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Regio-, Stereo-, and Enantioselective Synthesis of Cyclobutanols by Means of the Photoaddition of 1,3-Dioxin-4-ones and Lipase-Catalyzed Acetylation[1,2]

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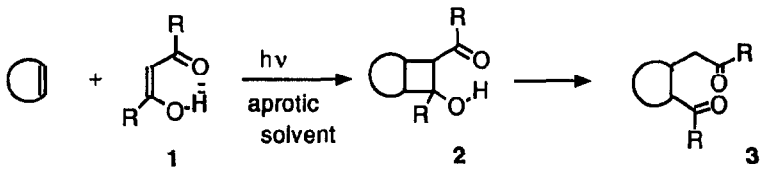
Abstract: Homochiral *cis*-2-hydroxymethylcyclobutanols, their all *cis* 3-methyl, and 4-hydroxymethyl derivatives were synthesized from 1,3-dioxin-4-ones *via* cyclobutane ring formation by [2+2]photocycloaddition, dioxanone ring cleavage, and reduction, followed by lipase-catalyzed kinetic resolution of the resulted cyclobutanols. The chiral cyclobutanols thus obtained have been converted to the corresponding γ-lactones which are potential precursors for a series of biologically active compounds.

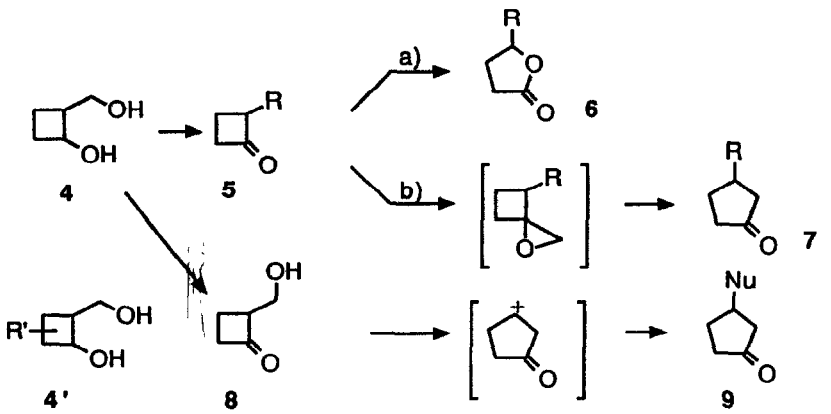
The application of cyclobutane derivatives in synthetic chemistry is well documented.[3] Their popularity has been attained due to their accessibility by [2+2]-photocycloaddition and their ready cleavage and/or ring expansion of cyclobutane rings due to their inherent strain.[4] Among the [2+2]photocycloaddition reactions, the photoaddition of alkenes to enolized 1,3-diketones and their derivatives is often referred to as the de Mayo reaction.[5] One of the earliest examples of the addition of enones to alkenes was the reaction of β-diketones (1) and alkenes to give 1,5-diketones (3). The primary photoproducts: acylcyclobutanols (2) undergo spontaneous retro-aldol cyclobutane cleavage and are seldom isolated.[6,7]



