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Pd(II)-mediated Intramolecular Acetal Formation Applied to a Substrate Prepared from D-Glucose : A Formal Synthesis of Enantiomeric Paniculide B

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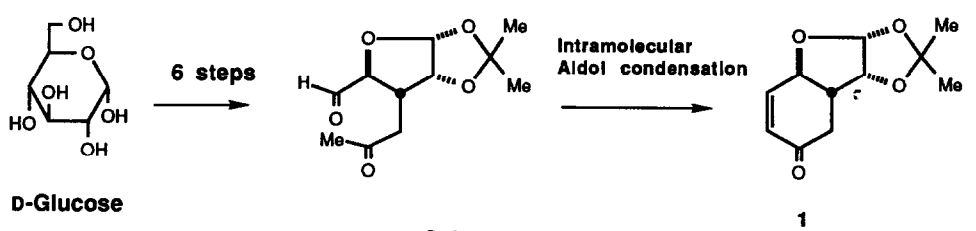
ABSTRACT The enantiomerically pure and densely functionalized cyclohexenol **3**, readily prepared from D-glucose, was subjected to the Pd(II)-mediated intramolecular acetal formation Further functional groups adjustment of the resulting acetal **4** effected an access to the key synthetic intermediate **2** of paniculide B, a bisabolene-like sesquiterpene The present work constitutes an enantiospecific formal synthesis of this natural product.

In previous papers,[1,2] we have reported a practical preparation of (1*R*,2*R*,7*R*,9*R*)-11,11-dimethyl-8,10,12-trioxatricyclo[7 3 0 $0^{2,7}$]dodec-5-en-4-one **1** (Scheme 1) The preparation of **1** relies on the intramolecular aldol condensation of a substrate readily prepared from D-glucose The potency of **1** as an enantiomerically pure building block was evidenced through highly stereoselective synthesis of a number of 5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrols and 2-amino-5-(hydroxymethyl)-1,3,4-cyclohexanetriols (so-called "pseudo-sugars" and "pseudo-aminosugars") [2,3] In this article, we disclose another synthetic utility of **1** through an enantiospecific synthesis of the key synthetic intermediate **2** of puniculide B (Scheme 2) Our synthesis of **2** features a Pd(II)-mediated five-membered cyclic acetal formation of a densely functionalized cyclohexenol **3**, derived from **1**, in order to construct the *cis*-fused γ-lactone part of **2**



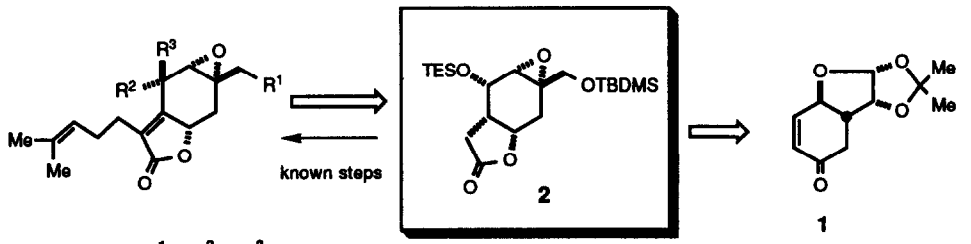
D-Glucose

1

Scheme 1

Paniculides A-C (Scheme 2) were isolated from the tissue cultures of *Andrographis paniculata* Nees (Acanthaceae) by Overton and co-workers in 1968, and the structures including relative stereochemistries were proposed by them [4] These highly oxygenated sesquiterpene epoxy-lactones are classified to a family of bisabolene-like sesquiterpenes, represented by bisabolangelone [5,6] Later, the absolute stereochemistry of paniculide B was established as depicted by an X-ray crystal analysis of its bis(*p*-bromobenzoate) [7] The

synthetic studies on these sesquiterpenes have been also investigated by several groups. Two total syntheses and two formal syntheses of paniculides have been published so far. Those are the total syntheses of paniculides A-C by Smith and Richmond based on the photochemical [2+2]cycloaddition for construction of the bicyclic framework, [8] and the total synthesis of paniculide A by Yoshikoshi and co-workers based on the vinylfuranone annelation strategy developed by them [9] Two formal syntheses of paniculides were reported by Baker and co-workers (paniculides B and C),[10] and by Jacobi and co-workers (paniculide A).[11] Although each total synthesis is conceptually intriguing, all of the reported syntheses led to the racemic natural products We wish to disclose herein an enantiospecific synthesis of the key intermediate **2**, which was successfully transformed into panuculide B by Smith and Richmond [8] The intermediate **2** includes all the necessary stereogenic centers in paniculide B synthesis Our synthesis constitutes a formal synthesis of enantiomeric paniculide B

