, 5.55; N, 8.58. Calcd. for $C_{20}H_{27}O_{11}N_3$: C, 49.48; H, 5.61, N, 8.66 %.

1-(Benzyl 5'-N-*tert*-butoxycarbonylamino-5'-deoxy-β-D-allofuranosyluronate)uracil 34 A stirred mixture of **33** (459 mg, 0.94 mmol), benzyl alcohol (2 ml, 19.3 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (0.09 ml, 3 mmol) in benzene (15 ml) was refluxed for 12 h. The reaction mixture was diluted with 1M aqueous HCl and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (40 g, EtOAc) to afford **34** (215 mg, 47%) as a colorless prisms and starting material **33** (108 mg, 23% recovery). **34**: mp 172~175 °C (from EtOAc); $[\alpha]_D^{28}$ +4.3 (c=1.04, MeOH); IR (KBr):3353 (br), 1726 cm^{-1}; NMR: δ 1.44 (9H, s), 4.16 (2H, t, *J*=5 Hz), 4.22~4.27 (1H, m), 4.54 (1H, d, *J*=5 Hz), 5.14 (1H, d, *J*=13 Hz), 5.23 (1H, d, *J*=13 Hz), 5.54 (1H, d, *J*=8 Hz), 5.82 (1H, d, *J*=5 Hz), 7.28~7.38 (5H, m), 7.44 (1H, d, *J*=8 Hz); *Anal.* Found: C, 54.98; H, 5.55; N, 8.82. Calcd. for $C_{22}H_{27}O_9N_3$: C, 55.34; H, 5.70, N, 8.80 %.

1-[5'-[(2*S*,3*S*,4*S*)-2-Azido-4-4-*tert*-butyldimethylsilyloxyphenyl-4-*tert*-butyldiphenylsilyloxy-3-methylbutanoyl]amino-5'-deoxy-β-allofuranosyluronic acid]uracil Benzyl Ester 36 To a solution of **34** (46 mg, 0.096 mmol) in EtOAc (1 ml) at 0 °C was added trifluoroacetic acid (5 ml) and the reaction mixture was stirred at rt for 30 min. The reaction mixture was evaporated and azeotroped with EtOAc. To the residue **35** in DMF (0.1 ml) was added N-methylmorpholine (21 μl, 0.19 mmol) followed by (*2S,3S,4S*)-**25** (84 mg, 0.11 mmol) in DMF (0.5 ml). The reaction mixture was stirred at rt for 3 d and it was acidified with 1M aqueous $NaHSO_4$, diluted with saturated brine, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (20 g, Et_2O) to give **36** (49 mg, 53% based on **34**) as a pale yellow foam. **36**: $[\alpha]_D^{28}$ -10.9 (c=1.26, $CHCl_3$); IR (neat): 3408 (br), 2107, 1683 cm^{-1}; ^{1}H-NMR(acetone-d_6): δ 0.18 (3H, s), 0.19 (3H, s), 0.47 (3H, d, *J*= 7 Hz), 0.96 (9H, s), 0.98 (9H, s), 2.65 (1H, m), 2.86 (3H, br. s), 4.19 (1H, t, *J*=5 Hz), 4.35 (1H, m), 4.49 (2H, m), 4.69 (1H, d, *J*=4 Hz), 4.95 (1H, dd, *J*=6, 8 Hz), 5.16 (2H, d, *J*=7 Hz), 5.55 (1H, dd, *J*=2, 8 Hz), 5.84 (1H, d, *J*=5 Hz), 6.70 (2H, d, *J*=8 Hz), 7.01 (2H, d, *J*=8 Hz), 7.28~7.49 (14H, m), 8.05 (1H, d, *J*=8 Hz); ^{13}C-NMR(125 MHz, acetone-d_6): δ 170.5, 169.8, 163.2, 156.0, 151.5, 141.7, 136.8, 136.7, 136.6, 135.7, 134.6, 134.1, 130.5, 130.4, 129.8, 129.2, 129.0, 128.4, 128.1, 120.4, 103.2, 91.3, 84.1, 78.0, 73.6, 71.5, 67.6, 65.0, 55.1, 44.5, 27.4, 26.0, 20.0, 18.8, 11.0. FAB MS *m/z*: 985 (M^++Na), 905 (M^+-C_4H_9).

1-[5'-[(2*S*,3*S*,4*S*)-2-Azido-4-4-*tert*-butyldimethylsilyloxyphenyl-4-*tert*-butyldiphenylsilyloxy-3-methylbutanoyl]amino-5'-deoxy-β-allofuranosyluronic acid]uracil Benzyl Ester 36 To a solution of **34** (40 mg, 0.083 mmol) in EtOAc (1 ml) at 0 °C was added trifluoroacetic acid (5 ml) and the reaction mixture was stirred at rt for 30 min. The reaction mixture was evaporated and azeotroped with EtOAc. To the residue **35** in DMF (0.2 ml) was added N-methylmorpholine (21 μl, 0.19 mmol) followed by (*2S,3S,4S*)-**27** (65 mg, 0.090 mmol) in DMF (1.5 ml). The reaction mixture was stirred at rt for 3 d and it was acidified with 1M aqueous $NaHSO_4$, diluted with saturated brine, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (20 g, Et_2O) to give recovery **27** (43 mg, 66%) from *n*-hexane/Et_2O (1:1) eluate and **36** (8 mg, 10% based on **34**) as a pale yellow foam from Et_2O eluate. **36**: $[\alpha]_D^{28}$ -10.0 (c=0.4, $CHCl_3$). NMR spectra of the present **36** was identical with those of the above mentioned **36**.