1 2 3

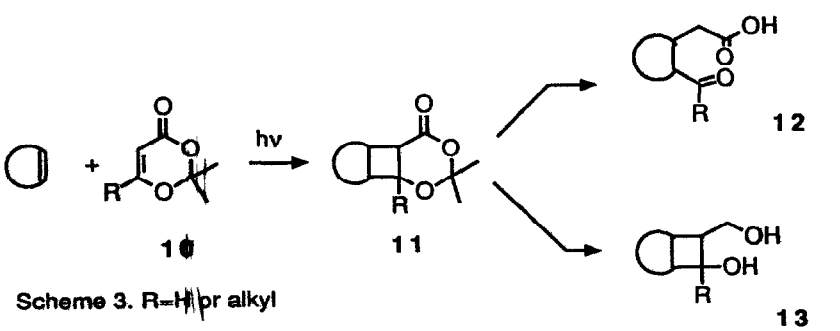
Scheme 1

We have been interested in synthesizing *cis*-2-hydroxymethylcyclobutanols (4) and their substituted derivatives (4') as enantiomerically pure compounds. Because cyclobutanones (5) are exceptionally facile starting materials for the preparation of γ-lactones: 6 (Baeyer-Villiger oxidation:[8] path a) as well as cyclopentanones: 7 (addition of carbenes[9] or their equivalents followed by ring expansion:[10] path b), while cyclobutanemethanol (8) affords cyclopentanone derivatives (9) *via* the



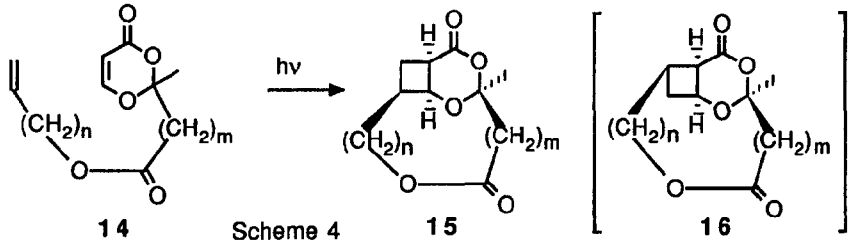
Scheme 2. R: the groups that can be manipulated from CH_2OH.

cyclobutylmethyl cation to cyclopentyl cation rearrangement.[11] All of these transformations proceed with retention of configuration of the substituents (e.g. R') in the four-membered ring. Acyclic β–keto esters[12] such as ethyl acetoacetate as well as their enol derivatives such as β–acetoxyacrylate[13] do not give cyclobutanes on irradiation with alkenes. The lack of participation in the photoaddition reactions as the enone components is due to the lower acidity of β-keto esters relative to β-diketones and hence weak configurationally restricting intramolecular hydrogen bond. β-Acetoxyacrylates are prone to *cis-trans* isomerization *via* the excited state and hence are incapable of the addition to alkenes. Successful use of dioxinones: **10** (chemical equivalents of formyl- and acetoacetic esters) as enones has extended the de Mayo reaction to permit ready access of the compounds having acyl (or formyl) and acetic acid appendages at the geminal position (**12**).[14,15] This methodology has been extended successfully by using homochiral dioxinones (spirocyclic[16] or non-spirocyclic derivatives[17,18]). Though most of the research work so far reported have used ring-opened products (**12**), it is desirable to explore a method which provides ready conversion of the adducts (**11**) to 2–hydroxymethylcyclobutanols (**13**) (cf. **4** → **6**, **7**, and **9** in Scheme 2).



Scheme 3. R=H or alkyl

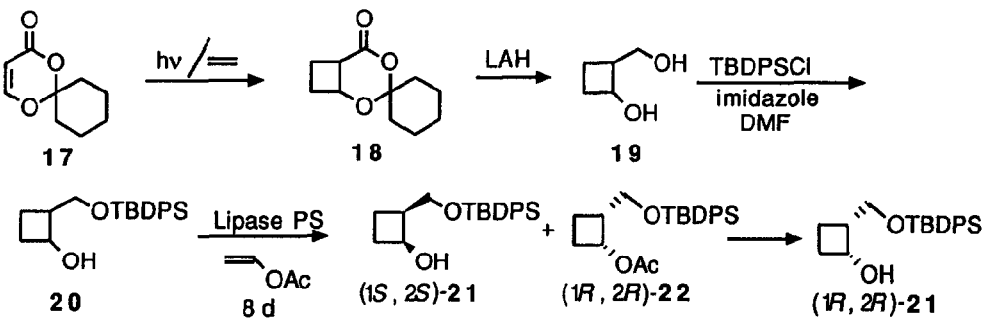
In connection with the above lines of work, we have developed previously the synthetic approach to all *cis*-1,2,3-trisubstututed cyclobutanes by means of intramolecular photoaddition of the dioxinones whose acetal carbon is connected with an appropriate olefin by an ester group (e.g. **14**).[18] Thus, when m+n=2 or 3, the parallel adducts (**15**) are formed predominantly (ratio of parallel/cross=5~100). An extension



