Chiral Preparation of Polyoxygenated Cyclopentanoids

Hiromi Nakashima, Masayuki Sato, Takahiko Taniguchi, Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan
Fax +81(22)2176845; E-mail: konol@mail.cc.tohoku.ac.jp

Received 27 January 2000; revised 28 February 2000

Abstract: A series of polyoxygenated cyclopentanoids, including 2,2-dimethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-one, has been prepared in both enantiomeric forms from cyclopentadiene by employing lipase-mediated kinetic resolution as the key step. Thus, cyclopentadiene is first transformed into racemic *cis*-4-cumyloxycyclopent-2-en-1-ol which is resolved under transesterification conditions in the presence of lipase PS. After transformation into the corresponding *tert*-butyldimethylsilyl (TBS) ethers, each of the enantiomers is *cis*-dihydroxylated diastereoselectively from the less hindered face which is transformed into the 2,3-*O*-isopropylidene-1,4-di-*O*-protected (*trans*-1,2:*cis*-2,3:*trans*-3,4)-1,2,3,4-cyclopentanetetraol. Selective removal of the 1,4-protecting group gives the corresponding 2,3,4-*O*-protected cyclopentanols which are further transformed into the 2,3,4-*O*-protected cyclopentanones on oxidation without suffering β-elimination. Exposure of the cyclopentanones to warm acetic acid allows β-elimination to give rise to the dehydration product 2,2,-dimethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-one having the corresponding chirality without losing their original chiral integrity.

Key words: lipase-mediated kinetic resolution, enantiodivergent synthesis, enantioconvergent synthesis, chiral building block, polyoxygenated cyclopentanoids, oxidations, osmium

Polyoxygenated chiral cyclopentane derivatives, in particular 2,2-dimethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-one (**1**),[1] serve as important precursors for the enantiocontrolled construction of a variety of biologically active natural and unnatural compounds (Figure).

Although several chiral syntheses of polyoxygenated cyclopentane derivatives leading to **1** have been established by using either chiral or achiral precursors,[1] a new procedure capable of producing these cyclopentanoids more efficiently is still required because of their high potential in chiral synthesis. We wish to report here an efficient preparation of a series of chiral polyoxygenated cyclopentanoids leading to **1** in both enantiomeric forms starting from cyclopentadiene by employing lipase-mediated kinetic transesterification[2] as the key step.

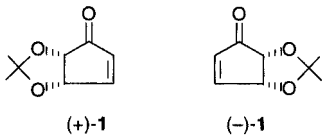
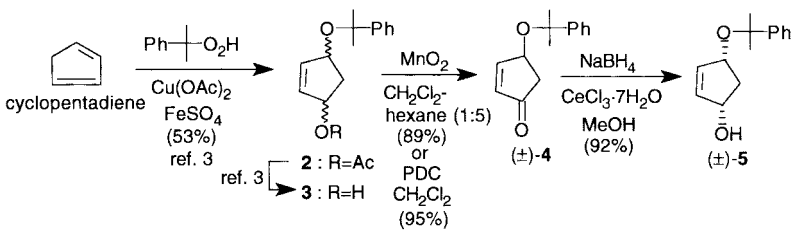


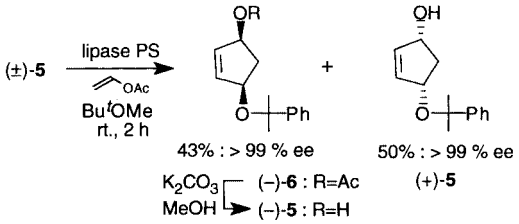
Figure Structures of (+)- and (−)-2,2-dimethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-ones

Cyclopentadiene was first transformed into racemic 4-cumyloxycyclopent-2-enone[3] [(±)-**4**] in three steps via the diastereomeric acetate **2**[4,5] and alcohol **3**. Although the overall yield of (±)-**4** was moderate (47% in 3 steps), the preparation may be carried out in a more than two-molar scale. Reduction of (±)-**4** with sodium borohydride and cerium(III) chloride[6] proceeded chemo- and diastereoselectively to give 1,4-*cis*-4-cumyloxycyclopent-2-en-1-ol [(±)-**5**] in 92% yield (Scheme 1).

Kinetic resolution was carried out at this stage by treating the racemic alcohol (±)-**5** with an excess vinyl acetate in *tert*-butyl methyl ether in the presence of immobilized lipase (lipase PS, *Pseudomonas* sp., Amano) which afforded the enantiopure acetate (−)-**6** in 43% yield, leaving the enantiopure alcohol (+)-**5** in 50% recovery yield. The acetate (−)-**6** afforded the enantiopure alcohol (−)-**5**, quantitatively, on alkaline methanolysis. Enantiomeric purity of the products was determined by HPLC using a column with chiral stationary phase (CHIRALCEL OD). The reaction rate of the lipase-mediated reaction was mostly dependent on the amount of the lipase used, the amount of which, however, did not affect the optical purities of the products. Since the *tert*-butoxy analogue of **5** failed to carry out the kinetic resolution in complete selectivity,[7] namely, 97% ee for the acetate and 91% ee for the remaining alcohol, the present result exhibiting complete resolution may be noteworthy from the practical viewpoint (Scheme 2).