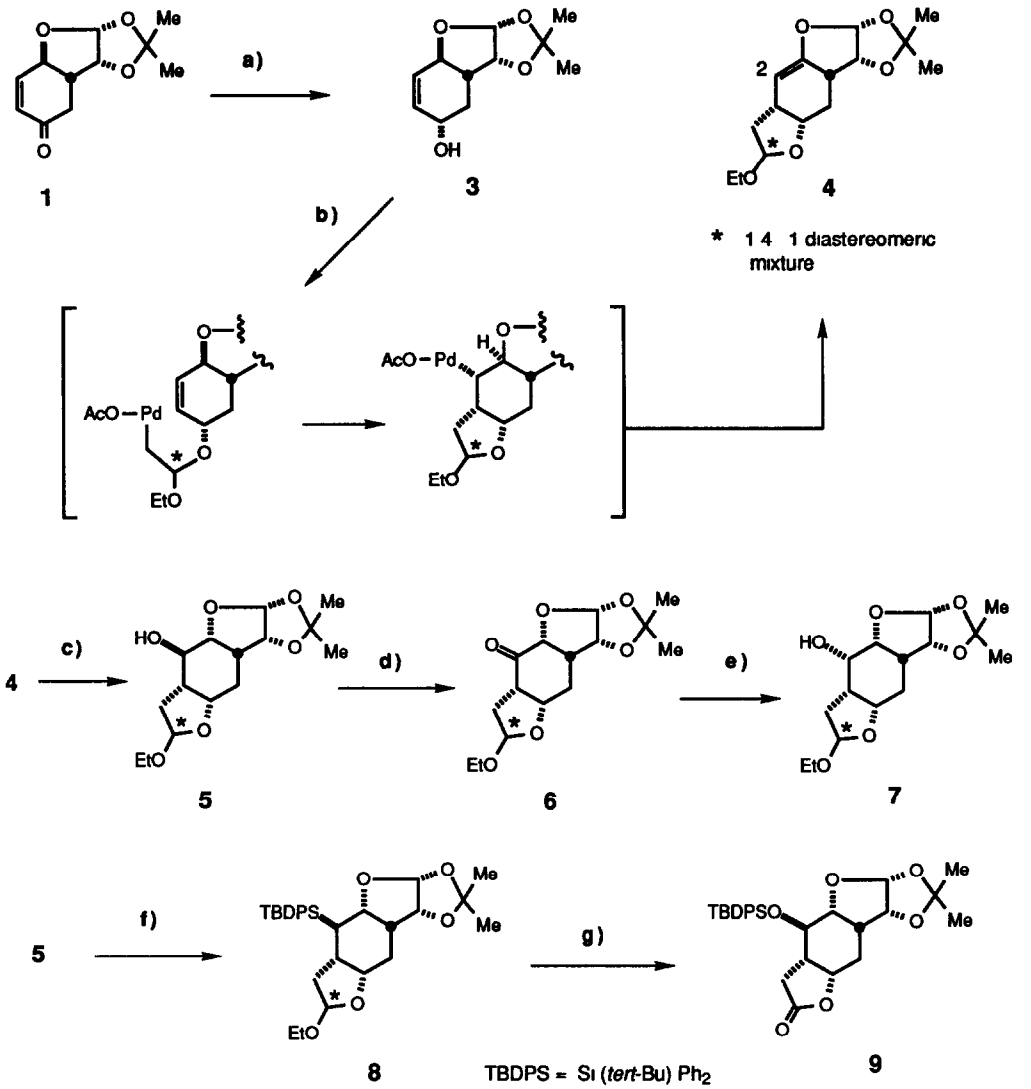


Paniculide	R^1	R^2	R^3
A	H	OH	H
B	OH	OH	H
C	OH	=O	

Scheme 2.

RESULTS AND DISCUSSION

The enantiomerically pure building block **1** was reduced according to the Luche's procedure[12] providing the cyclohexenol **3** possessing an α–hydroxyl group with high stereoselectivity [more than 20 1 based on its ^{1}H NMR (400 MHz) spectral analysis] (Scheme 3) Comparing with the diisobutylaluminum hydride reduction of **1** reported previously,[3] which resulted in the formation of ca. 7 1 mixture of the α- and β-hydroxyl derivatives, the diastereoselectivity was improved under the Luche's conditions. The inseparable mixture **3** was used directly The pivotal five-membered cyclic acetal formation for construction of the *cis*-fused γ-lactone in **2** was accomplished efficiently by taking advantage of the Pd(II)-mediated Oshima[13] and Larock[14] reactions Thus the mixture **3** in ethyl vinyl ether was exposed to palladium(II) acetate As a result, a cyclic acetal **4** as a 1 4 1 diastereomeric mixture on the acetal carbon was isolated in 62% yield from **1** The ratio of the diastereomers was estimated by ^{1}H NMR (270 MHz) spectral analysis Under these conditions, compound **1** and a cyclohexene derivative were also isolated in 15% and 13% yield, respectively The structure of the latter was tentatively assigned based on its ^{1}H NMR analysis (see Experimental) The previous reports[15,16] support the formation of ketones from secondary alcohols under the Pd(II)-catalyzed oxidation in the presence of O_2



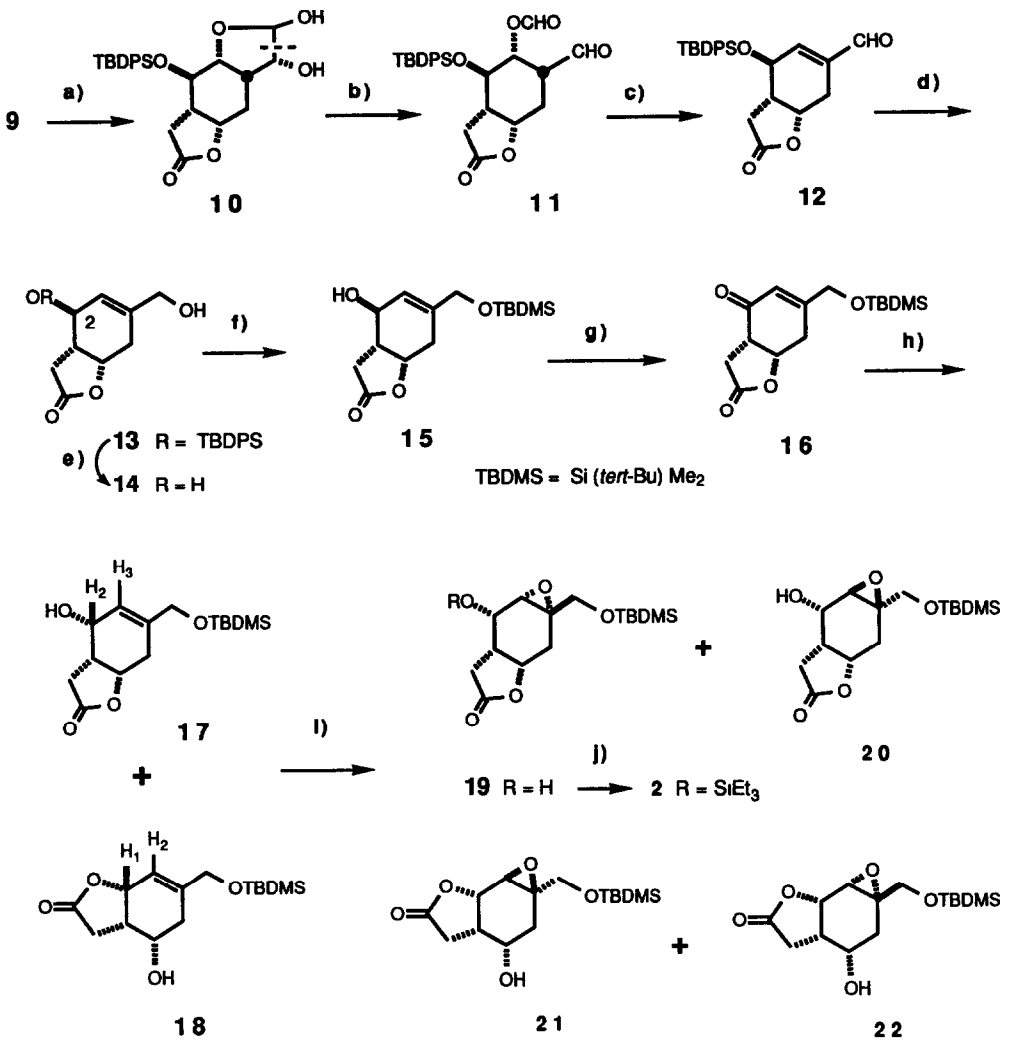
a) $NaBH_4$ / $CeCl_3 \cdot 7H_2O$ / MeOH / -10 °C, b) ethyl vinyl ether / $Pd(OAc)_2$, then pyridine (62% for 2 steps), c) B_2H_6-THF / THF / 0 °C followed by H_2O_2 / aq NaOH / 0 °C (74%), d) PCC / MS-4A / CH_2Cl_2, e) $NaBH_4$ / MeOH (74% or 70% for each diastereomer), f) *tert*-$BuPh_2SiCl$ / imidazole / DMF / 55 °C (68%, 8% recovery of **5**), g) Jones reagent / acetone / 0 °C (73%, 12% recovery of the diastereomeric mixture **8**)

Scheme 3.