Scheme 4

of this method to enantiocontrolled synthesis, however, is not easy. So far we have succeeded only in the resolution of **14** [m=0, $C_6H_5CH_2O$ instead of $CH{=}CH{-}(CH_2)_n{-}O$] by means of hplc with ChiraSpher. Therefore, in order to prepare the desired cyclobutanols (e.g. **4**) as enantiomerically pure, we examined the strategy involving intermolecular photo[2+2]cycloaddition of dioxinones, reduction, and separation of the cyclobutanols into each enantiomer. Throughout this paper, we have used 4-oxo-1,5-dioxaspiro[5.5]undec-2-ene (**17**) as the starting material.

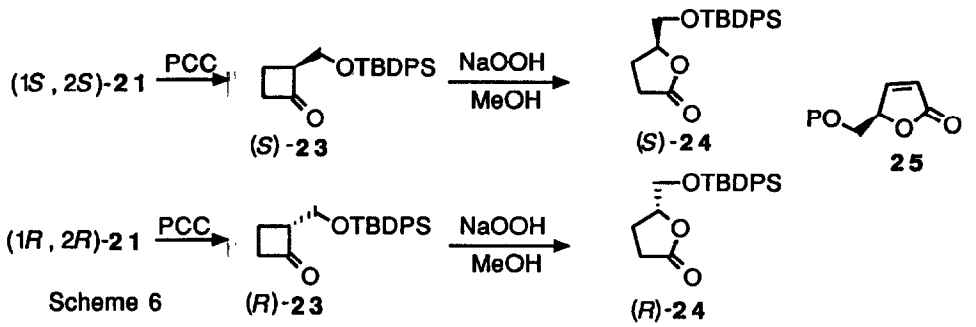
At first, synthesis of the parent compound (**19**) and its resolution into each enantiomer were investigated. The synthesis of racemic **19** was readily attained through photoaddition of **17** to ethylene. Reduction of the adduct (**18**) by lithium aluminum hydride (LAH) gave the racemic diol (**19**) in 80% yield. We then investigated lipase-catalyzed acetylation of the mono-*tert*-butyldiphenylsilylated cyclobutanol (**20**). Among several lipases tested, the use of lipase PS gave the best result. Thus, when **20** was treated with Lipase PS in vinyl acetate for 7 d, the acetate [(1*R*,2*R*)-**22**] and the alcohol [(1*S*,2*S*)-**21**] were obtained in nearly equal amounts. By



Scheme 5

treatment of the acetate with potassium carbonate in methanol, the enantiomeric alcohol [(1*R*,2*R*)-**21**] was obtained in quantitative yield. Both alcohols were transformed to (*R*)-MTPA esters and subjected to 500 MHz ^{1}H-NMR analysis. As a result, e.e.s of (1*S*,2*S*)-**21** and (1*R*,2*R*)-**22** obtained directly from lipase-catalyzed acetylation were determined as 98% for **21** and 90% for **22**. The absolute structure of each product was determined by the conversion to the known 5-substituted 2-furanones [(*S*)- and (*R*)-**24**].[19]