Acknowledgement: The authors are grateful to Professor Anthony G. M. Barrett, Imperial College of Science, for generously providing the spectral data (^{1}H-NMR, ^{13}C-NMR, FAB-MS and IR) of (2*S*,3*S*,4*S*)-**24** and **36**. This work was supported by a grant for the Biodesign Research Program from the Institute of Physical and Chemical Research (RIKEN) to H. A. and a Grant-in Aid for Scientific Research (No. 10672002) from the Ministry of Education, Science and Culture of Japan to H. A.

References and Notes

1. (a) Dähn, U., Hagenmaier, H., Höhne, M., König, W. A., Wolf, G., Zähner, H. *Arch. Microbiol.* **1976**, *107*, 249. (b) Hagenmaier, H., Keckeisen, A., Zähner, H., König, W. A. *Liebigs Ann. Chem.* **1979**, 1494-1502. (c) König, W. A., Hass, W., Dehler, W., Fiedler, H. P., Zähner, H. *Liebigs Ann. Chem.* **1980**, 622-628. (d) Hagenmaier, H., Keckeisen, A., Dehler, W., Fiedler, H. P., Zähner, H., König, W. A. *Liebigs Ann. Chem.* **1981**, 1018-1024.
2. (a) Kobinata, K., Uramoto, M., Nishii, M., Kusakabe, H., Nakamura, G., Isono, K. *Agric. Biol. Chem.* **1980**, *44*, 1709-1711. (b) Uramoto, M., Kobinata, K., Isono, K., Higashijima, T., Miyazawa, T., Jenkins. E. E., McCloskey, J. A. *Tetrahedron lett.* **1980**, *21*, 3395-3398. (c) Uramoto, M., Kobinata, K., Isono, K., Higashijima, T., Miyazawa. T., Jenkins, E. E., McCloskey. J. A. *Tetrahedron* **1982**, *38*, 1599-1608.
3. (a) Barrett, A. G. M., Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 5818-5821. (b) Barrett, A. G. M., Lebold, S. A. *J. Org. Chem.* **1991**, *56*, 4875-4884.
4. Hahn, H., Heitsch, H., Rathmann, R., Zimmerman, G., Bormann, C., Zähner, H., König, W. A. *Liebigs Ann. Chem.* **1987**, 803-807.
5. (a) Hass, W., König, W. A. *Liebigs Ann. Chem.* **1982**, 1615-1622. (b) Jäger, W., Grund, H., Buss, V. Schwab, W., Müller, I., Schohe, R., Franz, R., Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039-1054. (c) Banks, B., Barrett, A. G. M., Russell, M. A., Williams, D. J. *J. Chem. Soc. Chem. Commun.* **1983**, 873-875. (d) Melnick, M. J., Weinreb, S. M., *J. Org. Chem.* **1988**, *53*, 850-854. (e) Barrett, A. G. M., Dhanak, D., Lebold, S. A., Russell, M. A. *J. Org. Chem.* **1991**, *56*, 1894-1901.
6. (a) Zimmerman, G., Hass, W., Faash, H., Schmalle, H., König, W. A. *Liebigs Ann. Chem.* **1985**, 2165-2177. (b) Barluenga, J., Viado, A. L., Aguilar, E., Fustero, S., Olano, B. *J. Org. Chem.* **1993**, *58*,

5972-5975. (c) Mukai, C., Miyakawa, M., Hanaoka, M. *Synlett* **1994**, 165-166. (d) Mandville, G., Ahma, M., Bloch, R. *J. Org. Chem.* **1996**, *61*, 1122-1124. (e) Kapeller, H., Jary, W. G., Hayden, W., Griengl, H. *Tetrahedron:Asymmetry* **1997**, *8*, 245-251. (f) Tamura, O., Mita, N., Kusaka, N., Suzuki, H., Sakamoto, M. *Tetrahedron Lett.* **1997**, *38*, 429-432.

7. Taniguchi, M., Fujii, H., Oshim, K., Uchimoto, K. *Tetrahedron* **1993**, *49*, 11169-11182.
8. Nakata, T., Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641-1644.
9. (a) Akita, H., Chen, C-Y., Nagumo, S. *Tetrahedron:Asymmetry* **1994**, *5*, 1207-1210. (b) Akita, H., Chen, C-Y., Nagumo, S. *J. Chem. Soc. Perkin Trans.* **1995**, 2159-2164. (c) Chen, C-Y., Nagumo, S., Akita, H. *Chem. Pharm. Bull.* **1996**, *44*, 2153-2156.
10. Hiranuma, S., Shimizu, T., Nakata, T., Kajimoto, T., Wong, C-H. *Tetrahedron Lett.* **1995**, *36*, 8247-8250.
11. (a) Khorana, H. G. *Chem & Ind.* **1955**, 1087. (b) Muramatsu, I., Hagitani, H. *Nippon Kagaku Zasshi* **1959**, *80*, 1497-1501.
12. Kato, K., Chen, C-Y., Akita, H. *Synthesis* **1998**, in press.