Scheme 1



Scheme 2

In order to determine the absolute configuration of the resolved products as well as to demonstrate the synthetic potential of the resolved products as chiral building blocks, we examined their enantioconvergent transformation into a single enantiomeric oxabicyclo[3.3.0]oct-6-en-3-one[8,9] (−)-**8**, used for an important prostaglandin intermediate, on the basis of our originally established procedure.[10]

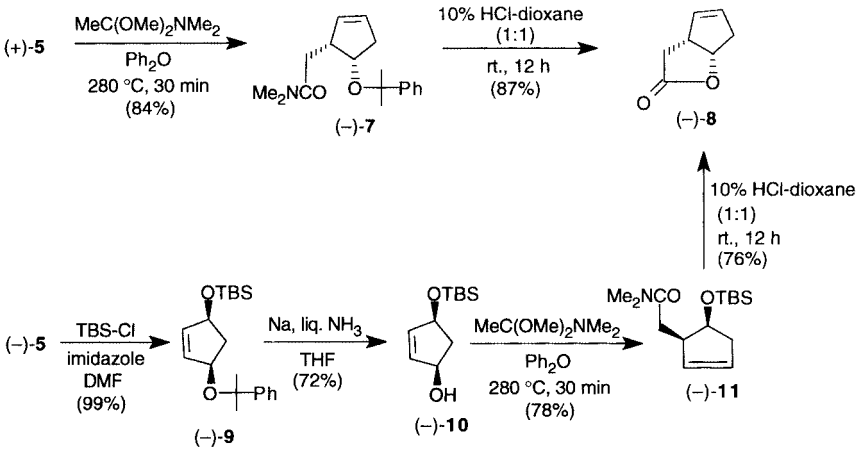
Thus, the alcohol (+)-**5** was heated with a 2.5-fold excess of dimethylacetamide dimethyl acetal[11] in refluxing diphenyl ether to give the cyclopenteneacetamide (−)-**7**, neatly, through a [3.3]-sigmatropic rearrangement. The Eschenmoser conditions employed were found to proceed in a much cleaner way than the Johnson conditions[9,12] as the latter required an acid catalyst which induced considerable decomposition. Upon exposure to diluted hydrochloric acid, the amide (−)-**7** furnished the target lactone (−)-**8** facilely with concurrent decumylation and lactonization. The absolute configuration of the starting alcohol (+)-**5**, thus, was determined as 1*R*,4*S* and, consequently, the enantiomeric alcohol (−)-**5** as 1*S*,4*R*.

On the other hand, the enantiomeric alcohol (−)-**5** was first transformed into the *tert*-butyldimethylsilyl (TBS) ether (−)-**9** whose cumyl functionality was next removed under Birch conditions to give the siloxy alcohol **10**. It was interesting to note that reductive cleavage did not take place at the allylic carbon−oxygen bond but selectively at the desired benzylic carbon−oxygen bond to give the cyclopentenol (−)-**10** in satisfactory yield under these conditions. In the Eschenmoser reaction under the same conditions as above, (−)-**10** gave the amide (−)-**11** which afforded the same lactone (−)-**8** on exposure to dilute acid to complete the enantioconvergent synthesis (Scheme 3).

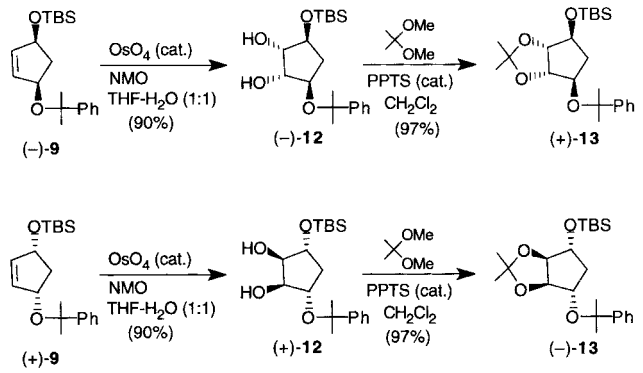
Having determined the stereochemistry of the resolved products, we next examined the conversion of the resolved products into the corresponding (*cis*-4,5)-4,5-*O*-isopropylidene-4,5-dihydroxycyclopent-2-enone (**1**) in a diastereocontrolled manner via *cis*-dihydroxylation.[1g,13] Thus, osmium-catalyzed dihydroxylation of the TBS ether (−)-**9** proceeded diastereoselectively from the opposite face of the 1,4-substituents to give the single diol (−)-**12** which was transformed into the acetonide (+)-**13**. By the same treatment, the enantiomeric TBS ether (+)-**9**, obtained from (+)-**5**, furnished the enantiomeric acetonide (−)-**13** via the enantiomeric diol (+)-**12** (Scheme 4).

To establish enantiodivergent and, at the same time, enantioconvergent synthesis of the cyclopentenone **1** from each enantiomer of the acetonide **13**, (−)-**13** was first subjected to catalytic hydrogenolysis to remove the cumyl functionality to give the 4-TBS-oxy alcohol (−)-**14**. Oxidation of (−)-**14** under Dess−Martin conditions[14] afforded the cyclopentanone (+)-**15** excellently, but other oxidation conditions induced considerable decomposition. Rather surprisingly, the ketone (+)-**15** was found to be fairly stable under ordinary conditions which gave the cyclopentenone (+)-**1** in satisfactory yield when it was stirred with warm acetic acid (60 °C) for 4 days (Scheme 5).

On the other hand, the same acetonide (−)-**13** was exposed to tetrabutylammonium fluoride (TBAF) to remove the TBS functionality to give the 4-cumyloxy alcohol (−)-**16** which afforded the cyclopentanone (−)-**17** in excellent overall yield under Dess−Martin conditions. Similarly to the siloxy counterpart (+)-**15**, (−)-**17** was found to be fairly stable under ordinary conditions though it gave the enantiomeric cyclopentenone (−)-**1** on warming in acetic acid for 4 days (Scheme 5). Thus, an enantiodivergent route to the enone **1** from the same (−)-**13** has been established.



Scheme 3



Scheme 4

On exactly the same treatment as for (−)-**13**, the enantiomeric (+)-**13** furnished enantiodivergently (−)-**1**, via (+)-**14** and (−)-**15**, and (+)-**1**, via (+)-**16** and (+)-**17**, both in comparable overall yields. Thus, (−)- and (+)-**13** produced the enone **1** in both enantiomeric forms enantiocomplementarily in enantioconvergent and enantiodivergent manners via the polyoxygenated chiral cyclopentane intermediates, **14**–**17**. Among these intermediates obtained, the isolation of the β-oxy-ketones **15** and **17** in stable form may be of particular interest from the synthetic viewpoint as they allow stereoselective modification of the ketone functionality with keeping the β-oxy functionality intact (Scheme 5).

In conclusion, we have established an efficient diastereocontrolled preparation of a series of polyoxygenated chiral cyclopentane derivatives starting from cyclopentadiene by employing lipase-mediated kinetic transesterification as the key step. On the basis of the latent *meso* symmetry in the key intermediates, the chiral products involved in the present synthesis may be used in both enantiodivergent and enantioconvergent ways. Exploitation of the prepared chiral products as chiral building blocks is presently under investigation.