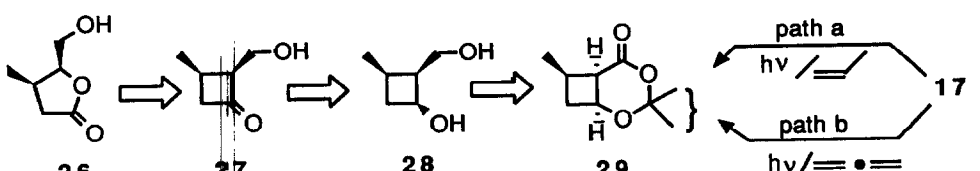
Enantiomerically pure 5-(hydroxymethyl)-2-furanone and its dihydro derivative are important building blocks for a variety of compounds. For example, 2-furanone derivatives, **25** (obtainable from **24** by introduction of phenyl selenyl group followed by oxidative removal of the selenyl group[20]) served as the key intermediates for the synthesis of (-)-verrucarinolactone [(3*S*,4*R*)-3-hydroxy-4-methyltetrahydropyran-2(2*H*)-one][21] and (+)-eldanolide [(4*S*,5*R*)-dihydro-4-methyl-5-(3-methyl-2-butenyl)-2(3*H*)-furanone].[20] Since introduction of a methyl group to 4α-position (*trans* to the hydroxymethyl group) of **25** is readily achieved by 1,4-conju-



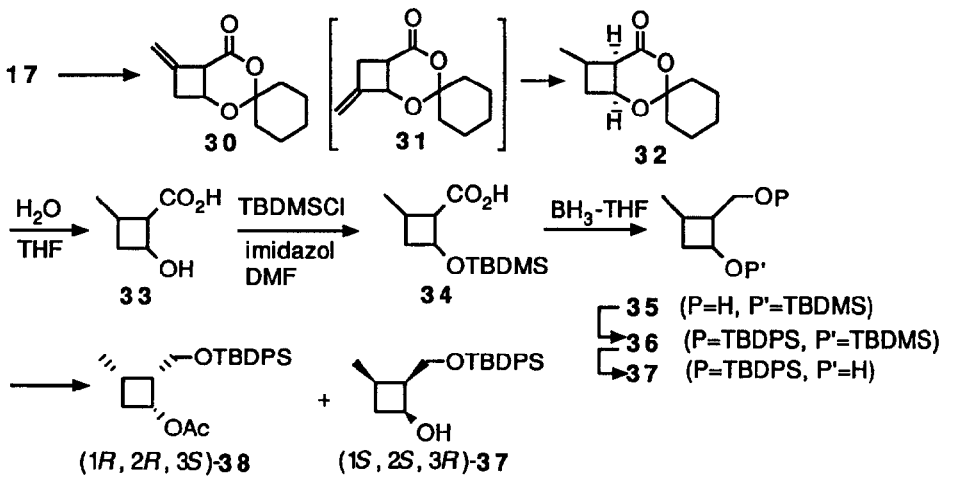
Scheme 6

gated addition of dimethyllithium cuprate,[20] we chose (4*R*,5*S*)-dihydro-5-(hydroxymethyl)-4-methyl-2(3*H*)-furanone (**26**: *cis*-relationship between 4- and 5-substituents) as the second target molecule. The retrosynthesis of **26** within the present methodology automatically suggests **29** as the adequate precursor. By knowing that the addition not only proceeds preferentially *via an exo*-transition state but also affords the head-to-tail (H-T) adduct in predominance,[16,22] path a was abandoned.

