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PROSTAGLANDIN CHEMISTRY—V

SYNTHESIS OF NEW PROSTAGLANDIN SYNTHONS; 4(*R*)-(+)- AND 4(*S*)-(−)-t-BUTYLDIMETHYLSILOXYCYCLOPENT-2-EN-1-ONE

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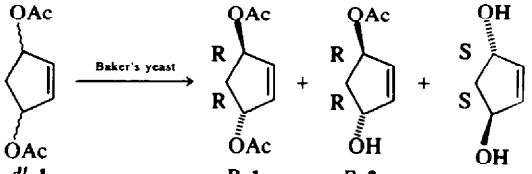
Abstract—Optically active prostaglandin intermediates, 4(*R*)-(+)- and 4(*S*)-(−)-hydroxycyclopent-2-en-1-one derivatives, were synthesized from 3(*R*),5(*R*)-diacetoxycyclopent-1-ene, 3(*R*)-acetoxy-5(*R*)-hydroxycyclopent-1-ene and 3(*S*),5(*S*)-dihydroxycyclopent-1-ene obtained by microbiological hydrolysis of 3,5-diacetoxycyclopent-1-ene. The absolute configurations of all these compounds were determined by the exciton chirality method and the induced CD method. The optical purities were determined by NMR measurements of the diastereomeric esters of a versatile optically pure acid, (+)-α-methoxy-α-trifluoromethylphenylacetic acid.

Prostaglandins have 4 (E type) or 5 (F type) chiral centers and intensive studies on the synthesis of prostaglandins have been carried out focusing on how to introduce these chiral centers into the prostaglandin skeleton. Corey's and other groups have been developing[1] the synthesis of optically active Corey's lactone[1e] which is very important as a prostaglandin synthon with four chiral centers. On the other hand, it has been shown by Sih's group that the 4-substituent of protected 2 - (6 - carbomethoxyhexyl) - 4(*R*) - hydroxycyclopent - 2 - en - 1 - one completely induced not only the C-12*R* stereochemistry but also the C-8*R* through conjugate addition of organocuprates.[5] Recently, Posner's and other groups have shown that alkylation of directed enolates generated by conjugate addition of organocuprates to cyclopent - 2 - en - 1 - one gives α,β-dialkylated cyclopentanone derivatives.[2] In particular, the Syntex group reported the synthesis of 11-deoxyprostaglandin utilizing the modified methodology.[3] While studying this method, we found that β-alkylated organocupper enolates are resiospecifically C-acylated to afford 7-oxoprostaglandin E_1 in high yield.[4] Thus application of the β,α-dialkylation method to the optically active 4(*R*) - hydroxycyclopent - 2 - en - 1 - one would give a short and convenient synthesis of naturally occurring prostaglandins. To date, the synthesis of the optically active 4 - hydroxycyclopent - 2 - en - 1 - one has not been known,[7] while synthesis of (*dl*) - 4 - hydroxycyclopent - 2 - en - 1 - one derivatives such as (*dl*) - 4 - acetoxycyclopent - 2 - en - 1 - one[8a] and (*dl*) - 4 - benzoyloxycyclopent - 2 - en - 1 - one[8b] have been reported. These racemic 4 - acyloxycyclopent - 2 - en - 1 - ones would not be prostaglandin synthons by themselves since the acyloxy groups in the molecules are not appropriate protecting groups when the above mentioned method was used.[9,20] Sih's group prepared the optically pure 2-substituted - 4(*R*) - hydroxycyclopent - 2 - en - 1 - one through microbial reduction of the corresponding cyclopentanetrione derivatives.[5] We also succeeded to introduce 4(*R*)-hydroxyl group on the 2-substituted cyclopentenone by microbial oxidation.[6] Thus our interest in the total synthesis of prostaglandins by β,α-dialkylation method[3,4] prompted us to synthesize optically active 4(*R*) - hydroxycyclopent - 2 - en - 1 - one making use of the microbiological transformation. In the preceeding paper[10] microbiological hydrolyses of (*dl*)-trans- and *cis* - 3,5 - diacetoxycyclopent - 1 - ene (*dl*-**1**)[11] are reported to give 3(*R*),5(*R*) - diacetoxycyclopent - 1 - ene (*R*-**1**), 3(*R*) - acetoxy - 5(*R*) - hydroxycyclopent - 1 - ene (*R*-**2**), and (*S*)-predominant 3,5 - dihydroxycyclopent - 1 - ene (*S*-**3**). We now wish to describe the synthesis of optically active prostaglandin key intermediates, 4(*R*)- and 4(*S*) - hydroxycyclopent - 2 - en - 1 - one derivatives, and the determination of their absolute configurations and optical purities.

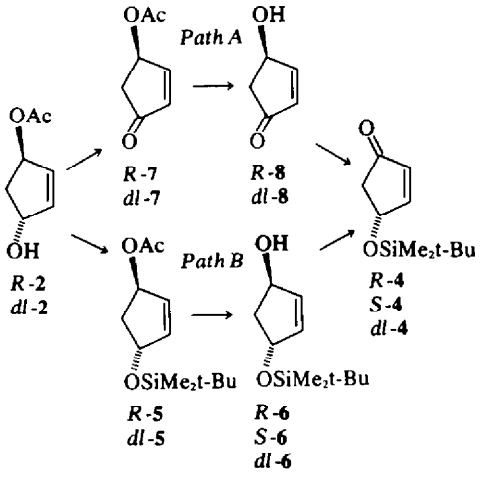
Synthesis of the synthons (R)-**4** *and* (S)-**4**

3(*R*),5(*R*) - diacetoxycyclopent - 1 - ene (*R*-**1**), 3(*R*) - acetoxy - 5(*R*) - hydroxycyclopent - 1 - ene (*R*-**2**), and (*S*)-predominant 3,5 - dihydroxycyclopent - 1 - ene (*S*-**3**) were obtained by microbiological hydrolysis of (*dl*)-trans- and *cis* - 3,5 - diacetoxycyclopent - 1 - ene (*dl*-**1**)[11] (Scheme 1). The *trans*-monoacetate, *R*-**2**, was converted into 4(*R*) - t - butyldimethyl-siloxycyclopent - 2 - en - 1 - one (*R*-**4**) by two different paths (Scheme 2).