Melting points are uncorrected. IR spectra were recorded on a JASCO-IR-700 spectrometer. ^{1}H NMR spectra were recorded on a Gemini 2000 (300 MHz) spectrometer. Enantiomeric excess was determined on a Gilson Model-307 instrument equipped with a chiral column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter.

(±)-4-Cumyloxycyclopent-2-enone (±)-4

(a) *Oxidation by MnO_2*: A solution of **3** (51 mg, 0.234 mmol) in hexane/CH_2Cl_2 (1.0 mL:0.2 mL) was stirred with MnO_2 (400 mg, 4.60 mmol) at r.t. for 2 h. After filtration through a Celile pad, the mixture was evaporated and chromatographed (silica gel, 4 g, elution with hexane/EtOAc, 4:1 v/v) to give the ketone (±)-**4** (45 mg, 89%).

(b) *Oxidation by Pyridinium Dichromate (PDC)*: To a stirred solution of **3** (15.6 g, 71.6 mmol) in CH_2Cl_2 (300 mL) was added PDC (32.3 g, 85.9 mmol) portionwise at r.t. After stirring at the same temperature for overnight, the mixture was filtered through a Celite pad and evaporated under reduced pressure. The residue was chromatographed (silica gel, 300 g, elution with hexane/EtOAc, 4:1 v/v) to give the ketone (±)-**4** (14.7 g, 95%).

IR (film): ν = 1719 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (3 H, s), 1.63 (3 H, s), 2.33 (1 H, dd, *J* = 18.3, 2.4 Hz), 2.54 (1 H, dd, *J* = 18.3, 6.0 Hz), 4.46 (1 H, ddd, *J* = 6.0, 3.9, 2.4 Hz), 6.14 (1 H, dd, *J* = 5.7, 1.2 Hz), 7.27–7.50 (6 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.88, 29.66, 44.29, 71.77, 78.50, 126.11, 127.60, 128.54, 134.79, 145.88, 163.41, 206.74.

MS: *m*/*z* = 216 (M^+).

HRMS: *m*/*z* calcd for $C_{14}H_{16}O_2$ (M^+) 216.1150. Found 216.1105.

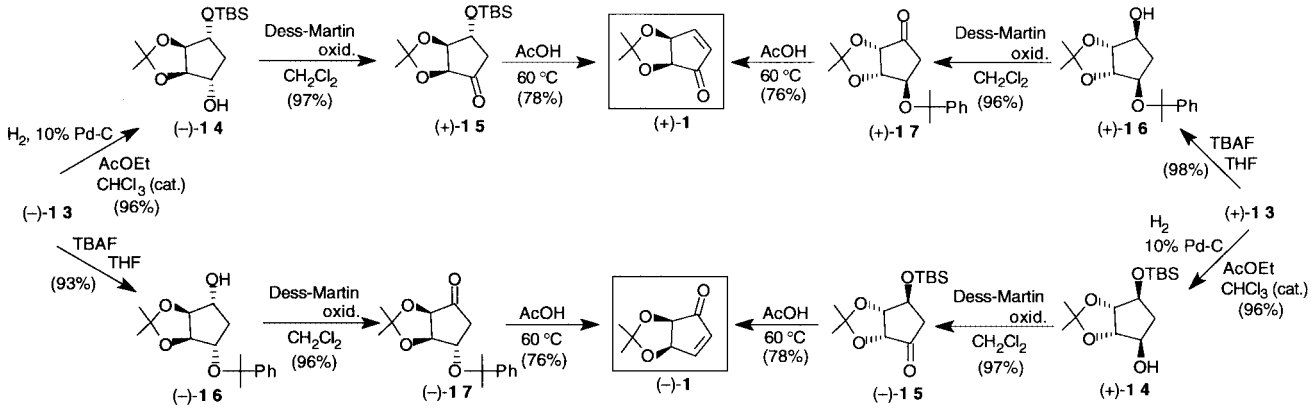
Anal. calcd for $C_{14}H_{16}O_2$ (216.3): C 77.75; H 7.64. Found: C 77.60; H 7.41.

(±)-(*cis*-1,4)-4-Cumyloxycyclopent-2-en-1-ol (±)-5

To a stirred solution of (±)-**4** (7.71 g, 35.6 mmol) and $CeCl_3.7H_2O$ (14.6 g, 39.2 mmol) in MeOH (100 mL) was added $NaBH_4$ (1.01 g, 26.7 mmol) portionwise at −78 °C. After stirring at the same temperature for 30 min, the reaction was quenched by addition of acetone (10 mL) and the mixture was extracted with EtOAc (4 × 50 mL). The extract was washed with brine (20 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 380 g, elution with hexane/EtOAc, 2:1 v/v) to give the alcohol (±)-**5** (7.18 g, 92%).

IR (film): ν = 3410 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (3 H, s), 1.58 (3 H, s), 1.61 (1 H, ddd, *J* = 13.8, 7.2, 7.2 Hz), 2.57 (1 H, ddd, *J* = 13.8, 4.8, 4.8 Hz), 4.05–4.12 (1 H, m), 4.43–4.52 (1 H, m), 5.83 (1 H, ddd, *J* = 5.7, 1.5, 1.5 Hz), 5.91 (1 H, ddd, *J* = 5.7, 1.5, 1.5 Hz), 7.23–7.48 (5 H, m).



Scheme 5

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.64, 29.60, 43.94, 74.98, 76.20, 77.84, 126.18, 127.17, 128.32, 136.07, 136.17, 146.82.

MS: *m*/*z* = 203 ($M^+ - CH_3$).

HRMS: *m*/*z* calcd for $C_{13}H_{15}O_2$ ($M^+ - CH_3$) 203.1072. Found 203.1054.

Anal. calcd for $C_{14}H_{18}O_2$ (218.3): C 77.03; H 8.31. Found: C 76.59; H 8.04.