Use of allene[23] instead of propene, as the alkene (path b) led to successful



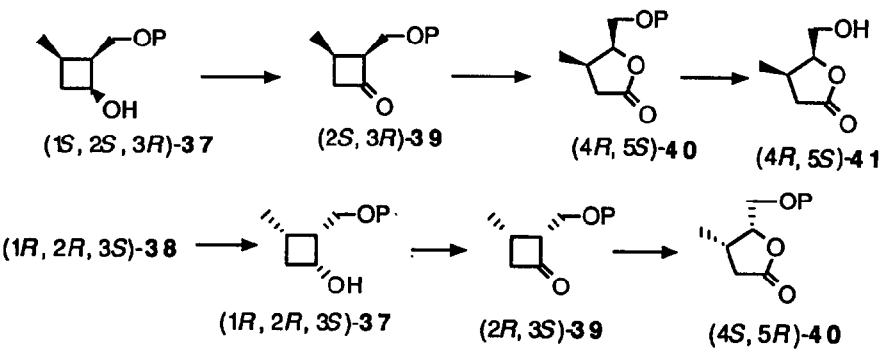
Scheme 7



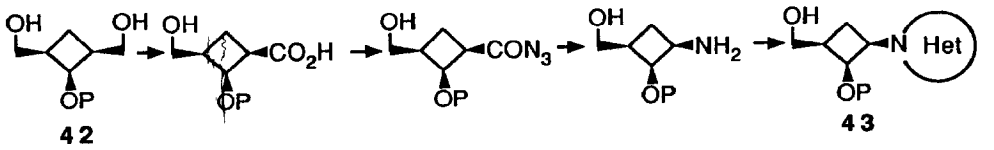
Scheme 8

route for the preparation of **29**. As expected, the H-H adduct (**30**) was formed preferentially (ratio of H-H/H-T=*ca.* 10) and its catalytic hydrogenation gave exclusively the *endo*-methyl product (**32**=**29**). Reductive dioxinone ring opening of **32** with LAH gave the desired diol (**28**) in only poor yield (*ca.* 10%), but the substrate (**37**) for the lipase-catalyzed acetylation reaction was obtained through the hydroxycarboxylic acid (**33**) by three steps with satisfactory overall yield (*ca.* 60%). The kinetic resolution of racemic **37** gave (1*S*,2*S*,3*R*)-**37** and (1*R*,2*R*,3*S*)-**38** in nearly equal amounts with high e.e.s (94% for the former and ≥98% for the latter). The absolute structure of each product was determined by their conversion to the furanones (**40**). Hence, synthesis of key intermediate [(4*R*,5*S*)-**40**] for (-)-verrucarinolactone[21] as well as its enantiomer [(4*S*,5*R*)-**40**] was accomplished.

Dissymmetrization of a prochiral meso compound is ideal, because, this leads quantitatively to a single enantiomer while the resolution of a racemic compound gives at most 50% of the desired enantiomer.[24] This fact as well as our interest in