The diastereomers **4** were separated cleanly in a small scale experiment, but we could not determine the stereochemistry on the acetal carbon for each diastereomer This Pd(II)-mediated acetal formation is considered to proceed as shown in Scheme 3 (in bracket). The organopalladium intermediate, formed by addition of the initially formed acyclic acetal to the double bond, allowed smoothly a *syn*-elimination to give the double bond migrated product **4** The introduced double bond in **4** would facilitate an introduction of an oxygen functionality at C-2 Kraus and Thurston have utilized recently the similar acetal formation strategy in their hydroxysemperoside degluside synthesis [17]

Introduction of an oxygen functionality to the trisubstituted olefin in the mixture **4** was accomplished by regio- and stereoselective hydroboration with B_2H_6-THF at 0 °C followed by H_2O_2 oxidation, providing a β-hydroxyl derivative **5** as a diastereomeric mixture on the acetal carbon in 74% combined yield When each diastereomer **4** was treated with the same conditions, each diastereomerically homogeneous **5** was obtained in good yield. In respect of the stereoselectivity of the hydroboration, it is anticipated that the attack of borane proceeds favorably from the less hindered convex-face of the bicyclo[4 3 0]non-2-ene structure Each diastereomer **5** was subjected to pyridinium chlorochromate (PCC) oxidation followed by $NaBH_4$ reduction of the resulting ketone **6** providing the corresponding α-hydroxyl derivative **7** in 74 and 70% yield, respectively Although these hydroxyl derivatives **7** were expected to be promising intermediates for puniculides synthesis, we encountered the difficulty in protection of the hydroxyl group It is likely that the hydroxyl group in **7** faces to hindered concave-side of the bicyclic structure Finally, we turned our synthetic plan to use the β-hydroxy derivative **5** For a proper protection of the hydroxyl group, *tert*-butyldiphenylsilyl group was best of choice The introduction of this bulky silyl group could be achieved under forcing conditions giving the silyl ether **8** in 68% yield (8% of **5** was recovered) The other ethers (*tert*-butyldimethylsilyl or methoxymethyl) or benzoyl ester were found not to be tolerant under advanced reaction steps such as Jones oxidation, acid hydrolysis or deprotection This diastereomeric mixture of the silyl ether **8** was then subjected to Jones oxidation in acetone at 0 °C to give rise to a γ-lactone **9** in 73% yield. Although 12% of the mixture **8** was recovered, a prolonged reaction time decreased the yield of **9**

A four-step functional group transformation from **9** provided a bicyclic γ-lactone **13** in 59% overall yield via glycol cleavage of a diol **10**, β-elimination of the resulting aldehyde **11** and successive hydride reduction of the resulting allylic aldehyde **12** (Scheme 4) The next requisite was stereochemical inversion of the carbon at C-2 in **13** For this purpose, the silyl group in **13** was removed in usual manner giving **14** The primary hydroxyl group in **14** was protected as a *tert*-butyldimethylsilyl ether giving mono silyl ether **15** in 76% yield from **13** PCC oxidation of **15** smoothly afforded **16** which was reduced under the Luche conditions [12] As a result, an α-hydroxyl derivative **17** and its γ-lactone migrated product **18** were obtained as a ca 1 2 to 1 (270 MHz ^{1}H NMR analysis) inseparable mixture in 79% combined yield from **15** Compound **15** was also obtained in 8% yield As anticipated, the hydride attack occurred preferentially from the less hindered β-side of **16** To our surprise, the γ-lactone migration took place substantially The structure of **18** was ascertained by decoupling experiment in ^{1}H NMR analysis (see, Experimental) We searched other reduction conditions for lessening the lactone-migration Super-hydride^R ($LiEt_3BH$) (THF, -75°C) and K-Selectride^R (THF, -65 °C) gave the lactone migrated product **18** exclusively Also, $NaBH_3CN$ (aq HCl-MeOH, pH 4, 0 °C) gave ca 7 5 mixture of **17** and **18**, but in a low yield We conclude that this observed facile lactone migration is an inevitable phenomenon for the bicyclic system like **17** The mixture of **17** and **18** was subjected to mCPBA-epoxidation according to



a) 60% aq AcOH / 90 °C, b) $NaIO_4$ / aq MeOH, c) 0 5 mol eq of DBU / PhH / 55 °C, d) 1 0 mol eq of $NaBH_4$ / $CeCl_3 \cdot 7H_2O$ / MeOH (59% overall yield for 4 steps), e) TBAF/ THF, f) *tert*-$BuMe_2SiCl$ / DMAP -Et_3N / CH_2Cl_2 (76% yield for 2 steps), g) PCC / MS-4A / CH_2Cl_2, h) 0 45 mol eq of $NaBH_4$ / 1 0 mol eq of $CeCl_3 \cdot 7H_2O$ / MeOH / 0 °C (as a ca 1 2 1 mixture, combined yield of 79% for 2 steps), i) mCPBA / $NaHCO_3$ / CH_2Cl_2 (combined yield of 93%), j) Et_3SiCl /Et_3N / CH_2Cl_2 (95%)

Scheme 4

the Smith's conditions [8] As a result, a mixture of four epoxides **19-22** was obtained in a combined yield of 93% The epoxidation proceeded with at most ca 3 . 1 stereoselectivity as mentioned by the Smith's group [8] The desired epoxide **19** was isolated as the main product in 42% yield after silica gel chromatographic separation The structure of **19** was determined by comparison of its ^1H NMR spectrum with the reported data for the

recemic **19**,[8] and ascertained by conversion it into **2** The α-epoxide **19** was the hydroxy-directed epoxidation product of **17** On the other hand, an inseparable mixture of **20** and **21** was obtained in 42% combined yield The ratio of **20** and **21** was estimated to be approximately 1 · 2 5 based on its ^{1}H NMR analysis. The fourth epoxide **22** derived from **18** was isolated in 9% yield. Besides, the structures of **21** and **22** were confirmed by direct comparison with authentic samples prepared from the diastereomerically pure **18**, which in turn was obtained by the Super-Hydride^R reduction of **16** m-Chloroberbenzoic acid (mCPBA)-epoxidation of **18** gave **21** and **22** in 65% and 23% yield, respectively In this case, the epoxidation took place from the less hindered β-side of **18** preferentially Comparing the ^{1}H NMR spectrum of the mixture **20** and **21** with that of pure **21**, the ratio of the former was determined. The silylation of **19**[8] provided the key synthetic intermediate **2** in 95% yield ^{1}H NMR spectral comparison of our **2** (270 MHz) with that of racemic **2** (250 MHz), kindly provided by Professor Smith, revealed their identity By the three-step manipulation, 4-methyl-3-pentenyl side chain introduction, selenenyl-ation-oxidation, and deprotection established by the Smith's group for racemic series,[8] the intermediate **2** would be transformed into natural paniculide B