Kinetic Transesterification of (±)-5

A solution of (±)-**5** (1.07 g, 4.91 mmol) and vinyl acetate (2.53 mL, 27.4 mmol) in *t*-BuOMe (30 ml) was suspended with immobilized lipase (Lipase PS, *pseudomonas* sp. AMANO) (1.07 g) and the suspension was stirred at r.t. for 2 h. After filtration through a Celite pad, the filtrate was evaporated under reduced pressure and chromatographed (silica gel, 70 g, elution with hexane/EtOAc, 4:1 v/v for (−)-**6** and hexane/EtOAc, 2:1 for (+)-**5**) to give the acetate (−)-**6** (543 mg, 43%) and the alcohol (+)-**5** (538.9 mg, 50%).

(−)-6

$[\alpha]_D^{29}$ −62.02 (*c* = 0.98, $CHCl_3$).

IR (film): ν = 1738 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (3 H, s), 1.57 (3 H, s), 1.71 (1 H, ddd, *J* = 14.1, 4.8, 4.8 Hz), 2.04 (3 H, s), 2.66 (1 H, ddd, *J* = 14.1, 7.5, 7.5 Hz), 4.00−4.17 (1 H, m), 5.32−5.38 (1 H, m), 5.86 (1 H, ddd, *J* = 6.0, 1.5, 1.5 Hz), 5.94 (1 H, ddd, *J* = 6.0, 1.5, 1.5 Hz), 7.23−7.48 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.09, 28.61, 29.49, 40.36, 75.92, 76.96, 77.78, 126.12, 127.17, 128.31, 131.65, 138.15, 146.76, 171.06.

MS: *m*/*z* = 260 (M^+).

HRMS: *m*/*z* calcd for $C_{16}H_{20}O_3$ (M^+) 260.1412. Found 260.1401.

Anal. calcd for $C_{16}H_{20}O_3$ (260.3): C 73.82; H 7.74. Found: C 73.56; H 7.79.

Optical purity was determined to be >99% ee by HPLC using a chiral column with chiral stationary phase (CHIRALCEL OD, elution: hexane/*i*-PrOH, 200:1 v/v).

(+)-5

$[\alpha]_D^{31}$ +27.52 (*c* = 1.11, $CHCl_3$).

Spectroscopic data were identical with those of (±)-**5**. Optical purity was determined to be >99% ee by HPLC using a chiral column with chiral stationary phase (CHIRALCEL OD, elution: hexane/*i*-PrOH, 200:1 v/v) after transformation into the acetate (+)-**6**.

Conversion of (−)-Acetate (−)-6 into (−)-Alcohol (−)-5

A solution of (−)-**6** (10.11 g, 38.84 mmol) in MeOH (150 ml) was stirred with K_2CO_3 (16.10 g, 116.5 mmol) at r.t. for 1.5 h. The mixture was diluted with H_2O (70 mL) and extracted with EtOAc (4 × 70 mL). The extract was washed with brine (30 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 500 g, elution with hexane/EtOAc, 2:1 v/v to give the alcohol (−)-**5** (8.09 g, 95%), $[\alpha]_D^{31}$ −27.43 (*c* = 1.01, $CHCl_3$). Spectroscopic data were identical with those of the enantiomer. Optical purity was determined to be >99% ee by HPLC using a chiral column as above.

Reaction of the (+)-Alcohol (+)-5 with *N*,*N*-Dimethylacetamide Dimethyl Acetal

A mixture of (+)-**5** (2.20 g, 10.08 mmol) and *N*,*N*-dimethylacetamide dimethyl Acetal (3.69 ml, 25.2 mmol) in diphenyl ether (53 mL) was refluxed for 30 min. After cooling, the mixture was chromatographed [silica gel, 150 g, elution with hexane/EtOAc, 4:1 v/v for diphenyl ether and 1:1 v/v for (−)-**7**] to give the acetamide (−)-**7** (2.44 g, 84%), $[\alpha]_D^{28}$ −140.57 (*c* = 1.08, $CHCl_3$); mp 50−51 °C (hexane) as colorless prisms.

IR (film): ν = 1651 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (3 H, s), 1.53 (3 H, s), 2.21 (1 H, dd, *J* = 15.6, 8.5 Hz), 2.26−2.29 (2 H, m), 2.77 (1 H, dd, *J* = 15.6, 2.7 Hz), 2.95 (3 H, s), 3.04 (3 H, s), 3.04−3.07 (1 H, m), 4.04 (1 H, dd, *J* = 8.5, 8.5 Hz), 5.58 (1 H, br d, *J* = 6.6 Hz), 5.75 (1 H, ddd, *J* = 6.6, 2.7, 1.8 Hz), 7.21−7.45 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.17, 29.35, 32.47, 35.41, 37.46, 38.67, 44.32, 78.85, 77.42, 126.00, 127.00, 128.19, 128.42, 134.49, 147.23, 173.13.

MS: *m*/*z* = 287 (M^+).

HRMS: *m*/*z* calcd for $C_{18}H_{25}O_2N$ (M^+) 287.1885. Found 287.1905.

Anal. calcd for $C_{18}H_{25}O_2N$ (287.4): C 75.22; H 8.77; N 4.87. Found: C 75.38; H 8.69; N 4.75.

Silylation of the (−)-Alcohol (−)-5

The alcohol (−)-**5** (4.02 g, 8.42 mmol), *tert*-butyldimethylsilyl chloride (3.92 g, 26.1 mmol) in DMF (40 mL) was mixed with imidazole (2.04 g, 29.96 mmol) at 0 °C and the mixture was stirred at r.t. for 3 h. The mixture was diluted with H_2O (20 mL) and was extracted with Et_2O (2 × 30 mL). The extract was washed with brine (10 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 200 g, elution with hexane/EtOAc, 8:1 v/v) to give the silyl ether (−)-**9** (6.07 g, 99%); $[\alpha]_D^{31}$ −47.01 (*c* = 1.01, $CHCl_3$) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.061 (6 H, s), 0.896 (9 H, s), 1.57 (6 H, s), 1.64 (1 H, ddd, *J* = 13.8, 6.3, 6.3 Hz), 2.53 (1 H, ddd, *J* = 13.8, 7.0, 7.0 Hz), 4.05 (1 H, dd, *J* = 7.0, 6.3 Hz), 4.50 (1 H, dd, *J* = 7.0, 6.3 Hz), 5.77 (1 H, s), 5.78 (1 H, s), 7.23−7.50 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.72, −4.64, 18.07, 25.86, 29.05, 29.40, 44.58, 74.81, 76.07, 77.48, 126.23, 127.03, 128.28, 135.00, 136.54, 147.27.