In path A (scheme 2), oxidation of the alcohol, *R*-**2**, ($[\alpha]_D^{20}$ +229°, 90% *R* e.e., *vide post*), with active manganese dioxide[12] gave the enone, *R*-**7**[13] (78%) ($[\alpha]_D^{20}$ +82°). In this oxidation, a mixed solvent system of petroleum ether–dioxane (25:2) was chosen. Hydrolysis[14] of the acetoxy function of *R*-**7** with wheat germ lipase afforded the hydroxy enone, *R*-**8** (87%) ($[\alpha]_D^{20}$ +59°) which showed a positive Cotton effect at 216 nm and a negative one at 320 nm in the CD spectrum. Acetylation of the resulting hydroxy enone, *R*-**8** with acetyl chloride in the presence of pyridine at room temperature gave the enone, *R*-**7** (73%) ($[\alpha]_D^{20}$ +76°). Hydrolysis of *dl*-**7**, prepared from the (*dl*)-monoacetate, *dl*-**2**,[10] with wheat



Scheme 1.



All of the structures are illustrated as R-isomer.

Scheme 2.

germ lipase gave optically inactive *dl*-**8** (80%). These results supported the fact that hydrolysis of *R*-**7** to *R*-**8** with wheat germ lipase proceeded with retention of configuration. The compound *R*-**8** served to determine the absolute configuration and to estimate the optical purities as described later. Protection of the OH group of *R*-**8** with t-butyldimentylchlorosilane[15] gave the expected silyl ether, *R*-**4** (35%) ($[\alpha]_D^{20}$ +53°) which exhibited a positive Cotton effect at 218 nm ($[\theta]_{218}$ +62,700°). The overall yield of the siloxy enone, *R*-**4** from the monoacetate, *R*-**2** by this procedure (path A) was 24% though not optimized. The siloxy enone, *R*-**4** was identical (IR, NMR and MS) with the authentic *dl*-**4**[4] prepared by monosilylation of the *trans*- and *cis*-diol, *dl*-**3**[8b] and subsequent oxidation of the monosilyl ether, *dl*-**6**.

The alternative pathway (path B) at first involves silylation of the alcohol, *R*-**2** ($[\alpha]_D^{20}$ +143°, 56% *R* e.e., *vide post*), to give the silyl ether, *R*-**5** (99%) ($[\alpha]_D^{20}$ +89°). Reduction of *R*-**5** with LAH gave the alcohol, *R*-**6** (96%) ($[\alpha]_D^{20}$ +81°) while hydrolysis of *R*-**5** in an aqueous sodium hydroxide solution gave *R*-**6** only in 14% yield. Oxidation of the alcohol *R*-**6** with active manganese dioxide afforded the siloxy enone *R*-**4** (85%) ($[\alpha]_D^{20}$ +32°) which showed the same positive Cotton effect at 218 nm ($[\theta]_{218}$ + 37,000°) as that of *R*-**4** obtained via path A. Thus the siloxy enone *R*-**4** was synthesized from the monoacetate *R*-**2** in the overall yield of 24% and 81% via paths A and B, respectively, showing the advantage of path B for preparative use. In addition, the siloxy enone *R*-**4** obtained via path B was quantitatively desilylated[15] by exposure to acetic acid–water–tetrahydrofuran (3 : 1 : 1) at room temperature to afford the hydroxyl enone *R*-**8**, whose CD spectrum was identical with that of *R*-**8** obtained from the acetoxy enone *R*-**7**. This observation confirmed that this kind of silylation and desilylation[15] proceeded with retention of configuration. It was concluded that the reactions through path A and B proceeded with retention of configuration. By the same procedures (path A and B) starting from *dl-trans*-**2**, *dl*-**5**, -**6**, -**7**, -**8** and -**4** were synthesized as authentic samples to identify the chemical structures of the corresponding optically active compounds obtained above and to estimate their optical purities as described later.

The optically active diacetate *R*-**1** ($[\alpha]_D^{20}$ +199°), obtained by kinetic resolution[10] of *dl-trans*- and *cis*-**1**, was converted into the synthon *R*-**4** ($[\alpha]_D^{20}$ +50°) via the monoacetate *R*-**2** ($[\alpha]_D^{20}$ +220°) by half-methanolysis with n-butylamine.

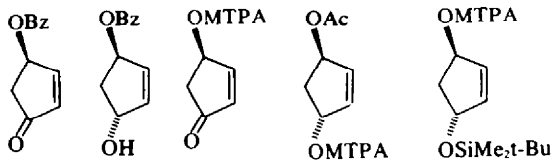
The synthon *S*-**4** was conveniently synthesized from *S*-**3**. Monosilylation of *S*-**3** ($[\alpha]_D^{20}$ −44°, with 47% *cis*-isomer) with t-butyldimethylchlorosilane was accomplished by one-equivalent addition of the reagent to give *S*-**6** (46%) ($[\alpha]_D^{20}$ −24°) which was oxidized with manganese dioxide to afford the product *S*-**4** (94%) ($[\alpha]_D^{20}$ −10°).

Since the diacetate **1**, the monoacetate **2**, and the diol **3** can be mutually interconverted as reported,[8b,10] these optically active compounds *R*-**1**, *R*-**2**, *S*-**3** are considered to be synthetically equivalent.