In conclusion, we have achieved the formal synthesis of paniculide B in natural enantiomeric form The effectiveness of the Pd(II)-mediated intramolecular acetal formation strategy for *cis*-fused lactone construction is also verified through the present work

EXPERIMENTAL

Melting points are uncorrected Specific rotations in $CHCl_3$ were measured using JASCO Model DIP-370 polarimeter in a 10 mm cell IR spectra were recorded using JASCO Model A-202 spectrometer (neat) or Hitachi Model 225 spectrometer (KBr-disk or $CHCl_3$ solution) ^{1}H NMR spectra were recorded using JEOL EX-90 (90 MHz) , JEOL GX-270 (270 MHz), or JEOL JNM-GX 400 FT spectrometer (400 MHz) in a $CDCl_3$ solution with tetramethysilane as an internal standard Microanalyses were carried out using YANACO Model MT-3 analyzer Thin-layer chromatography (TLC) was performed with a glass plate coated Kieselgel 60 F_{254} (Merck) Crude reaction mixtures were chromatographed on Silicagel 60 K070 (Katayama Chemicals) or Silicagel C-300 (Wako Pure Chemicals)

Unless otherwise specified, reactions were carried out at room temperature Reactions involving organometallics or moisture-sensitive reagents were performed under an argon atmosphere Organic extracts were dried over anhydrous Na_2SO_4 Solvents were removed by concentration in vacuo using an evaporater with bath at 35-45 °C

Solvents were dried and distilled prior to use as follows acetone ($CaSO_4$), CH_2Cl_2 (CaH_2), pyridine (NaH), Et_3N ($CaSO_4$), DMF (CaH_2), and THF ($LiAlH_4$, then Na-benzophenone)

(1*R*,5*R*,9*R*,10*S*,12*S*,14*R*)-14-Ethoxy-7,7-dimethyl-4,6,8,13-tetraoxatetracyclo-[10.3.0.0^{3,10}.0^{5,9}]pentadec-2-ene and its 14*S* epimer (4).

To a stirred solution of **1** (3 50 g, 16 7 mmol) in MeOH (70 ml) was added $CeCl_3$·$7H_2O$ (6 22 g, 16 7 mmol) at -10 °C After the mixture was stirred for 15 min, $NaBH_4$ (316 mg, 8 35 mmol) was added. The mixture was further stirred for 20 min and diluted with H_2O (200 ml) This was extracted with AcOEt (150 ml x

3). The combined extracts were dried and concentrated to give crude **3** (3.62 g) which was used directly ^1H NMR (400 MHz) spectrum of the crude **3** showed that less than 5% of the β-allylic alcohol coexisted.

A mixture of thus obtained **3** (3.62 g) and palladium(II) acetate (3.75 g, 16 7 mmol) in ethyl vinyl ether (16 7 ml) was stirred for 2 h Hexane (160 ml) and pyridine (3 ml) were added to the mixture The resulting black precipitates were removed through a Celite-pad and washed well with CH_2Cl_2 The combined filtrate and washing were concentrated with the aid of toluene The residue was chromatographed on silica gel (AcOEt/hexane=1/6) 2 93 g (62%) of the diastereomeric mixture **4** was obtained as pale yellow crystals 0 522 g (15%) of **1**, and 0 418 g (13%) of (1*R*,2*R*,7*R*,9*R*)-11,11-dimethyl-8,10,12-trioxatricyclo-[7 3 0 $0^{2,7}$]dodec-4-ene were also isolated The structure of the latter was assigned by its spectral data R_f 0.73 (AcOEt/hexane=1/2), IR (neat) 2990, 2925, 1640, 1440, 1370, 1305, 1250 cm^{-1}, ^1H NMR (400 MHz) δ 1 34, 1 51 (each s, each 3H), 1.56-1.64 (m, 1H), 2 10-2.57 (m, 4H), 3 87 (dt, 1H, J=5 4, 10 3 Hz), 4.63 (t, 1H, J=3 9 Hz), 5 61-5 63 (m, 1H), 5 70-5 72 (m, 1H), 5 87 (d, 1H, J=3.9 Hz)

In a small scale experiment, the mixture **4** was cleanly separated **4** having R_f 0 60 (AcOEt/hexane=1/2) mp 97 0-98 0 °C, $[\alpha]_D^{21}$ -84 5° (c 1 07), IR (KBr) 2980, 2960, 2860, 1700, 1450, 1380, 1330, 1260 cm^{-1}, ^1H NMR (400 MHz) δ 1.19 (t, 3H, J=7 1 Hz), 1 39, 1 45 (each s, each 3H), 1 60-1 70 (m, 2H), 2 02-2 12 (m, 2H), 2 57-2 63 (m, 1H), 3.05-3 10 (m, 1H), 3 42, 3.74 (each dq, each 1H, J=9 5, 7 1 Hz), 4 38 (ddd, 1H, J=5 4, 7 8, 11 7 Hz), 4 63 (dd, 1H, J=3 2, 4 4 Hz), 4 98 (t, 1H, J=2 9 Hz), 5 13 (d, 1H, J=4 4 Hz), 5 99 (d, 1H, J=3 2 Hz) Anal calcd for $C_{15}H_{22}O_5$ C, 63 81, H, 7 85 Found C, 63 61, H, 7 53 **4** having R_f 0 53 (AcOEt/hexane=1/2) as a colorless oil $[\alpha]_D^{21}$ +51 8° (c 1 62), IR (neat) 2980, 2940, 1700, 1460, 1370, 1350, 1325, 1240 cm^{-1}: ^1H NMR (400 MHz) δ 1 21 (t, 3H, J=7 1 Hz), 1 40, 1 48 (each s, each 3H), 1 67 (ddd, 1H, J=5 4, 11 2, 13 2 Hz), 2 02-2 07 (m, 2H), 2 43 (ddd, 1H, J=5 9, 8 8, 13 2 Hz), 2 57-2 62 (m, 1H), 2 82-2 86 (m, 1H), 3 47, 3 80 (each dq, each 1H, J=9 5, 7 1 Hz), 4 22-4 28 (m, 1H), 4 62-4 64 (m, 1H), 4 97 (t, 1H, J=2 9 Hz), 5 20 (t, 1H, J=5 6 Hz), 5 99 (d, 1H, J=2 9 Hz) Anal calcd for $C_{15}H_{22}O_5$ C, 63 81, H, 7 85 Found C, 63 57, H, 7 57

(1*R*,2*R*,3*R*,5*R*,9*R*,10*R*,12*S*,14*R*)-14-Ethoxy-7,7-dimethyl-4,6,8,13-tetraoxatetracyclo-[10.3.0.$0^{3,10}$.$0^{5,9}$]pentadecan-2-ol and its 14*S* epimer (5).