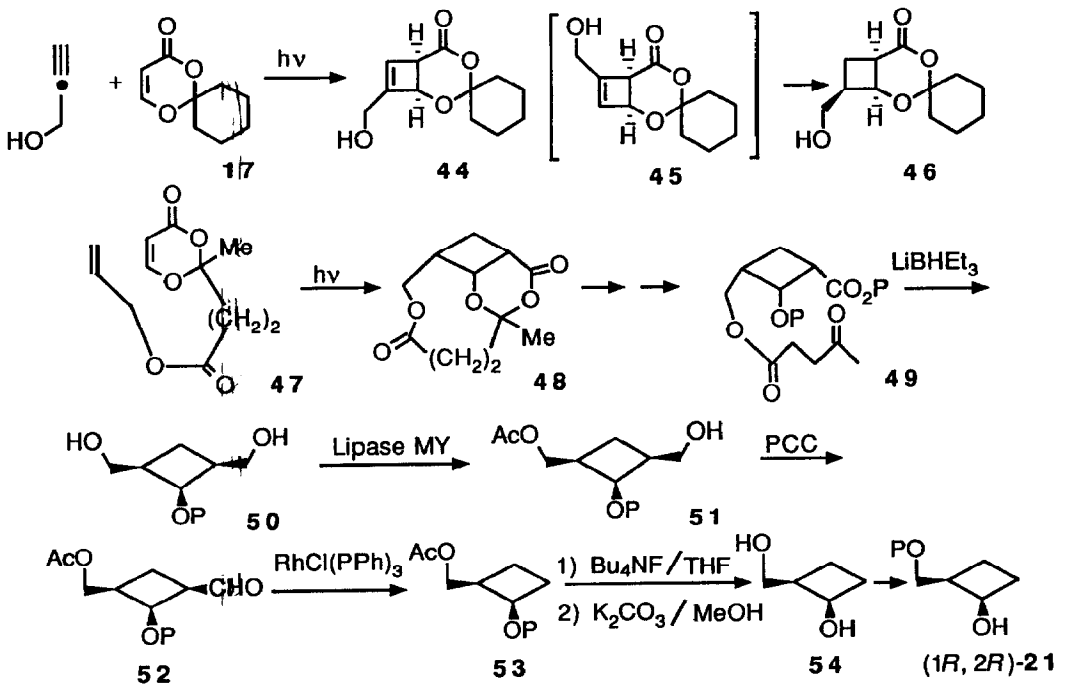
Scheme 9. P=TBDPS



Scheme 10. P= an appropriate protecting group

an enantioselective synthesis of carbocyclic epinor-oxetanocin[25] (**43**, *cf.* Scheme 10[26]) led us to apply the lipase-mediated acetylation to an appropriately protected all *cis*-1,3-(bishydroxymethyl)cyclobutanol (**42**).

The desired substrate (**50**) was synthesized by two routes shown in Scheme 11. In route a, the dioxinone underwent photoaddition to propargyl acetate to give the H-T adduct (**44**) as the major product [ratio of H-T (**44**)/H-H (**45**)=3:1]. Catalytic hydrogenation of **44** gave the expected *endo* derivative (**46**) as the sole product. Due to the long irradition time and low yield of the adducts, however, route (a) was abandoned. Finally, the more satisfactory route (b) was developed using intramolecular photoaddition of **47**. The adduct (**48**) obtained was converted to **49** in two steps. Direct reduction of **49** with lithium triethylborohydride gave the desired compound (**50**) and by lipase-mediated acetylation of **50**, the monoacetate (**51**) was



Scheme 11. P= TBDPS

obtained in almost quantitative yield with 95% e.e. The absolute structure of **51** was determined by its conversion to (1*R*,2*R*)-**21**.

Conclusion

α–Hydroxymethylated cyclobutanols, and the corresponding substituted derivatives, in which one hydroxyl group is protected by *tert*-butyldiphenylsilyl group and its substituted derivatives were found to be acetylated by lipase catalysis in vinyl acetate in high e.e.s, irrespective of the substituents. Other synthetic applications of the homochiral four-membered ring compounds presented in this paper will be reported in the future.

Experimental Section

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Optical rotations were determined on a JASCO DIP-340 polarimeter. IR spectra were recorded on a JASCO A-102 spectrometer. ^{1}H-NMR spectra were recorded with a JEOL JNM PMX 60SI or a JEOL JNM-GX 500 spectrometer with tetramethysilane as an internal standard. Mass spectra (MS) were taken with a JEOL-JMS-01SG-2 spectrometer. Silica gel used for column chromatography was Wakogel C-200 and the ratio of solvent mixtures is shown as v/v.

Irradiation Conditions. A: The photoreaction was carried out at room temperature in a quartz vessel with Rayonet RPR 3000 Å lamps; B: The photoreaction was carried out using an Ushio 400 W high-pressure mercury lamp (immersion type) with a Vycor filter under ice-cooling.

4-Oxo-1,5-dioxaspiro[5.5]undec-2-ene (17). Compound **17** was prepared by a modification of the previous method.[15] Thus, formylated Meldrum's acid[27] (0.2 mol) was added portionwise over 10 min to a boiling solution of cyclohexanone (0.4 mol) in xylene (1 l). The solution was refluxed for an additional 30 min. The solvent and excess cyclohexanone were evaporated *in vacuo*. The residue was dissolved in hexane and passed through a short column of silica gel to give **17** (25.2 g, 75%), mp 42 °C (pentane).