Determination of the absolute configuration of the enone R-**4** *and* S-**4**

The absolute configurations of the diacetate *R*-**1**, the monoacetate *R*-**2**, and the diol *S*-**3** obtained by the microbiological hydrolysis of 3,5-diacetoxycyclopent-1-ene, and those of their derivatives were determined by the exciton chirality method[16] and the induced CD method.[17] In order to apply the exciton chirality method, two enantiomeric 4 - benzoyloxycyclopent - 2 - en - 1 - one (*R*-**9** and *S*-**9**) were prepared from *R*-**2** and *S*-**3** via the hydroxy enone *R*-**8** and the monobenzoate *S*-**10** respectively. According to the method developed by Nakanishi's group,[16] the enone benzoate *R*-**9** which has a positive chirality was predicted to show a positive Cotton effect, whereas *S*-**9** a negative one. Benzoylation of the hydroxy enone *R*-**8** obtained from the monoacetate *R*-**2** ($[\alpha]_D^{20}$ +229°) through path A gave the enone benzoate *R*-**9**, which showed a positive Cotton effect at 227 nm ($[\theta]_{227}$ +102,300°) in the CD spectrum. This positive chirality indicated that *R*-**9** had the *R* configuration in the light of the exciton chirality method. This result was further verified by the fact that oxidation with active manganese dioxide of the benzoyloxy alcohol *S*-**10** obtained from the diol *S*-**3** ($[\alpha]_D^{20}$ −44°, with 47% *cis*-isomer) gave the enone benzoate *S*-**9**, which exhibited a negative Cotton effect at 226 nm ($[\theta]_{226}$ −47,900°) in the CD spectrum showing a negative chirality. As reported in the preceding paper,[10] acylation of the monoacetate *R*-**2** ($[\alpha]_D^{20}$ +229°) with acetic anhydride and pyridine gave the diacetate *R*-**1**, ($[\alpha]_D^{20}$ +208°), whereas the diol *S*-**3** ($[\alpha]_D^{20}$ −54°, with 34% *cis*-isomer) gave the diacetate *S*-**1** ($[\alpha]_D^{20}$ −49°). Hence it was demonstrated that *R*-**2** and *S*-**3** possessed the opposite absolute configurations.

When the induced CD method[17] is applied to the siloxy alcohol, *R*-**6**, the compound *R*-**6** having a predicted negative chirality is expected to show a negative Cotton effect. The induced CD spectrum of *R*-**6** ($[\alpha]_D^{20}$ +81°) with copper hexafluoroacetylacetonate in carbon tetrachloride actually showed a negative Cotton effect at 335 nm ($[\theta]_{335}$ −1300°) which was coincident with the *R* configuration of the siloxy alcohol *R*-**6**. Since all the employed reactions proceeded with retention of configuration as described above, it was concluded that *R*-**1**, *R*-**2** and *S*-**3** with



R-**9** *S*-**10** *R*-**11** *dl*-**11** *R*-**12** *dl*-**12** *R*-**13** *dl*-**13**

S-**9**

All structures are illustrated as *R*-enantiomers.

trans-geometry obtained by microbiological hydrolysis[10] possessed (3*R*, 5*R*), (3*R*, 5*R*) and (3*S*, 5*S*) configurations, respectively, and that the siloxy enone *R*-4 and *S*-4 derived from them had the 4*R* and 4*S* configurations.

Determination of the optical purity of the enone (R)-4

The optical purity of the monoacetate *R*-2 was successfully estimated by the NMR measurement using a chiral shift reagent, as reported in the preceding paper.[10] However, the siloxy alcohol *R*-6 was not appropriate for this method. Since the reactions employed in path A and B proceeded with retention of configuration as described before, the optical purity of 4 is essentially the same as that of 2. It was also confirmed by the NMR measurement of the diastereomeric esters, *dl*-11 and *R*-11 prepared from the respective hydroxy enones *dl*-8 and *R*-8 via either path A or B. The esters 11, 12 and 13 were prepared from the corresponding alcohols 8, 2 and 6 by acylation with (+) - α - methoxy - α - trifluoromethylphenylacetyl chloride and pyridine.[18] The enone 11 was eventually preferred to 12 and 13 for this purpose. The NMR spectrum of two diastereomeric mixture 11 exhibited considerably different chemical shifts for the C-5 methylene groups of the cyclopentenone ring. The hydroxy enone *R*-8 ($[\alpha]_D^{20}$ +59°) prepared from the monoacetate *R*-2 ($[\alpha]_D^{20}$ +229°, 90% *R* e.e.[19]) *via* path A was converted into *R*-11 which was found to be 90% *R* enantiomeric excess (90% *R* e.e) on the basis of the NMR spectrum. Furthermore, *R*-8 prepared from *R*-2 ($[\alpha]_D^{20}$ +143°, 56% *R* e.e.[19]) via path B was also converted into *R*-11 which was 54% *R* e.e. Since the enantiomeric ratio of the ester 11 was coincident with that of the monoacetate 2, these results also supported the conclusion that all the employed reactions proceeded with retention of configuration and consequently the enantiomeric compositions of the series of these compounds did not change through these reactions. Thus the maximum optical rotations for the optically pure compounds in this paper can be calculated comparing with the observed specific rotations and the enantiomeric compositions.

In conclusion, the optically active synthons *R*-4 and *S*-4 were synthesized in high yield from optically active *R*-1, *R*-2 and *S*-3 which were effectively produced from the readily available diacetate *dl*-1[11] by microbiological hydrolysis. These key intermediates are useful not only as new prostaglandin synthons[20] but also for the synthesis of some other biologically active cyclopentanoids.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. M.ps were observed with a Yanaco micro m.p. apparatus. IR spectra were recorded on a Hitachi EPI-S10 spectrometer. NMR spectra were determined in CCl_4 or $CDCl_3$ soln on a Varian EM 360 (60 MHz), a Jeol JNM-MH-100 (100 MHz), and a Jeol JNM-PS-100 (100 MHz) spectrometer; chemical shifts are given in ppm on the δ scale from TMS as the internal standard and coupling constants in Hz. Splitting patterns are designed as s, singlet; d, doublet; t, triplet; bs, broad singlet; dd, doublet of doublet; m, multiplet. UV spectra were measured in MeOH with a Hitachi 124 spectrophotometer. Mass spectra were taken at 70 eV or 11 eV on a GLC-linked LKB 9000 mass spectrometer equipped with a Simazu GC-MSPAC 300 computer; only the major ions and their relative intensities are listed. Optical rotations were measured in MeOH on a JASCO Model DIP-SL automatic polarimeter. CD spectra were recorded on a JASCO J-20 automatic recording spectropolarimeter. GLC was carried out with a Hitachi 073 gas chromatograph (for analysis) equipped with a column (2 m × 3 mm i.d.) packed with 20% Carbowax 20M on chromosorb W (NAW) (oven temp. 180°, injection temp. 250°, N_2, 35 ml/min) with Takeda Riken TR-2215A digital integrator, and Varian 920 preparative gas chromatograph. Layer chromatography was performed using Merck silica gel (Kieselgel 60 F_{254}) analytical and preparative plates. Column chromatography was carried out on Wako gel C-200 (silica gel). All reactions were carried out under N_2. Magnetic stirring devices were used in all cases. Solvents for reactions were purified if necessary before use by distillation from suitable drying agents. Solvents for extraction were GR grades. Organic extracts were always dried over Na_2SO_4 or $MgSO_4$. Active MnO_2[12] and (+) - α - methoxy - α - trifluoromethylphenylacetyl chloride ((+)-MTPA-Cl)[18] were prepared as described in the literature. The shift reagent, tris - (3 - trifluoromethylhydroxymethylene - d - camphorato) europiem(III), was purchased from Willow Brook Lab. Inc., U.S.A. Anhydrous copper hexafluoroacetylacetonate for induced CD measurement was used after being kept under a vacuum over P_2O_5 for 8 hr. As the esterase for enzymatic hydrolysis was used wheat germ lipase type I (Glycerolester hydrolase, EC No. 3.1.1.3.) from Sigma Chemical Co.