MS: *m*/*z* = 275 ($M^+ - t$-C_4H_9).

HRMS: *m*/*z* calcd for $C_{16}H_{23}O_2Si$ ($M^+ - t$-C_4H_9) 275.1468. Found: 275.1456.

Anal. calcd for $C_{20}H_{32}O_2Si$ (332.6): C 72.23; H 9.70. Found: C 72.27; H 9.74.

The enantiomeric silyl ether (+)-**9**; $[\alpha]_D^{28}$ +48.90 (*c* = 1.61, $CHCl_3$), was obtained quantitatively from the (+)-alcohol (+)-**5** by the same treatment.

Birch Reduction of the Silyl Ether (−)-9

To a stirred solution of (−)-**9** (3.01 g, 9.05 mmol) in THF (20 mL) was introduced liq. NH_3 (ca. 30 mL) at −78 °C. Then, Na (ca. 1.0 g) was added to the mixture, piece by piece, until blue color was maintained and NH_4Cl (200 mg) was added to quench the reaction. After evaporation of ammonia by stirring at room temperature, the mixture, after dilution with water (20 mL), was extracted with Et_2O (2 × 50 mL), washed with brine (10 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 150 g, elution with hexane/EtOAc, 6:1 v/v) to give the silyl alcohol (−)-**10** (1.39 g, 72%), $[\alpha]_D^{30}$ −24.53 (*c* = 1.59, CH_2Cl_2) [Lit[15] for 1*S*,4*R* enantiomer, $[\alpha]_D^{20}$ +24.29 (*c* = 2.47, CH_2Cl_2)], as a colorless oil.

IR (film): ν = 3307 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.079 (6 H, s), 0.889 (9 H, s), 1.50 (1 H, ddd, *J* = 13.8, 4.5, 4.5 Hz), 2.00 (1 H, br s), 2.68 (1 H, ddd, *J* = 13.8, 6.9, 6.9 Hz), 4.57−4.59 (1 H, m), 4.63−4.67 (1 H, m), 5.87 (1 H, d, *J* = 6.0 Hz), 5.94 (1 H, d, *J* = 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.72, 18.15, 25.88, 44.69, 75.23, 135.82, 137.10.

MS: *m*/*z* = 157 ($M^+ - t$-C_4H_9).

HRMS: *m*/*z* calcd for $C_7H_{13}O_2$ ($M^+ - t$-C_4H_9) 175.0685. Found 175.0666.

Reaction of the Silyl Alcohol (−)-10 with *N*,*N*-Dimethylacetamide Dimethyl Acetal

A mixture of (−)-**10** (1.00 g, 4.68 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (1.71 ml, 11.7 mmol) in diphenyl ether (20 mL) was refluxed for 30 min. After cooling, the mixture was chromatographed (silica gel, 70 g, elution with hexane/EtOAc, 4:1 v/v for diphenyl ether and 1:1 v/v for (−)-**11**) to give the acetamide (−)-**11** (1.03 g, 78%); $[\alpha]_D^{27}$ −56.55 (*c* = 1.01, $CHCl_3$), as a colorless oil.

IR (film): ν = 1655 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.002 (3 H, s), 0.030 (3 H, s), 0.850 (9 H, s), 2.18−2.23 (2 H, m), 2.52 (1 H, dd, *J* = 16.8, 6.6 Hz), 2.64 (1 H, dd, *J* = 15.9, 7.5 Hz), 2.92 (3 H, s), 2.98 (3 H, s), 3.15 (1 H, dd, *J* = 13.8, 6.6 Hz), 4.51 (1 H, ddd, *J* = 6.6, 6.6, 4.2 Hz), 5.66 (2 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.43, −4.99, 18.06, 25.79, 31.92, 35.30, 37.11, 41.59, 45.83, 73.18, 128.16, 133.76, 172.82.

MS: *m*/*z* = 283 (M^+).

HRMS: *m*/*z* calcd for $C_{15}H_{29}O_2NSi$ (M^+) 283.1968. Found 283.1950.

Anal. calcd for $C_{15}H_{29}O_2NSi$ (283.5): C 63.55; H 10.31; N 4.94. Found: C 63.33; H 10.09; N 4.81.

Conversion of the Acetamide (−)-7 into Oxabicyclo[3.3.0]oct-6-en-3-one [(−)-8]

A solution of the acetamide (−)-**7** (2.41 g, 8.38 mmol) in a solution of 10% HCl (20 mL) and dioxane (20 mL) was stirred at r.t. for 10 h. The mixture was extracted with Et_2O (3 × 30 mL), washed with brine (10 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 140 g, elution with hexane/Et_2O, 1:1 v/v) to give the lactone (−)-**8** (909 mg, 87%); mp 43−44 °C; $[\alpha]_D^{29}$ −103.21 (*c* = 1.02, MeOH) [Lit.[9] mp 42 °C; $[\alpha]_D^{26}$ −102.3 (*c* = 0.7, MeOH)], as colorless crystals. Spectroscopic data were identical with those of an authentic material.

Conversion of the Acetamide (−)-11 into Oxabicyclo[3.3.0]oct-6-en-3-one [(−)-8]

A solution of the acetamide (−)-**11** (857 mg, 3.02 mmol) in a solution of 10% HCl (10 mL) and dioxane (10 mL) was stirred at r.t. for 15 h. The mixture was extracted with Et_2O (3 × 20 mL), washed with brine (5 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 60 g, elution with hexane/Et_2O, 1:1 v/v) to give the lactone (−)-**8** (286 mg, 76%); mp 44 °C, $[\alpha]_D^{30}$ −103.11 (*c* = 1.02, MeOH), as colorless crystals. Spectroscopic data were identical with those of an authentic material.