2-Oxo-3,5-dioxabicyclo[4.2.0]octane-4-spirocyclohexane (18). a) A solution of dioxinone **17** (168 mg, 1 mmol) in ethyl acetate (20 ml) was irradiated (condition A) while ethylene was bubbled through the solution for 5 h. The residue obtained after evaporation of the solvent was chromatographed on silica gel (hexane-ethyl acetate, 10:1) to give **18** (143 mg, 73%), mp 51-51 °C (pentane-ether). *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.32; H, 8.25. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.10-2.00 (10H, m, cyclohexyl), 2.00-2.77 (4H, m, C_7- and C_8-H), 2.95-3.45 (1H, m, C_1-H), 4.47-4.85 (1H, m, C_6-H).

b) A solution of **17** (4.03 g, 24 mmol) in a mixture of benzene (100 ml) and ethyl acetate (400 ml) was irradiated (condition B) while ethylene was bubbled through the solution for 4 h. The reaction mixture was worked up in the same manner as in a) giving **18** (2.5 g, 51 %).

***cis*-2-Hydroxymethylcyclobutan-1-ol (19).** To an ice-cooled suspension of $LiAlH_4$ (152 mg, 4 mmol) in dry THF (10 ml) was added a solution of **18** (364 mg, 2 mmol) in dry THF (2 ml) dropwise under argon atmosphere. After the addition, the ice-bath was removed and the mixture was stirred for 3 h. After decomposition of an excess of $LiAlH_4$ by 50% aq. NaOH, the precipitate was removed by filtration through Celite and the filtrate was dried over $MgSO_4$. The residue obtained after evaporation of the solvent was chromatographed on silica gel (hexane-ether, 2:7) to give **19** (196 mg, 96%) as an oil. High-resolution MS *m/z* Calcd $C_5H_{10}O_2$ (M^+): 102.0680. Found: 102.0702. IR ($CHCl_3$): 3445 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.680-1.766 (1H, m), 2.030-2.119 (1H, m), 2.284-2.362 (1H, m), 2.448, 2.564 (each 1H, br s, OH), 2.649-2.730 (1H, m), 3.825 (1H, br dd, *J*=11.0, 4.5 Hz, CHHOH), 4.038 (1H, br dd, *J*=11.0, 8.9 Hz, CHHOH), 4.538 (1H, br q, *J*=7.0 Hz, C_1-H).

***cis*-2-(*tert*-Butyldiphenylsiloxymethyl)cyclobutan-1-ol (20).** To an ice-cooled solution of **19** (252 mg, 2.5 mmol) in DMF (10 ml) was added *tert*-butylchlorodiphenylsilane (687 mg, 2.5 mmol) and imidazole (255 mg, 3.75 mmol). After removing the ice-bath, the mixture was stirred at room temperature for 10 h. After addition of water (50 ml), the product was extracted with ether and the ether layer was washed with water and dried over $MgSO_4$. The residue thus obtained was chromatographed on silica gel (hexane-ethyl acetate, 20:1) to give the silylated product **20**. (534 mg, 80%) as an oil. High-resolution MS *m/z* Calcd $C_{17}H_{19}O_2Si$ (M^+-*tert*-Bu): 283.1153. Found: 283.1168. IR ($CHCl_3$): 3550 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 1.5-2.9 (5H, m), 3.23 (1H, br d, *J*=7.8 Hz, OH), 4.00 (1H, d, *J*=6.0 Hz, O-CH_2), 4.25 (1H, d, *J*=7.2 Hz, O-CH_2), 4.38-4.78 (1H, m, C_1-H), 7.2-7.9 (10H, m, 2 x Ph).