To a stirred solution of the diastereomeric mixture **4** (2 93 g, 10 4 mmol) in THF (60 ml) was added B_2H_6-THF (1 0 M solution in THF, 26 0 ml, 26 0 mmol) The mixture was stirred at 0 °C for 1 5 h, and H_2O (26 ml) and 3 N aqueous NaOH (26 ml) were added After the mixture was stirred for 20 min at room temperature, 35% aqueous H_2O_2 (24 5 ml) was added The mixture was stirred at 0 °C for 17 h The reaction was quenched with saturated aqueous Na_2SO_3 (30 ml) and diluted with saturated brine (30 ml) and H_2O (100 ml) The whole was extracted with AcOEt (150 ml x 3) The combined extracts were dried and concentrated The residue was chromatographed on silica gel (acetone/$PhCH_3$=1/6). 2 31 g (74%) of **5**, the diastereomeric mixture on the acetal carbon, was obtained as a colorless oil, which was gradually crystallized upon standing

By the same reaction conditions, **4** having R_f 0 60 (AcOEt/hexane=1/2) gave **5** having R_f 0 51 (AcOEt) mp 104 0-105 5 °C, $[\alpha]_D^{21}$ -108 7° (c 1 03), IR (KBr) 3480, 2970, 2920, 1380, 1240 cm^{-1} ^1H NMR (270 MHz) δ 1 18 (t, 3H, J=7 0 Hz), 1 33, 1 55 (each s, each 3H), 1 7-2 0 (m, 3H), 2 25-2 60 (m, 4H), 3 43, 3 70 (each dq, each 1H, J=9 5, 7 0 Hz), 3 6-3 9 (m, 3H), 4 31 (ddd, 1H, J=5 5, 8 8, 12 1 Hz), 4 62 (dd, 1H, J=3 3, 6 0 Hz), 5 18 (d, 1H, J=4 8 Hz), 5 83 (d, 1H, J=3 3 Hz) Anal cacld for $C_{15}H_{24}O_6$ C, 59 99, H, 8 05 Found C, 60 18, H, 7 94 **4** having R_f 0 53 (AcOEt/hexane=1/2) gave **5** having R_f 0 42 (AcOEt) mp 72 5-73 5 °C,

$[\alpha]_D^{20}$ +66 4° (c 1 94), IR (KBr) 3450, 2970, 2930, 2910, 1480, 1230 cm^{-1}, ^1H NMR (270 MHz) δ 1 18 (t, 3H, J=7 0 Hz), 1 35, 1 59 (each s, each 3H), 1 85-2 25 (m, 5H), 2 4-2.5 (m, 1H), 2.64 (br s, 1H), 3.39 (dq, 1H, J=9 2, 7 0 Hz), 3 7-3 8 (m, 2H), 4 06 (t, 1H, J=9 9 Hz), 4 37 (ddd, 1H, J=6.2, 8.8, 11.7 Hz), 4 63 (dd, 1H, J=3 5, 6 2 Hz), 5.13 (dd, 1H, J=2 0, 4 2 Hz), 5.82 (d, 1H, J=3.5 Hz) Anal. calcd for $C_{15}H_{24}O_6$: C, 59 99, H, 8.05 Found C, 60.22, H, 7 85

(1*R*,2*S*,3*R*,5*R*,9*R*,10*R*,12*S*,14*R*)-14-Ethoxy-7,7-dimethyl-4,6,8,13-tetraoxatetracyclo-[10.3.0.0^{3,10}.0^{5,9}]pentadecan-2-ol and its 14*S* epimer (7).

The diastereomer **5** having R_f 0.51 (AcOEt) (33 mg, 0.11 mmol), PCC (113 mg, 0 53 mmol) were dissolved in CH_2Cl_2 (1 ml), and molecular sieves (4A, 48 mg) was added The mixture was stirred for 3.5 h, then the whole was put on a short silica gel column The column was eluted with ether, and the 2-keto derivative **6** (26 mg) was obtained by concentration of the eluate. R_f 0 52 (acetone/$PhCH_3$=1/3), IR (neat) 1730 cm^{-1}

To a solution of thus obtained **6** (26 mg) in MeOH (1 ml) was added $NaBH_4$ (4.8 mg, 0 13 mmol). After the mixture was stirred for 30 min, IR-120 (H^+) resin was added for neutralization The resin was removed, and the filtrate was concentrated. The residue was chromatographed on silica gel (AcOEt/$PhCH_3$=1/3) to give **7** (25 mg, 74%) R_f 0 60 (AcOEt/$PhCH_3$=2/1), IR (neat) 3500, 2940, 2910, 2880, 1375 cm^{-1}, ^1H NMR (270 MHz) δ 1 19 (t, 3H, J=7 1 Hz), 1 37, 1 59 (each s, each 3H), 1.87-2 15 (m, 3H), 2 30-2 60 (m, 3H), 3.01 (d, 1H, J=2.6 Hz), 3 45, 3 71 (each dq, each 1H, J=9 7, 7 1 Hz), 4 05 (dd, 1H, J=2 9 Hz), 4 10-4 19 (m, 1H), 4 70 (dd, 1H, J=3 7, 7 0 Hz), 5 20 (d, 1H, J=4 0 Hz), 5 86 (d, 1H, J=3 7 Hz)

Analogously, the diastereomer **5** having R_f 0 42 (AcOEt) (32 mg) was subjected to PCC oxidation followed by $NaBH_4$ reduction to give 23 mg (70%) of **7** having R_f 0 37 (AcOEt/$PhCH_3$=2/1) IR (neat) 3460, 2980, 2940, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1 21 (t, 3H, J=7 0 Hz), 1 36, 1 65 (each s, each 3H), 1 95-2 05 (m, 1H), 2 2-2 5 (m, 5H), 3 47, 3 83 (each dq, each 1H, J=9.5, 7 0 Hz), 3 74 (d, 1H, J=3.3 Hz), 4 00-4 08 (m, 2H), 4 24 (ddd, 1H, J=5 9, 8 4, 12 1 Hz), 4 69 (dd, 1H, J=3 7, 6 6 Hz), 5 13-5 15 (m, 1H), 5 86 (d, 1H, J=3 7 Hz)

(1*R*,2*R*,3*R*,5*R*,9*R*,10*R*,12*S*,14*R*)-14-Ethoxy-7,7-dimethyl-2-(*tert*-butyldiphenylsilyloxy)-4,6,8,13-tetraoxatetracyclo[10.3.0.0^{3,10}.0^{5,9}]pentadecane and its 14*S* epimer (8).