4(R) - *Acetoxycyclopent* - 2 - *en* - 1 - *one* (R)-7 *from the monoacetate* (R)-2 (via *path A*)

A soln of *R*-2 (327 mg, 2.30 mmol, $[\alpha]_D^{20}$ +229° (*c*, 0.027), 90% *R* e.e.) obtained by microbiological half-hydrolysis[10] of *dl*-1[11] in petroleum ether (25 ml) and dioxane (2 ml) was refluxed for 3 hr in the presence of active MnO_2 (1.0 g) the reaction being monitored by TLC. Mn residues were filtered off and washed several times with petroleum ether. The combined filtrate and washings were concentrated *in vacuo* to afford 251 mg (1.79 mmol, 78%) of *R*-7 ($[\alpha]_D^{20}$ +82°, (*c*, 0.063)) which was homogeneous by TLC without further purification and exhibited a positive Cotton effect at 223 nm in the CD spectrum. The *R*-7 was not suitable for GLC analysis because of its thermal unstability; TLC (hexane–EtOAc, 2:3): R_f 0.45; m.p. 10–15°; IR (film): 1735, 1710, 1370, 1230, 1180, 1100, 1030, 985, 910 and 790 cm^{-1}; NMR (60 MHz, CCl_4): 2.00 (3H, s, $OCOCH_3$), 2.25 (1H, dd, J = 3 Hz and 19 Hz, H–C_5), 2.75 (1H, dd, J = 6 Hz and 19 Hz, H–C_5), 4.77 (1H, m, H–C_4), 6.26 (1H, dd, J = 1 Hz and 7 Hz, H–C_2), 7.52 (1H, dd, J = 2 Hz and 7 Hz, H–C_3), UV (MeOH): λ_{max} 210 nm (ε 13,000); MS (70 eV; *m/e*, %): 140 (M^+, 16), 112 (12), 98 (50), 97 (33), 80 (18), 70 (12), 53 (29) and 43 (100). These data were identical with those of *dl*-7 reported in the lit.[8a]

dl-7 was similarly obtained from *dl-trans*- and *cis*-2 prepared by monoacetylation of *dl-trans*- and *cis*-3[8b] by oxidation with active MnO_2 (81%) or with DDQ (71%).

4(R) - *Hydroxycyclopent* - 2 - *en* - 1 - *one*, R-8 *from* R-7 (via *path A*)

Commercial wheat germ lipase (100 mg) was suspended in 40 ml of 0.1 M acetate buffer (pH 5.0). The acetate, *R*-7 (234 mg, 1.67 mmol, $[\alpha]_D^{20}$ +82° (*c*, 0.063)) was added to the suspension. After stirring vigorously at 32° for 48 hr, the mixture was saturated with $(NH_4)_2SO_4$ and extracted with EtOAc (4 × 30 ml). The combined extracts, after washing with sat Na_2SO_4 aq. and drying, were concentrated *in vacuo* to afford 143 mg (1.46 mmol, $[\alpha]_D^{20}$ +59° (*c*, 0.065), 87%) of *R*-8, which was homogeneous by TLC without further purification; TLC (hexane–EtOAc, 2:3): R_f 0.43; IR (film): 3350, 1710, 1660, 1585, 1250, 1100 and 1040 cm^{-1}; NMR (60 MHz, $CDCl_3$): 2.27 (1H, dd, J = 3 Hz and 18 Hz, H–C_5), 2.80 (1H, dd, J = 6 Hz and 18 Hz, H–C_5), 3.27 (1H, bs, OH), 4.88–5.22 (1H, m, H–C_4), 6.25 (1H, d, J = 6 Hz, H–C_2), 7.60 (1H, dd, J = 2 Hz and 6 Hz, H–C_3); UV (MeOH): λ_{max} 210 nm (ε 11,000); MS (70 eV and 11 eV); 98 (M^+). This compound *R*-8 exhibited a positive Cotton effect at 215 nm and a negative one at 320 nm.

Wheat germ lipase hydrolysis of *dl*-7 (70 mg, 0.5 mmol) also gave *dl*-8 (39 mg, 0.4 mmol, 80%), which was optically inactive ($[\alpha]_D^{20}$ +0° (*c*, 0.045)).

R-7 *from* R-8. To a stirred soln of *R*-8 (26 mg, 0.26 mmol, $[\alpha]_D^{20}$ +59° (*c*, 0.065)) in CCl_4 (0.8 ml), acetyl chloride (39 mg, 0.5 mmol) and subsequently pyridine (40 mg, 0.5 mmol) were added. After standing at room temp. for 48 hr, water (*ca.* 3 ml) was added and the mixture was extracted with ether (3 × 20 ml). The combined organic layer was washed with sat brine, dried, and concentrated

in vacuo to afford 27 mg (0.19 mmol, 73%) of *R*-7 ($[\alpha]_D^{20}$ +76° (*c*, 0.017)), which was homogeneous by TLC (hexane–EtOAc, 2:3, R_f 0.43) and identical (TLC, IR, NMR, UV and MS) with *R*-7 derived from *R*-2.