Dihydroxylation of the Bis-Ether (+)-9

A solution of (+)-**9** (11.25 g, 33.83 mmol) in 50% aq THF (150 mL) was stirred with NMO (5.95 g, 50.8 mmol) and a solution of OsO_4 (0.196 M in THF, 4.3 mL, 0.85 mmol) at r.t. for 3 d. After treatment with sat. aq Na_2SO_3 (5 mL), the mixture was extracted with EtOAc (3 × 200 mL). The extract was washed with brine (50 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 500 g, elution with hexane/EtOAc, 4:1 v/v) to give the *cis*-diol (+)-**12** (11.16 g, 90%); mp 48-49 °C (hexane); $[\alpha]_D^{30}$ +10.16 (*c* = 0.734, $CHCl_3$) as colorless needles.

IR (film): ν = 3390 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.034 (3 H, s), 0.042 (3 H, s), 0.881 (9 H, s), 1.48 (1 H, ddd, *J* = 13.5, 7.2, 7.2 Hz), 1.54 (3 H, s), 1.58 (3 H, s), 2.19 (1 H, ddd, *J* = 13.5, 8.0, 6.7 Hz), 2.29 (1 H, br s), 2.50 (1 H, br s), 3.55 (1 H, ddd, *J* = 8.0, 7.2, 6.7 Hz), 3.80 (1 H, dd, *J* = 4.7, 4.7 Hz), 3.83 (1 H, ddd, *J* = 7.2, 6.7, 4.7 Hz), 3.98 (1 H, dd, *J* = 4.7, 4.7 Hz), 7.23−7.48 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.89, 17.90, 25.65, 28.71, 28.78, 39.24, 74.89, 76.33, 76.89, 77.38, 77.50, 126.08, 127.21, 128.27, 146.85.

MS: *m*/*z* = 351 ($M^+ - CH_3$), 309 ($M^+ - t$-C_4H_9), 229 ($M^+ - C_9H_{13}O$).

HRMS: *m*/*z* calcd for $C_{11}H_{21}O_3Si$ ($M^+ - C_9H_{13}O$) 229.1260. Found: 229.1278.

Anal. calcd for $C_{20}H_{34}O_4Si$ (366.6): C 65.53; H 9.35. Found: C 65.64; H 9.35.

The enantiomeric *cis*-diol (−)-**12** was obtained in 90% yield from the enantiomeric bis-ether (−)-**9** by the same treatment; mp 48−49 °C (hexane); $[\alpha]_D^{30}$ −10.25 (*c* = 0.752, $CHCl_3$)

Conversion of the Diol (+)-12 into the Acetonide (−)-13

A solution of the diol (+)-**12** (11.16 g, 30.44 mmol) and 2,2-dimethoxypropane (37 mL, 300 mmol) in CH_2Cl_2 (115 mL) containing a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) (76 mg, 0.3 mmol) was stirred at r.t. for 24 h. To the mixture was added sat. aq $NaHCO_3$ (100 mL) and extracted with Et_2O (2 × 150 mL). The combined Et_2O extracts were dried ($MgSO_4$), evaporated under reduced pressure, and the residue chromatographed (silica gel, 500 g, elution with hexane/EtOAc, 20:1 v/v) to give the acetonide (−)-**13** (12.04 g, 97%); $[\alpha]_D^{32}$ −20.76 (*c* = 1.01, $CHCl_3$) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.060 (3 H, s), 0.071 (3 H, s), 0.897 (3 H, s), 1.24 (3 H, s), 1.33 (3 H, s), 1.50 (3 H, s), 1.61 (3 H, s), 1.71 (1 H, ddd, *J* = 13.5, 6.6, 6.6 Hz), 2.07 (1 H, ddd, *J* = 13.5, 6.6, 6.6 Hz), 3.66 (1 H, ddd, *J* = 6.5, 6.5, 2.9 Hz), 3.98 (1 H, ddd, *J* = 6.5, 6.5, 2.7 Hz), 4.37 (1 H, dd, *J* = 6.9, 2.7 Hz), 4.51 (1 H, dd, *J* = 6.9, 2.0 Hz), 7.21−7.47 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.88, 17.91, 24.55, 25.70, 26.73, 27.32, 30.42, 40.52, 76.62, 77.14, 77.67, 86.49, 86.78, 110.87, 126.08, 126.86, 128.09, 147.16.

MS: *m*/*z* = 391 ($M^+ - CH_3$), 287 ($M^+ - C_9H_{11}$).

HRMS: *m*/*z* calcd for $C_{14}H_{27}O_4Si$ ($M^+ - C_9H_{11}$) 287.1679. Found: 287.1678.

Anal. calcd for $C_{23}H_{38}O_4Si$ (406.6): C 67.94; H 9.42. Found: C 67.85; H 9.51.

The enantiomeric acetonide (+)-**13** was obtained in 97% yield from the enantiomeric diol (−)-**12** by the same treatment; $[\alpha]_D^{30}$ +20.76 (*c* = 0.95, $CHCl_3$).

Hydrogenolysis of the Bis-Ether (−)-13 to the Cyclopentanol (−)-14

The cumyl ether (−)-**13** (10.00 g, 24.62 mmol) was stirred under an hydrogen atmosphere in EtOAc (100 mL) containing 3 drops of $CHCl_3$ in the presence of 10% Pd-C (756 mg) at r.t. for 17 h. After filtration through a Celite pad, the filtrate was evaporated under reduced pressure and chromatographed (silica gel, 500 g, elution with hexane/EtOAc, 8:1 v/v) to give the alcohol (−)-**14** (6.80 g, 96%); $[\alpha]_D^{28}$ −5.42 (*c* = 1.11, $CHCl_3$), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.124 (3 H, s), 0.134 (3 H, s), 0.892 (9 H, s), 1.29 (3 H, s), 1.39 (3 H, s), 1.76 (1 H, d, *J* = 14.4 Hz), 2.09 (1 H, ddd, *J* = 14.4, 4.2, 4.2 Hz), 3.21 (1 H, d, *J* = 11.3 Hz), 4.09 (1 H, dd, *J* = 11.3, 4.2 Hz), 4.25 (1 H, d, *J* = 4.2 Hz), 4.51 (1 H, dd, *J* = 5.7, 1.5 Hz), 4.66 (1 H, dd, *J* = 5.7, 1.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.27, −5.15, 17.74, 23.68, 25.58, 26.02, 37.24, 77.53, 78.40, 85.82, 86.43, 110.10.