The diastereomeric mixture **5** (2 28 g, 7 6 mmol), *tert*-butylchlorodiphenylsilane (7 09 ml, 30 4 mmol) and imidazole (3 09 g, 45 4 mmol) were dissolved in DMF (45 ml) The mixture was stirred at 55 °C for 13 h, then diluted with AcOEt (200 ml) This was washed with 0 5 N aq HCl (100 ml) , saturated aq $NaHCO_3$ (100 ml x 5) and saturated brine (100 ml x 3) successively The organic layer was dried and concentrated. The residue was chromatographed on silica gel (AcOEt/hexane=1/8) 2 79 g (68%) of **8**, as a diastereomeric mixture on the acetal carbon, was obtained as a colorless oil 0 184 g (8%) of **5** was recovered **8** R_f 0 56 (AcOEt/$PhCH_3$=1/5), IR (neat) 2940, 2860, 1590, 1470, 1430, 1370 cm^{-1}, ^1H NMR (90 MHz) δ 1 05 (s, 9H), 1 05-1 4 (m, 9H), 1 5-2 5 (m, 6H), 3 2-4 4 (m, 5H), 4 57 (dd, 1H, J=3 7, 6 8 Hz), 4 89 (d, 1H, J=4 5 Hz), 5 52 , 5 62 (each d, total 1H, each J=3 7 Hz), 7 3-7 8 (m, 10H) Anal calcd for $C_{31}H_{42}O_6Si$ C, 69 11, H, 7 86 Found C, 69 32, H, 7 79

(1*R*,2*R*,3*R*,5*R*,9*R*,10*R*,12*S*)-7,7-Dimethyl-2-(*tert*-butyldiphenylsilyloxy)-4,6,8,13-tetraoxatetrocyclo[10.3.0.0^{3,10}.0^{5,9}]pentadecan-14-one (9).

To a stirred solution of the diastereomeric mixture **8** (2.79 g, 5 2 mmol) in acetone (100 ml) was added Jones reagent (2 67 M, 5 83 ml, 15.6 mmol) at 0 °C The mixture was stirred at 0 °C for 2 5 h, then 2-propanol (3 ml) was added The resulting dark-green solids were removed through a Celite-pad and washed with AcOEt (300 ml). The combined filtrate and washing were concentrated to ca. half volume This was washed with H_2O (30 ml x 2), saturated $NaHCO_3$ (20 ml), and saturated brine (30 ml) successively The organic layer was dried and concentrated The residue was chromatographed on silica gel (AcOEt/$PhCH_3$=1/8) 1 93 g (73%) of **9** was obtained as a colorless oil 0 334 g (12%) of **8** was recovered. **9** Rf 0 52 (AcOEt/$PhCH_3$=1/3), $[\alpha]_D^{27}$ -28 1° (c 0.86), IR (neat) 2940, 2860, 1780, 1590, 1480, 1430, 1380, 1250 cm^{-1}, ^{1}H NMR (270 MHz) δ 1 05 (s, 9H), 1 23 1 28 (each s, each 3H), 1.58-1 72 (m, 1H), 1 90-2.17 (m, 2H), 2 30-2 63 (m, 3H), 3 86 (t, 1H, J=9 0 Hz), 4 01 (t, 1H, J=9 0 Hz), 4 60 (dd, 1H, J=3 7, 7 0 Hz), 4 58-4.70 (m, 1H), 5 67 (d, 1H, J=3 7 Hz), 7 32-7.46, 7 65-7 76 (m, total 10H) Anal Calcd for $C_{29}H_{36}O_6Si$ C, 68 47, H, 7 13 Found C, 68 85, H, 7 33

(1*S*,2*S*,6*S*)-4-Hydroxymethyl-2-(*tert*-butyldiphenylsilyloxy)-7-oxabicyclo[4.3.0]non-3-en-8-one (13).

A solution of **9** (1 89 g, 3 7 mmol) in 60% aqueous AcOH (40 ml) was heated at 90 °C for 35 min The solvents were removed by concentration with the aid of toluene and ethanol to give crude de-O-isopropylidene derivative **10** (1 84 g) as a colorless oil, which was used without purification Rf 0 35 (AcOEt/$PhCH_3$=1/1).

To a stirred solution of the crude **10** (1 84 g) in MeOH (37 ml) was added an aqueous solution (22 ml) of $NaIO_4$ (2 71 g, 12 7 mmol) The mixture was stirred for 2 h The resulting white precipitates were removed by filtration and washed well with MeOH The combined filtrate and washing were concentrated to ca 20 ml volume The remainder was diluted with AcOEt (90 ml) and washed with saturated brine (15 ml x 2) The organic layer was dried and concentrated to give crude **11** (1 76 g) as a colorless oil, which was used without purification. Rf 0.42 (EtOH/$PhCH_3$=1/8)

A solution of the crude **11** (1 76 g) in benzene (35 ml) in the presence of 1,8-diazabicyclo[5 4 0]undec-7-ene (DBU) (0 28 ml, 1 87 mmol) was heated at 55 °C for 6 5 h The mixture was diluted with AcOEt (100 ml), washed with 0 5 N aqueous HCl (20 ml), saturated aqueous $NaHCO_3$ (20 ml x 2) and saturated brine (20 ml x 2) The organic layer was dried and concentrated to give α,β-unsaturated aldehyde **12** (1 51 g) as a pale yellow oil, which was used without purification Rf 0 68 (EtOH/$PhCH_3$=1/4), IR (neat) 3070, 2940, 2860, 1780, 1690, 1590, 1470, 1430, 1360, 1250 cm^{-1}, ^{1}H NMR (270 MHz) δ 1 09 (s, 9H), 2 2-2 8 (m 4H), 2.98 (dd, 1H, J=7 0, 17 8 Hz), 4 25-4 28 (m, 1H), 4 77 (ddd, 1H, J=4 4, 6 9, 6 9 Hz), 6 69 (br s, 1H), 7 35-7 51, 7 58-7 75 (m, total 10H), 9 33 (s, 1H)

To a stirred solution of the crude **12** (1 51 g) in MeOH (30 ml) were added $CeCl_3$·$7H_2O$ (1 39 g, 3 73 mmol) and, after 10 min, $NaBH_4$ (62 mg, 1 6 mmol) at 0 °C The mixture was stirred at 0 °C for 25 min and quenched by addition of H_2O (10 ml) After warming to room temperature, the mixture was diluted with H_2O (60 ml) The whole was extracted with AcOEt (100 ml x 3) The combined extracts were dried and concentrated The residue was chromatographed on silica gel (AcOEt/hexane=1/2) 0 929 g (59%) of **13** was obtained as a colorless oil Rf 0 45 (AcOEt/hexane=1/1), $[\alpha]_D^{27}$ +71 9° (c 1 03), IR (neat) 3440, 3070, 2940, 2860, 1780, 1590, 1470, 1430, 1360 cm^{-1}, ^{1}H NMR (270 MHz) δ 1 06 (s, 9H), 1 57 (br s, 1H), 2 11 (dd, 1H, J=6 2, 18 0 Hz), 2 22 (dd, 1H, J=3 8, 17 3 Hz), 2 45 (dd, 1H, J=9 5, 18 0 Hz), 2 67-2.80 (m, 2H), 3 98 (s, 2H), 4 15 (br t,

1H, J=4 0 Hz), 4 89 (ddd, 1H, J=4 0, 6 2, 7.3 Hz), 5 75 (dt, 1H, J=3.7, 1.5 Hz), 7 36-7 47, 7.62-7 67 (m, total 10H) Anal calcd for $C_{25}H_{30}O_4Si$ C, 71.05, H, 7 15 Found C, 70 86, H, 7 07

(1*S*,2*S*,6*S*)-2-Hydroxy-4-(*tert*-butyldimethylsilyloxy)methyl-7-oxabicyclo[4.3.0]non-3-en-8-one (15).