4(R) - t - *Butyldimethylsiloxycyclopent* - 2 - *en* - 1 - *one* R-4 *from* R-8 (via *path A*)

To a stirred soln of R-8 (25 mg, 0.25 mmol, $[\alpha]_D^{20}$ +59° (*c*, 0.065)) in DMF (0.4 ml) were added t-butyldimethylchlorosilane (38 mg, 0.25 mmol) and imidazole (35 mg, 0.51 mmol) at room temp. After standing at room temp. for 15 hr, water (3 ml) was added and the mixture was extracted with hexane (3 × 30 ml). The combined extracts, after washing thoroughly with water, were dried and concentrated *in vacuo* to afford 56 mg of an oily crude product, which was chromatographed on preparative thin layer plate with hexane–EtOAc (2:3) to give 18 mg (0.09 mmol, 35%) of *R*-4 ($[\alpha]_D^{20}$ +53° (*c*, 0.011); GLC: R_t 8 min; TLC (hexane–EtOAc, 2:3): R_f 0.58; IR (film): 3020, 1715, 1585, 1110, 1070, 900, 835 and 775 cm^{-1}; NMR (100 MHz, CCl_4): 0.09 (6H, s, $SiCH_3$), 0.87 (9H, s, t-Bu), 2.04 (1H, dd, J = 3 Hz and 19 Hz, H–C_3), 2.57 (1H, dd, J = 6 Hz and 19 Hz, H–C_3), 4.93 (1H, m, H–C_4), 6.10 (1H, dd, J = 1 Hz and 7 Hz, H–C_2), 7.34 (1H, dd, J = 2 Hz and 7 Hz, H–C_3); UV (MeOH): λ_{max} 209 nm (ϵ 12,000); CD (MeOH): $[\theta]_{218}$ + 62,700° (*c*, 6.6×10^{-5} M); MS (70 eV; *m/e*, %): 212 (M^+, 0.5), 197 (2), 155 (100), 117 (10), 81 (38) and 75 (24).

The similar silylation of *dl*-8 (60 mg, 0.61 mmol) afforded *dl*-4 (44 mg, 0.21 mmol, 35%).

dl - 3 - *t* - *Butyldimethylsiloxy* - 5 - *hydroxycyclopent* - 1 - *ene* dl-6 *from* dl-3

To a stirred soln of *dl-trans*- and *cis*-3 (1.00 g, 10 mmol) and imidazole (1.70 g, 25 mmol) in DMF (4 ml) was added *t*-butyldimethylchlorosilane (1.65 g, 11 mmol) at room temp. After standing at room temp. for 12 hr, water (10 ml) was added and the mixture was extracted with hexane (3 × 50 ml). The combined organic layers, after washing with sat brine and drying, were concentrated *in vacuo* to afford 1.86 g of an oily crude product, which was distilled to give 756 mg (3.5 mmol, 35%) of *dl-trans*- and *cis*-6; b.p.: 73–76° (0.06 mmHg); TLC (hexane–EtOAc, 2:3) R_f 0.48; IR (film): 3250, 3000, 1460, 1360, 1250, 1120, 1060, 900, 830 and 770 cm^{-1}; NMR (60 MHz, CCl_4), 0.03 (6H, s, $SiCH_3$), 0.80 (9H, s, t-Bu), 2.73 (1H, bs, OH), 1.36 (dt, J = 6 Hz and 15 Hz) and 2.60 (dt, J = 7 Hz and 15 Hz) and 1.84 (t, J = 7 Hz) (2H, CH_2), 4.40 (1H, m, H–C_5), 4.87 (1H, t, J = 7 Hz, H–C_3), 5.68 (2H, s, CH=CH): MS (70 eV; *m/e*, %): 214 (M^+, 16), 199 (18), 197 (3), 157 (40), 139 (4), 75 (100), 65 (7) and 57 (3); by-product *dl-trans*- and *cis* - 3,5 - bis(t - butyldimethylsiloxy)cyclopent - 1 - ene (715 mg, 2.2 mmol, 22%); b.p.: 76° (0.06 mmHg): TLC (hexane–EtOAc, 2:3): R_f 0.70; IR (film): 3050, 1460, 1365, 1250, 1130, 1080, 900, 835 and 770 cm^{-1}; NMR (60 MHz, CCl_4): 0.03 (12H, s, $SiCH_3$), 0.80 (18H, s, t-Bu), 1.40 (dt, J = 7 Hz and 18 Hz) and 2.57 (dt, J = 7 Hz and 15 Hz) and 1.87 (t, J = 6 Hz) (2H, CH_2), 4.46 and 4.87 (2H, t, J = 7 Hz, H–C_3 and H–C_5), 5.64 (2H, d, J = 3 Hz, CH=CH); MS (70 eV; *m/e*, %); 328 (M^+, 3), 327 (4), 313 (10), 271 (36), 197 (4), 189 (8), 147 (100), 133 (7), 107 (6), 75 (22), 73 (44), 66 (5) and 57 (5).

Compound dl-4 *from* dl-6 (via *path B*)

(a) A soln of *dl-trans*- and *cis*-6 (400 mg, 1.87 mmol) in petroleum ether (25 ml) was stirred with active MnO_2 (1.40 g) at room temp. for 18 hr, monitoring by GLC. The usual work up afforded 364 mg (1.72 mmol, 93%) of *dl*-4.

(b) To a stirred soln of DDQ (1.13 g, 5 mmol) in dioxane (15 ml) was added *dl*-6 (488 mg, 2.3 mmol). After heating at 55° for 16 hr, the mixture was cooled and filtered from the resulting ppt, which was washed with cold dioxane (10 ml). The combined filtrate was concentrated *in vacuo* to afford 1.83 g of a crude product, which was chromatographed with hexane–EtOAc (7:3, 200 ml) to give 0.53 g of a pale yellow oil. This oil was further purified by preparative TLC (hexane–EtOAc, 3:2) to give *dl*-4 (336 mg, 1.6 mmol, 70%).