MS: *m*/*z* = 289 (M^+ + H), 273 (M^+ – Me).

HRMS: *m*/*z* calcd for $C_{13}H_{25}O_4Si$ ($M^+ - CH_3$) 273.1522. Found: 273.1524.

Anal. calcd for $C_{14}H_{28}O_4Si$ (288.5): C 58.29; H 9.78. Found: C 58.31; H 9.60.

The enantiomeric cyclopentanol (+)-**14** was obtained in 96% yield from the enantiomeric cumyl ether (+)-**13** by the same treatment; $[\alpha]_D^{25}$ +5.52 (*c* = 1.02, $CHCl_3$).

Oxidation of the Cyclopentanol (−)-14 into the Cyclopentanone (+)-15

To a stirred solution of the alcohol (−)-**14** (6.14 g, 21.29 mmol) in CH_2Cl_2 (100 mL) was added the Dess−Martin reagent (14.60 g, 35.00 mmol) portionwise at r.t. After stirring at the same temperature for 30 min, the mixture was treated with 0.5 N NaOH (100 mL), extracted with EtOAc (2 × 100 mL), and the organic layer was separated. The organic layer was washed with brine (20 mL), dried ($MgSO_4$), evaporated under pressure, and chromatographed (silica gel, 420 g, elution with hexane/EtOAc, 8:1 v/v) to give the cyclopentanone (+)-**15** (5.94 g, 97%); $[\alpha]_D^{31}$ +133.48 (*c* = 1.16, $CHCl_3$), as a colorless oil.

IR (film): ν = 1764 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.085 (3 H, s), 0.11 (3 H, s), 0.87 (9 H, s), 1.35 (3 H, s), 1.42 (3 H, s), 2.17 (1 H, d, *J* = 18.0 Hz), 2.28 (1 H, dd, *J* = 18.0, 5.0 Hz), 4.30 (1 H, d, *J* = 5.4 Hz), 4.42 (1 H, d, *J* = 5.0 Hz), 4.54 (1 H, d, *J* = 5.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.11, 17.79, 24.68, 25.49, 26.63, 43.07, 69.18, 77.99, 82.75, 112.80, 212.24.

MS: *m*/*z* = 271 ($M^+ - CH_3$).

HRMS: *m*/*z* calcd for $C_{13}H_{23}O_4Si$ ($M^+ - CH_3$) 271.1366. Found: 271.1350.

Anal. calcd for $C_{14}H_{26}O_4Si$ (286.5): C 58.76; H 9.15. Found: C 58.76; H 9.30.

The enantiomeric ketone (−)-**15** was obtained in 97% yield by the same treatment; $[\alpha]_D^{28}$ −136.59 (*c* = 1.22, $CHCl_3$).

(+)-(3a*S*,6a*S*)-2,2-Dimethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-one [(+)-1] from Cyclopentanone (+)-15

A solution of the ketone (+)-**15** (5.17 g, 18.05 mmol) in AcOH (100 mL) was stirred at 60 °C for 4 d. After cooling, the mixture was diluted with Et_2O (300 mL) and the solution was washed successively with brine (100 mL) and 1 N NaOH (100 mL). The organic layer was dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 250 g, elution with hexane/Et_2O, 3:1 to 1:1 v/v) to give the cyclopentenone (+)-**1** (2.18 mg, 78%); mp 68−69 °C; $[\alpha]_D^{32}$ +69.70 (*c* = 1.18, $CHCl_3$) [Lit[1i] mp 68−69 °C $[\alpha]_D^{25}$ +70.49 (*c* 0.95, $CHCl_3$)]. Spectroscopic data were identical with those of an authentic material.

The enantiomeric enone (−)-**1**, mp 68−69 °C $[\alpha]_D^{31}$ −69.33 (*c* 1.22, $CHCl_3$), was obtained in 78% yield from the enantiomeric ketone (−)-**15** by the same treatment.

Desilylation of the Bis-Ether (−)-13 to Cyclopentanol (−)-16

To a stirred solution of the ether (−)-**13** (9.18 g, 22.58 mmol) in THF (50 mL) was added TBAF (1.0 M in THF; 27 mL, 27 mmol) dropwise at 0 °C. After stirring at r.t. for 2.5 h, the mixture was extracted with EtOAc (2 × 100 mL), The extract was washed with brine (20 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 450 g, elution with hexane/EtOAc, 4:1 v/v) to give the cyclopentanol (−)-**16** (6.17 g, 93%) as a colorless oil; mp 110−111 °C (EtOAc/hexane); $[\alpha]_D^{31}$ −19.53 (*c* = 1.08, $CHCl_3$).

IR (film): ν = 3500 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (3 H, s), 1.31 (3 H, s), 1.56 (3 H, s), 1.63 (3 H, s), 1.74 (1 H, d, *J* = 14.4 Hz), 1.96 (1 H, ddd, *J* = 14.4, 4.5, 4.5 Hz), 3.33 (1 H, d, *J* = 11.0 Hz), 3.87 (1 H, d, *J* = 4.5 Hz), 4.05 (1 H, dd, *J* = 11.0, 4.5 Hz), 4.60 (1 H, dd, *J* = 5.7, 1.5 Hz), 4.61 (1 H, dd, *J* = 5.7, 1.5 Hz), 7.25−7.45 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.67, 25.96, 27.37, 29.60, 36.45, 77.26, 78.67, 79.17, 85.32, 86.37, 109.98, 126.02, 127.50, 128.38, 145.20.

MS: *m*/*z* = 292 (M^+).

HRMS: *m*/*z* calcd for $C_{17}H_{24}O_4$ 292.1675. Found 292.1695.

Anal. calcd for $C_{17}H_{24}O_4$ (292.4): C 69.84; H 8.27. Found: C 69.89; H 8.24.