To a stirred solution of **13** (695 mg, 1 64 mmol) in THF (14 ml) was added tetrabutylammonium fluoride (1 M solution in THF, 2 46 ml, 2.46 mmol). The mixture was stirred for 1 h and concentrated. The residue was purified on a short silica gel column (EtOH/$PhCH_3$=2/7) to give 316 mg of the de-O-silyl derivative **14** as a colorless oil R_f 0 23 (EtOH/$PhCH_3$=1/4)

To a stirred solution of thus obtained **14** (316 mg) in CH_2Cl_2 (6 ml) were added *tert*-butylchlorodimethylsilane (304 mg, 2 02 mmol), 4-dimethylaminopyridine (300 mg) and Et_3N (0 35 ml) After the mixture was stirred for 2 h, the silylating reagent (50 mg) was added. The mixture was further stirred for 45 min and diluted with AcOEt (50 ml) This was washed with H_2O (30 ml), 0 5 N aqueous HCl (15 ml), saturated aqueous $NaHCO_3$ (15 ml) and saturated brine (15 ml) successively The organic layer was dried and concentrated The reidue was chromatographed on silica gel (acetone/$PhCH_3$=1/4) 374 mg (76%) of **15** was obtained as a colorless oil, which gradually crystallized upon standing at -5 °C R_f 0 69 (EtOH/$PhCH_3$=1/3), mp 37 5-38 5 °C; $[\alpha]_D^{27}$ +14 9° (c 1 31), IR (KBr) 3445, 2955, 2930, 2855, 1765, 1470, 1420, 1360, 1255 cm^{-1}, ^1H NMR (270 MHz) δ 0 08 (s, 6H), 0 92 (s, 9H), 1 80 (br s, 1H), 2 22-2 30 (m, 1H), 2 49-2 82 (m, 4H), 4 08 (s, 2H), 4 06-4 12 (m, 1H), 4 88 (dt, 1H, J=3 7, 6 8 Hz), 5 91-5 94 (m, 1H) Anal calcd for $C_{15}H_{26}O_4Si$ C, 60 36, H, 8 78 Found C, 60 13, H, 8 53

(1*S*,2*R*,6*S*)-2-Hydroxy-4-(*tert*-butyldimethylsilyloxy)methyl-7-oxabicyclo[4.3.0]non-3-en-8-one (17) and (1*R*,5*S*,6*S*)-5-hydroxy-3-(*tert*-butyldimethylsiyloxy)methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (18).

A mixture of **15** (262 mg, 0 88 mmol), PCC (748 mg, 3 47 mmol) and molecular sieves (385 mg) in CH_2Cl_2 (5 ml) was stirred for 1 h The mixture was put on a short silica gel coulmn The column was eluted with ether The α,β-unsaturated ketone **16** (228 mg) was obtained by concentration of the eluate, which was reduced directly **16** R_f 0 54 (acetone/$PhCH_3$=1/3), IR (neat) 2960, 2930, 2860, 1780, 1670, 1470, 1460, 1415, 1360 cm^{-1}, ^1H NMR (270 MHz) δ 0 10 (s, 6H), 0 92 (s, 9H), 2 71-3 16 (m, 5H), 4 26 (s, 2H), 5 04-5 09 (m, 1H), 6 32 (t, 1H, J=1 5 Hz)

To a stirred solution of thus obtained **16** (228 mg) in MeOH (20 ml) was added $CeCl_3 \cdot 7H_2O$ (334 mg, 0 90 mmol) After 15 min, $NaBH_4$ (15 mg, 0 40 mmol) was added bit by bit for 20 min The mixture was stirred at 0 °C for 50 min and then diluted with H_2O (30 ml), extracted with AcOEt (60 ml x 3) The combined extracts were dried and concentrated The resdiue was chromatographed on silica gel (Silicagel C-300, AcOEt/hexane=1/2) 206 mg (79% combined yield) of 1 2 :1 inseparable mixture of **17** and **18** was obtained as a colorless oil, which was directly subjected to epoxidation 22 mg (8%) of **15** was also obtained The mixture of **17** and **18** R_f 0 41 (acetone/$PhCH_3$=1/3), ^1H NMR (270 MHz) δ 0 07, 0 08 (each s, total 6H), 0 91, 0 92 (each s, total 9H), 2 23-2 95 (m, 5H), 4 08, 4 09 (each s , total 2H), 4 08-4 14 , 4 33-4 40 (each m, total 1H), 4 90 (ddd, J=2 7, 6 0, 7 5 Hz, ca 0 5 H), 4 96-5 01 (m, ca 0 5 H), 5 90-5 93, 5 94-5 99 (each m, total 1H) When the miltiplets attributable to the vinyl protons (H-3 of **17** and H-2 of **18**) at δ 5 90-5 93 and 5 94-5 99

were simultaneously irradiated, both of the peaks at δ 4 33-4 40 (H-2 of **17**) and at δ 4.96-5 01 (H-1 of **18**) changed to doublet like signals These results indicate that a ring carbon bearing a hydroxyl group and a ring carbon bearing an acyloxy group (i. e , γ-lactone) are both adjacent to double bond.

Reduction of 16 using Super-Hydride^R. Exclusive Formation of 18.

The α,β-unsaturated ketone **16** (7 8 mg, 26 μmol), which was prepared as described above, was dissolved in THF (1 ml) To this was added Super-Hydride^R (Aldrich, 1 0 M solution in THF, 75 μl, 75 μmol) at -75 °C The mixture was stirred at -75 °C for 3 5 h and quenched by addition of 2 drops of H_2O This was diluted with H_2O (3 ml) and extracted with AcOEt (10 ml x 3) The combined extracts were dried and concentrated The residue was chromatographed on silica gel to give 5 4 mg (70%) of **18**. ^{1}H NMR (270 MHz) of **18** revealed its diastereomeric homogeneity ^{1}H NMR (270 MHz) δ 0 08 (s, 6H), 0 92 (s, 9H), 1 65-1 72 (br s, 1H) 2 17-2 27 (m, 2H), 2 56-2 81 (m, 3H), 4 09 (s, 2H), 4 09-4 13 (m, 1H), 4 96-5 00 (m, 1H), 5 97-5 99 (m, 1H)

Epoxidation of the Mixture 17 and 18. (1*S*,3*S*,7*S*,8*S*,9*S*)- (19) and (1*R*,3*S*,7*S*,8*S*,9*R*)-8-Hydroxy-1-(*tert*-butyldimethylsilyloxy)methyl-4,10-dioxatricyclo[7.1.0.0^{3,7}]decan-5-one (20), and (1*R*,2*S*,6*S*,7*S*,9*R*)- (21) and (1*S*,2*S*,6*S*,7*S*,9*S*)-7-hydroxy-9-(*tert*-butyldimethylsilyloxy)methyl-3,10-dioxatricyclo[7.1.0.0^{2,6}]decan-4-one (22).