3(R) - *Acetoxy* - 5(R) - *t* - *butyldimethylsiloxycyclopent* - 1 - *ene* - R-5 - *from* - R-2 (via *path B*)

To a stirred soln of *R*-2 (590 mg, 4.15 mmol, $[\alpha]_D^{20}$ +143° (*c*, 0.103), 56% *R* e.e.) in DMF (2 ml) were added t-butyldimethylchlorosilane (1.0 g, 6.7 mmol) and imidazole (1.0 g, 14.7 mmol) at room temp. After stirring at room temp. for 64 hr, water (20 ml) was added and the mixture was extracted with hexane (3 × 5 ml). The combined organic extracts were washed with water, dried, and concentrated *in vacuo* to afford 1.34 g of an oily crude product, which was column chromatographed with hexane (200 ml) and then hexane–EtOAc (2:1, 200 ml) to give 1.06 g (4.10 mmol, 99%) of *R*-5 ($[\alpha]_D^{20}$ +89° (*c*, 0.059)). This compound *R*-5 was homogeneous both by TLC and GLC; GLC: R_t 8.4 min; TLC (hexane–EtOAc, 2:1): R_f 0.60; IR (film): 3020, 1730, 1245, 1125, 1070, 1030, 900, 835 and 775 cm^{-1}; NMR (60 MHz, CCl_4): 0.05 (6 H, s, $SiCH_3$), 0.88 (9H, s, t-Bu), 1.94 (3H, s, $OCOCH_3$), 2.0 (2H, m, CH_2), 5.0 (1H, m, H–C_5), 5.65 (1H, m, H–C_3), 5.90 (2H, s, CH=CH); MS (70 eV; *m/e*, %): 256 (M^+, 18), 215 (7), 213 (7), 197 (6), 155 (43), 117 (100), 81 (92), 75 (39), 73 (20) and 43 (31).

The similar silylation of *dl-trans*-2 (19 mg, 0.134 mmol) gave *dl*-5 (33 mg, 0.129 mmol, 96%).

3(R) - *t* - *Butyldimethylsiloxy* - 5(R) - *hydroxycyclopent* - 1 - *ene* R-6 *from* R-5 (via *path B*)

To a stirred suspension of LAH (160 mg, 4.2 mmol) in ether (10 ml) was added dropwise at 0° a soln of *R*-5 (970 mg, 3.97 mmol, $[\alpha]_D^{20}$ +89° (c, 0.059)) in ether (5 ml). After stirring at room temp. for 2 hr and refluxing for 30 min, sat Na_2SO_4 aq. (*ca.* 5 ml) was added dropwise to the mixture until complete formation of the alum cake. The resulting cake was separated from the organic layer and washed several times with ether. The combined organic layer was dried and concentrated *in vacuo* to afford *R*-6 (780 mg, 3.64 mmol, 96%, $[\alpha]_D^{20}$ +81° (*c*, 0.057)). The product *R*-6 was homogeneous both by TLC (hexane–EtOAc, 1:1, R_f 0.50) and by GLC (183°, R_t 11.5 min); IR (film): 3300, 3020, 1250, 1120, 1070, 900, 835 and 775 cm^{-1}; NMR (100 MHz, CCl_4): 0.05 (6H, s, $SiCH_3$), 0.88 (9H, s, t-Bu), 1.92 (2H, t, J = 5 Hz, CH_2), 3.60 (1H, bs, OH), 4.90 (2H, m, H–C_3 and H–C_5), 5.84 (2H, s, CH=CH); MS (70 eV; *m/e*, %); 214 (M^+, 0.5), 199 (1), 157 (46) and 75 (100). The NMR measurement of *R*-6 with use of the chiral shift reagent failed to estimate its enantiomeric composition.

LAH (20 mg, 0.53 mmol) reduction of *trans-dl*-5 (33 mg, 0.129 mmol) in ether (3 ml) produced 23 mg (0.107 mmol, 83%) of *dl*-6.

4(R) - *t* - *Butyldimethylsiloxycyclopent* - 2 - *en* - 1 - *one* (R)-4 (via *path B*)

A mixture of *R*-6 (530 mg, 2.48 mmol, $[\alpha]_D^{20}$ +81° (*c*, 0.057)) and active MnO_2 (1.94 g) in petroleum ether (50 ml) was refluxed for 4 hr. Usual work-up yielded 448 mg (2.11 mmol, 85%) of *R*-4 ($[\alpha]_D^{20}$ +32° (*c*, 0.051)), which exhibited a positive Cotton effect at 218 nm; $[\theta]_{218}$ +37,000° (*c*, 6.7×10^{-5} M, MeOH).

Compound R-8 *from* R-4

To a mixture (1 ml) of acetic acid–water–THF (3:1:1) was added *R*-4 (30 mg, 0.14 mmol, $[\alpha]_D^{20}$ +32° (*c*, 0.051)) obtained from *R*-2 ($[\alpha]_D^{20}$ 143°, 56% *R* e.e.) via path B. After standing at room temp. for 48 hr, toluene (10 ml) was added and the mixture was concentrated azeotropically *in vacuo* below 30° to produce 13 mg (0.13 mmol, 94%) of *R*-8 ($[\alpha]_D^{20}$ +36° (*c*, 0.050)), which was homogeneous by TLC (hexane–EtOAc, 1:1, R_f 0.14) and identical (TLC, IR, NMR, UV and MS) with *R*-8 from *R*-2 via path A. The same Cotton effects as those of *R*-8 derived from *R*-7 were observed.

The similar desilylation of *dl*-4 (134 mg, 0.63 mmol) afforded *dl*-8 (55 mg, 0.56 mmol, 89%).

Compound R-2 *from* R-1

A mixture of *R*-1 (42 mg, 0.23 mmol, $[\alpha]_D^{20}$ +199° (*c*, 0.026)) and n-$BuNH_2$ (17 mg, 0.23 mmol) in MeOH (1 ml) was stirred at room temp. for 21 hr. The solvent was removed. The residue was taken up with ether (50 ml) and the soln was washed with dil HCl (3 × 5 ml) and brine (3 × 5 ml), dried, and evaporated to leave an oil, which was purified by TLC (EtOAc–MeOH, 98:2, R_f 0.55) to afford 23 mg (0.16 mmol, 70%, $[\alpha]_D^{20}$ +220° (*c*, 0.021)) of *R*-2.