The enantiomeric alcohol (+)-**16** was obtained in 98% yield from the enantiomeric ether (+)-**13** by the same treatment; mp 110−111 °C (EtOAc/hexane); $[\alpha]_D^{29}$ +19.75 (*c* = 0.75, $CHCl_3$).

Oxidation of Cyclopentanol (−)-16 into Cyclopentanone (−)-17

To a stirred solution of the alcohol (−)-**16** (2.98 g, 10.19 mmol) in CH_2Cl_2 (50 mL) was added the Dess−Martin reagent (6.39 g, 15.29 mmol) portionwise at r.t. After stirring at the same temperature for 30 min, the mixture was treated with 0.5 N NaOH (50 mL), extracted with EtOAc (3 × 50 mL), and the organic layer was separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 150 g, elution with hexane/EtOAc, 4:1 v/v) to give the cyclopentanone (−)-**17** (2.85 g, 96%) as colorless needles; mp 98−99 °C (hexane); $[\alpha]_D^{31}$ −142.81 (*c* = 1.13, $CHCl_3$).

IR (film): ν = 1758 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (3 H, s), 1.34 (3 H, s), 1.55 (3 H, s), 1.62 (3 H, s), 2.23 (1 H, ddd, *J* = 18.3, 3.0, 1.5 Hz), 2.67 (1 H, dd, *J* = 18.3, 6.3 Hz), 3.99 (1 H, ddd, *J* = 6.3, 1.5, 1.5 Hz), 4.36 (1 H, br d, *J* = 4.36 Hz), 4.58 (1 H, d, *J* = 5.4 Hz), 7.25−7.44 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.76, 26.63, 27.78, 29.09, 42.63, 69.91, 78.37, 78.64, 82.51, 112.54, 125.95, 127.51, 128.39, 145.58, 212.68.

MS: *m*/*z* = 290 (M^+).

HRMS: *m*/*z* calcd for $C_{17}H_{22}O_4$ (M^+) 290.1518. Found 290.1553.

Anal. calcd for $C_{17}H_{22}O_4$ (290.4): C 70.32; H 7.64. Found: C 70.19; H 7.58.

The enantiomeric ketone (+)-**17** was obtained in 96% yield from the enantiomeric alcohol (+)-**16** by the same treatment; mp 98−99 °C (hexane), $[\alpha]_D^{29}$ +144.15 (*c* = 0.92, $CHCl_3$),

(−)-(3a*R*,6a*R*)-2,2-Dimethyl-3a,6a-dihydro-4*H*-cyclopenta-[*d*][1,3]dioxol-4-one (−)-1

A solution of the ketone (−)-**17** (2.57 g, 8.85 mmol) in AcOH (50 mL) was stirred at 60 °C for 4 d. After cooling, the mixture was diluted with Et_2O (150 mL) and the solution was washed successively with brine (50 mL) and 1 **N** NaOH (50 mL). The organic layer was dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 150 g, elution with hexane/Et_2O, 1:1 v/v) to give the cyclopentenone (−)-**1** (1.03 g, 76%); mp 68−69 °C (hexane); $[\alpha]_D^{32}$ −69.88 (*c* = 1.00, $CHCl_3$).

The enantiomeric cyclopentenone (+)-**1**, mp 68-69 °C (hexane), $[\alpha]_D^{31}$ +69.36 (*c* = 1.05, $CHCl_3$), was obtained in 76% yield from the enantiomeric cyclopentenone (+)-**17** by the same treatment.

References

(1) (a) Cocu, F. G.; Posternak, T. *Helv. Chim. Acta* **1972**, *55*, 2838.
(b) Bestmann, H, J.; Moenius, T. *Angew. Chem. Int. Ed. Engl*. **1986**, *25*, 994.
(c) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc*. **1986**, *108*, 5655.
(d) Ohrui, H.; Konno, M.; Meguro, H. *Agric. Biol. Chem*. **1987**, *51*, 625.
(e) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem*. **1987**, *52*, 5457.
(f) Deardorff, D. R.; Shambayati, S.; Myles, D. C.; Heerding, D. *J. Org. Chem*. **1988**, *53*, 3614.
(g) Flann, C. J.; Mash, E. A. *Synth. Commun*. **1988**, *18*, 391.
(h) Belanger, P.; Prasit, P. *Tetrahedron Lett*. **1988**, *29*, 5521.
(i) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc*. **1988**, *110*, 4726.
(j) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc*. **1988**, *110*, 4735.
(k) Takano, S.; Inomata, K.; Ogasawara, K. *Chem. Lett*. **1989**, 359.
(l) Ali, S. M.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett*. **1990**, *31*, 1509.
(m) See also reviews: Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769. Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Acc. Chem. Res*. **1998**, *31*, 333.

(2) A pertinent monograph, see: Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*, Pergamon: Oxford, 1994.

(3) Takano, S.; Iwabuchi, Y.; Takahashi, M.; Ogasawara, K. *Chem. Pharm. Bull*. **1986**, *34*, 3445.

(4) Haubenstock. H.; Mennitt, P. G.; Butler, E. *J. Org. Chem*. **1970**, *35*, 3208.

(5) Stork, G.; Isobe, M. *J. Am. Chem. Soc*. **1975**, *97*, 6260.

(6) Gemal, A. L.; Luche, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 5454.

(7) Sugahara, T.; Kuroyanagi, Y.; Ogasawara, K. *Synthesis* **1996**, 1101.

(8) A part of the present study has been reported in a preliminary form, see: Nakashima, H.; Sato, M.; Taniguchi, T.; Ogasawara, K. *Synlett* **1999**, 1754.

(9) Sugahara, T.; Ogasawara, K. *Synlett* **1996**, 319.

(10) Takano, S.; Tanigawa, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun*. **1976**, 189.

(11) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425.

(12) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Lee, T. -t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc*. **1970**, *92*, 741.

(13) Schroder, M. *Chem. Rev*. **1980**, *80*, 187.

(14) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.

(15) Myers, A. G.; Hammond, M.; Wu, Y. *Tetrahedron Lett*. **1986**, *37*, 3083.

Article Identifier:
1437-210X,E;2000,0,06,0817,0823,ftx,en;F00800SS.pdf