To a solution of the mixture **17** and **18** (195 mg, 0 65 mmol) in CH_2Cl_2 (15 ml) were added mCPBA (162 mg, 0 94 mmol) and $NaHCO_3$ (26 mg) The mixture was stirred at 5 °C for 20 h and then at room temperature for 26 h Then mCPBA (90 mg) and $NaHCO_3$ (45 mg) were added, and the mixture was further stirred for 5 h To the mixture was added saturated aqueous Na_2SO_3 (8 ml), and this was diluted with AcOEt (120 ml) The whole was washed with H_2O (8 ml), saturated $NaHCO_3$ (16 ml) and saturated brine (16 ml) successively The organic layer was dried and concentrated. The residue was chromatographed on silica gel repeatedly (Silicagel C-300, AcOEt/hexane=1/1) 87 mg (42%) of **19** was obtained as a colorless oil, which crystallized upon standing at -5 °C 85 mg (42% of combined yield) of 1 2 5 inseparable mixture (estimated by its ^{1}H NMR spectrum) of **20** and **21** was obtained as a colorless oil 19 mg (9%) of **22** was obtained as white needles 6 mg (3%) of **18** was recovered **19** R_f 0 24 (AcOEt/hexane=1/2), mp 56 0-57 0 °C, $[\alpha]_D^{21}$ -12 4° (c 0 98), IR ($CHCl_3$) 3440, 2960, 2930, 2860, 1760, 1465, 1415, 1365, 1255 cm^{-1}, ^{1}H NMR (270 MHz) δ 0 05, 0 06 (each s, each 3H), 0 88 (s, 9H), 2 05 (dd, 1H, J=5 5, 16 3 Hz), 2 36 (dd, 1H, J=1 8, 16 1 Hz), 2 42-2 57 (m, 2H), 2 96-3 09 (m, 2H), 3 30 (s, 1H), 3 67 (ABq, 2H, J=11 7 Hz), 4 29 (d, 1H, J=6 3 Hz), 4 79 (ddd, 1H, J=1.8, 5 5, 9 9 Hz) Anal calcd for $C_{15}H_{26}O_5Si$ C, 57 30, H, 8 33 Found C, 56 99, H, 8 17 The mixture of **20** and **21** R_f 0 56 (AcOEt/hexane=1/2), ^{1}H NMR (270 MHz) δ 0 07, 0 08 (each s, each 3H), 0 90 (s, 9H), 2 04-2 34, 2 49-2 74 (each m, each 3H), 3 27 (s, for **21**), 3 31 (d, J=4 Hz for **20**), 3 58, 3 70 (ABq, J=11 4 Hz for **21**), 3 60, 3 80 ABq, J=10 7 Hz for **20**), 4 02 (ddd, J=3 5, 4 4, 6 6 Hz for **21**), 4 37 (t, J=3 7 Hz for **20**), 4 69-4 77 (m for **20**), 4 85 (d, J=7 0 Hz for **21**) **22** R_f 0 29 (AcOEt/hexane=1/2), mp 120 0-121 0 °C, $[\alpha]_D^{21}$ +23 0° (c 0 42), IR ($CHCl_3$) 3500, 3010, 2950, 2920, 2850, 1780, 1470, 1410, 1360, 1330 cm^{-1}, ^{1}H NMR (270 MHz) δ 0 07, 0 08 (each s, each 3H), 0 90 (s, 9H), 1 96 (dd, 1H, J=3 5, 15 6 Hz), 2 39-2 49 (m, 2H), 2 69-2 71 (m, 2H), 3 66 (d, 1H, J=4 0 Hz), 3 75 (s, 2H), 3 77-3 80 (m, 1H), 4 98 (dd, 1H, J=4 2, 7 5 Hz) Anal calcd for $C_{15}H_{26}O_5Si$ C, 57 30, H, 8 33 Found C, 57 11, H, 8 06

Epoxidation of 18. Formation of 21 and 22.

5 4 mg of the diastereomerically homogeneous **18** was oxidized with mCPBA (4 0 mg, 2 8 mol equiv) as described above Silica gel chromatography of the reaction mixture gave 3 7 mg (65%) of **21** and 1 3 mg (23%) of **22** **21** as a colorless oil IR ($CHCl_3$) 3450, 2950, 2930, 2860, 1775, 1460, 1255 cm^{-1}, ^1H NMR (270 MHz) δ 0 07, 0 08 (each s, each 3H), 0.90 (s, 9H), 1 60 (br s, 1H), 2.05-2.21, 2 52-2 73 (each m, 2H, 3H), 3 26 (s 1H), 3 53, 3 72 (ABq, each 1H, J=11.0 Hz), 4.01-4 06 (m, 1H), 4.85 (d, 1H, J=6.6 Hz).

(1*S*,3*S*,7*S*,8*S*,9*S*)-8-(Triethylsilyloxy)-1-(*tert*-butyldimethylsilyloxy)methyl-4,10-dioxatricyclo[7.1.0.$0^{3,7}$]decan-5-one (2).

4-Dimethylaminopyridine (7.6 mg) was dissolved in CH_2Cl_2 (0.5 ml). To this were added Et_3N (65 μl) and chlorotriethylsilane (65 μl, 0 38 mmol) After the mixture was stirred for 10 min, a CH_2Cl_2 solution (3 ml) of **19** (39 mg, 0 12 mmol) was added Extractive workup (CH_2Cl_2) and silica gel chromatographic purification (AcOEt/hexane=1/4) provided 51 mg (95%) of **2** as a colorless oil, which crystallized upon standing at -5 °C **2** as colorless needles R_f 0.39 (AcOEt/hexane=1/3), mp 61 0-62 0 °C, $[\alpha]_D^{28}$ -3 4° (c 0 57), IR ($CHCl_3$) 3025, 2960, 2935, 2880, 2860, 1765, 1470, 1420, 1370, 1340, 1255 cm^{-1}, ^1H NMR (270 MHz) δ 0 05, 0 06 (each s, each 3H), 0 62 (q, 2Hx3, J=8 0 Hz), 0.88 (s, 9H), 0 97 (t, 3Hx3, J=8 0 Hz), 2.00 (dd, 1H, J=5 5, 16 1 Hz), 2 37 (d, 1H, J=16 1 Hz), 2 42 (dd, 1H, J=11 4, 18 7 Hz), 2 94 (heptet, J=5 9, 7 0, 7 0, 11 3 Hz), 3 11 (dd, 1H, J=5 9, 18 7 Hz), 3 18 (s, 1H), 3.61, 3 67 (ABq, each 1H, J=11 4 Hz), 4 21 (d, 1H, J=6 6 Hz), 4 75 (ddd, 1H, J=1 5, 5 3, 9 9 Hz) Anal. calcd for $C_{21}H_{40}O_5Si_2$. C, 58 83, H, 9 40 Found C, 58 94, H, 9 09

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