Compound S-6 *from* S-3

To a stirred soln of *S*-3[10] (210 mg, 2.1 mmol, $[\alpha]_D^{20}$ −44° (*c*, 0.050), contaminated with 47% *cis*-isomer) and imidazole (260 mg, 3.8 mmol) in DMF (0.8 ml) was added at room temp. t-butyldimethylchlorosilane (240 mg, 1.6 mmol) in 5 portions every 1 hr. Then water (5 ml) was added and the mixture was extracted with ether (3 × 30 ml). The combined organic soln, after washing with sat brine and drying, was concentrated *in vacuo* to afford 216 mg of a crude product, which was found to contain *S*-6 and the disilyl ether (3:2) by GLC. This crude product was purified by preparative TLC (hexane–ether, 4:1) to give *S*-6 (210 mg, 0.98 mmol, 46%, $[\alpha]_D^{20}$ −24° (*c*, 0.055)), which was identical (GLC, IR, NMR and MS) with *dl*-6.

Compound S-4 *from* S-6

A mixture of *S*-6 (105 mg, 0.49 mmol, $[\alpha]_D^{20}$ −24° (*c*, 0.055)) and active MnO_2 (400 mg) in petroleum ether (10 ml) was refluxed for 4 hr. Usual work-up gave 90 mg (0.42 mmol, 87%) of *R*-4 ($[\alpha]_D^{20}$ −10° (*c*, 0.049)), which was homogeneous both by TLC and GLC and identical (GLC, TLC, IR, NMR, UV and MS) with *R*-4 and *dl*-4. This compound *S*-4 exhibited a negative Cotton effect at 218 nm; $[\theta]_{218}$ −23,000° (*c*, 6.0×10^{-5} M, MeOH).

Determination of the absolute configuration

4(R) - *Benzoyloxycyclopent* - 2 - *en* - 1 - *one*, R-9 *from* R-8. To a stirred soln of *R*-8 (9 mg, 0.09 mmol, $[\alpha]_D^{20}$ +59° (*c*, 0.065)) in dioxane (0.5 ml) were added benzoyl chloride (18 mg, 0.13 mmol) in CCl_4 (0.25 ml) and pyridine (40 mg, 0.5 mmol). After standing at room temp. for 12 hr, water (5 ml) was added and the mixture was extracted with ether (3 × 30 ml). The combined organic layers, after washing with dil HCl, sat $NaHCO_3$ aq., and sat brine, were dried and concentrated *in vacuo* to afford 9 mg of a solid crude product, which was purified by preparative TLC (hexane–EtOAc, 2:3) to give 4 mg (0.02 mmol, 22%) of *R*-9. This compound, *R*-9 exhibited a positive Cotton effect at 227 nm and a negative one at 320 nm in the CD spectrum showing positive chirality; $[\theta]_{227}$ +102300°, $[\theta]_{320}$ −4950° (*c*, 3.2×10^{-5} M); TLC (hexane–EtOAc, 2:3): R_f 0.60; IR (KBr); 3050, 1730, 1713, 1270, 1110, 795 and 710 cm^{-1}; NMR (100 MHz, $CDCl_3$): 2.52 (1H, dd, J = 2Hz and 19 Hz, H-C_5), 2.96 (1H, dd, J = 6 Hz and 19Hz, H-C_5), 6.12 (1H, m, H-C_4), 6.44 (1H, dd, J = 1.5 Hz and 6 Hz, H-C_2), 7.72 (1H, dd, J = 2.5 Hz and 6 Hz, H-C_3), 7.53 and 8.06 (3H and 2H, m, Ph); UV (MeOH): λ_{max} 228 nm (ε 18,000); MS (70 eV: *m/e*, %): 202 (M^+, 1), 105 (100), 80 (9), 77 (26) and 53 (10). These data were identical with those of *dl*-9 reported in the literature.[8a,b]

3(S) - *Benzoyloxy* - 5(S) - *hydroxycyclopent* - 1 - *ene*, S-10 *from* S-3. A soln of benzoyl chloride (110 mg, 0.78 mmol) in THF (2.5 ml) was added at room temp. over 13.5 hr with a motor syringe drive to a stirred soln of *trans*- and *cis*- *S*-3 predominantly containing *trans*-3(*S*), 5(*S*)-3 (71 mg, 0.71 mmol, *cis* : *trans* = 47:53, $[\alpha]_D^{20}$ −44° (*c*, 0.030) and pyridine (79 mg, 1.0 mmol) in THF (1.5 ml). After THF was removed *in vacuo*, ether (50 ml) was added and the resulting organic layer, after washing with sat $NaHCO_3$ aq (2 × 5 ml), dil HCl (2 × 5 ml), and sat brine (2 × 5 ml), was dried and concentrated *in vacuo* to afford a crude product, which was purified by preparative TLC (benzene–ether, 95:5, 10 irrigations) to give *cis*-10 (48.6 mg, 0.24 mmol, 74% based on *cis*-3, R_f 0.46) and *trans*-*S*-10 (48.3 mg, 0.24 mmol, 61% based on *trans*-3, R_f 0.32). *cis*-10; IR (film): 3250, 3020, 1705, 1600, 1580, 1275, 1110 and 710 cm⁻¹; NMR (100 MHz, $CDCl_3$): 1.31 (1H, dt, J = 4.3 Hz and 14.5 Hz, H-C_4), 2.92 (1H, dt, J = 7.5 Hz and 14.5 Hz, H-C_4), 3.40 (1H, bs, OH), 4.80 (1H, m, H-C_5), 5.75 (1H, m, H-C_3), 6.14 (2H, m, CH=CH), 7.50 and 8.06 (3H and 2H, m, Ph); MS (70 eV; *m/e*, %): 204 (M', 1) 187 (8), 123 (5), 105 (100), 83 (20), 77 (27) and 55 (10). *trans*-*S*-10; IR (film): 3350, 3050, 1710, 1600, 1580, 1275, 1110 and 710 cm^{-1}; NMR (100 MHz, $CDCl_3$): 2.00 and 2.34 (1H and 1H, m, CH_2), 2.64 (1H, bs, OH), 5.17 (1H, m, H-C_5), 6.13 (1H, m, H-C_3), 6.18 (2H, s, CH=CH), 7.50 and 8.06 (3H and 2H, m, Ph); MS (70 eV; *m/e*, %): 204 (M', 0.5), 187 (1.5), 123 (8), 105 (100), 83 (20), 77 (23) and 55 (6).

Compound S-9 *from* S-10

A soln of *trans*-*S*-10 (37 mg, 0.18 mmol) in benzene (1 ml) and petroleum ether (8 ml) was refluxed for 9 hr with active MnO_2 (150 mg). The Mn residue was filtered off and washed with ether (20 ml). The combined filtrate and washings were concentrated *in vacuo* to afford a solid crude product, which was purified by preparative TCL (benzene–acetone, 4:1, R_f 0.53) to give 25 mg (0.12 mmol, 68%) of *S*-9. This compound was identical (TLC, IR, NMR, UV and MS) with *R*-9 and exhibited a negative Cotton effect at 226 nm in the CD spectrum showing negative chirality: $[\theta]_{226}$ −47,900° (*c*, 3.2×10^{-5} *M*).

Induced CD measurement of the siloxy alcohol R-6

A soln of anhyd copper hexafluoroacetylacetonate (0.05 ml of 10^{-3} M CCl_4) was added to a soln of *R*-6 (4.28 mg, 0.02 mmol) in CCl_4 (4 ml) in 10 cm cell for the CD measurement. This soln exhibited a negative Cotton effect at 335 nm and a positive one at 305 nm in the CD spectrum; $[\theta]_{335}$ −1300° (*c*, 1.3×10^{-5} M of copper hexafluoroacetylacetonate).

Determination of the optical purity

dl - 4 - ((+) - α - *Methoxy* - α - *trifluoromethylphenylacetoxy*)*cyclopent* - 2 - *en* - 1 - *one* dl-11 *from* dl-8. A soln of (+)-MTPA-Cl (1.1 ml of 0.53 M CCl_4 soln, 0.58 mmol) was added at room temp. to *dl*-8 (55 mg, 0.56 mmol). Pyridine (80 mg, 1.0 mmol) was added to the mixture, which was stirred at room temp. for 12 hr. Water (5 ml) was added and the mixture was extracted with ether (50 ml). The separated organic layer, after washing with 5% $NaHCO_3$ aq, 5% HCl, sat Na_2SO_4 aq, and water, was dried and concentrated *in vacuo* to afford 150 mg, (0.48 mmol, 86%) of *dl*-11 which was homogeneous by TLC (hexane–EtOAc, 2:3, R_f 0.52) without further purification; IR (film): 3000, 1745, 1725, 1250, 1170, 1015 and 710 cm^{-1}; PMR (100 MHz, CCl_4): 2.22(*R*) and 2.32(*S*) (0.5H and 0.5H, dd, J = 3 Hz and 18 Hz, H-C_5), 2.73(*R*) and 2.84(*S*) (0.5H and 0.5H, dd, J = 6 Hz and 18 Hz, H-C_5), 3.52 (*R* and *S*) (3H, s, OCH_3), 5.94–6.11 (*R* and *S*) (1H, m, H-C_4), 6.36(*R*) and 6.34(*S*) (0.5H and 0.5H, dd, J = 2.5 Hz and 6 Hz, H-C_2), 7.42 (*R* and *S*) (5H, m, Ph), 7.62(*R*) and 7.55(*S*) (0.5H and 0.5H, dd, J = 2.5 Hz and 6 Hz, H-C_3); PMR (100 MHz, $CDCl_3$): 2.32(*R*) and 2.40(*S*) (0.5H and 0.5H, dd, J = 2.5 Hz and 19 Hz, H-C_5), 2.85(*R*) and 2.93(*S*) (0.5H and 0.5H, dd, J = 6 Hz and 19 Hz, H-C_5), 3.55 (*R* and *S*) (3H, s, OCH_3), 6.10 (1H, m, H-C_4), 6.42(*R*) and 6.40(*S*) (1H, dd, J = 1.5 Hz and 6 Hz, H-C_2), 7.44 (*R* and *S*) (5H, m, Ph), 7.56(*R*) and 7.50(*S*) (1H, dd, J = 2.5 Hz and 6 Hz, H-C_3); UV (MeOH): λ_{max} 210 nm (ε 14,000): MS (70 eV; *m/e*, %): 314 (M^+, 0.1), 245 (0.1), 233 (0.2), 189 (100), 141 (4), 139 (5), 129 (5), 105 (17), 91 (4), 81 (13), 77 (11), 69 (5) and 53 (16).

Compound R-11 *from* R-8

(a) A soln of (+)-MTPA-Cl (0.28 ml of 0.47 M CCl_4 soln, 0.13 mmol) was added at room temp. to *R*-8 (10 mg, 0.10 mmol, $[\alpha]_D^{20}$ +59° (*c*, 0.065)). Pyridine (30 mg, 0.38 mmol) was added to the mixture, which was stirred at room temp for 48 hr. The same work-up as mentioned above afforded 40 mg of a crude product, which was purified by preparative TLC (hexane–EtOAc, 2:3) to give *R*-11 (7 mg, 0.02 mmol, 20%). The compound *R*-11 was identical (TLC, IR, UV and MS) with *dl*-11. The PMR spectrum of the product was superimposable with that of a diastereomer of *dl*-11; PMR (100 MHz, $CDCl_3$): 2.32 (1H, dd, J = 2.5 Hz and 19 Hz, H-C_5), 2.85 (1H, dd, J = 6 Hz and 19 Hz, H-C_5), 3.55 (3H, s, OCH_3), 6.10 (1H, m, H-C_4), 6.42 (1H, dd, J = 1.5 Hz and 6 Hz, H-C_2), 7.44 (5H, m, Ph), 7.56 (1H, dd, J = 2.5 Hz and 6 Hz, H-C_3). The enantiomeric purity was estimated to be 95% (90% *R* e.e.) from the C-5 methylene signals.

(b) Acylation of *R*-8 (13 mg, 0.133 mmol, $[\alpha]_D^{20}$ +37° (*c*, 0.039)) with (+)-MTPA-Cl (36 mg, 0.16 mmol) and pyridine (50 mg, 0.63 mmol) in CCl_4 (0.34 ml) gave *R*-11 (6 mg, 0.019 mmol, 14%), which was identical (TLC, IR, UV and MS) with *dl*-11. The enantiomeric purity was estimated to be 78% (56% *R* e.e.) from the PMR spectrum.

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