Resolution of 20 by lipase in vinyl acetate. To a solution of **20** (50 mg, 0.15 mmol) in vinyl acetate (10 ml) was added Lipase PS (Amano Pharmaceutical Co. Ltd.) and the mixture was shaken 1 d at 28 °C. The same procedure was repeated 6 times. After 1 week, the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-ethyl acetate, 20:1). The acetate [(1*R*,2*R*)-**22**; 26 mg, 52%] was eluted first as an oil. $[\alpha]_D^{21}$ +22.8 (*c* 2.68, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{19}H_{21}O_3Si$ (M^+-*tert*-Bu): 325.1259. Found: 325.1293. IR ($CHCl_3$): 1733 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.07 (9H, s, *tert*-Bu), 1.60-2.47 (4H, m, C_3- and C_4-H), 2.47-3.03 (1H, m, C_2-H), 3.67 (1H, d, *J*=3.0 Hz, O-CH_2), 3.80 (1H, d, *J*=4.0 Hz, O-CH_2), 5.10 (1H, q, *J*=7.6 Hz, C_1-H), 7.13-7.73 (10H, m, 2 x Ph).

The alcohol [(1*S*,2*S*)-**21**; 27 mg, 48%] was eluted next as an oil. $[\alpha]_D^{21}$ -4.5 (*c* 2.47, $CHCl_3$). Spectral data are identical with those of the racemic compound **20**.

(1*R*,2*R*)-2-(*tert*-Butyldiphenylsiloxymethyl)cyclobutan-1-ol [(1*R*,2*R*)-21]. A mixture of (1*R*, 2*R*)-**22** (203 mg, 0.53 mmol), K_2CO_3 (366 mg, 2.7 mmol), water (2 ml), and methanol (5 ml) was stirred under ice-cooling for 1 h. The reaction mixture was diluted with water and extracted with ether. The extract thus obtained was chromatographed on silica gel (hexane-ethyl acetate, 20:1) to give

(1*R*,2*R*)-**21** (145 mg, 80%) as an oil. $[\alpha]^{25}$ +4.3 (*c* 2.15, $CHCl_3$). Spectral data are indentical with those of **20**.

(*S*)-2-(*tert*-Butyldiphenylsiloxymethyl)cyclobutan-1-one [(*S*)-23]. To a suspension of PCC (647 mg, 3 mmol) in CH_2Cl_2 (10 ml) was added a solution of (1*S*,2*S*)-**21** (518 mg, 1.5 mmol) in the same solvent (2 ml) in one portion. After stirring for 3 h, the mixture was passed through a short column of silica gel (3 g). The residue thus obtained was chromatographed on silica gel (hexane-ethyl acetate, 20:1) to give (*S*)-**23** (477 mg, 94%), mp 45-46 °C (pentane). $[\alpha]_D^{20}$ -24.1 (*c* 2.37, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{17}H_{17}O_2Si$ (M^+-*tert*-Bu): 281.0997. Found: 281.0968. IR ($CHCl_3$): 1784 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03 (9H, s, *tert*-Bu), 2.00-2.33 (2H, m, C_3-H_2), 2.89-4.18 (5H, m).

(*R*)-2-(*tert*-Butyldiphenylsiloxymethyl)cyclobutan-1-one [(*R*)-23]. Exactly in the same manner, (*R*)-**23** was prepared from the corresponding alcohol (1*R*,2*R*)-**21** in 92% yield, mp 43-44 °C (pentane). $[\alpha]_D^{20}$ +22.5 (*c* 2.02, $CHCl_3$).

Oxidation of racemic **21** in the same manner gave racemic **23**, mp 51-52 °C (pentane).

(*S*)- and (*R*)-5-(*tert*-Butyldiphenylsiloxymethyl)dihydro-2(3*H*)-furanone [(*S*)- and (R)-24]. To a solution of (*S*)-**23** (450 mg, 1.3 mmol) in methanol (10 ml) under argon atmosphere was added 30% hydrogen peroxide solution (377 mg, 3.3 mmol) followed by 10N NaOH (0.13 ml, 1.3 mmol). After 2 h, the mixture was neutralized by addition of 10% HCl. The product was extracted with ether and the organic layer was separated, washed with water, and dried on $MgSO_4$. The residue thus obtained was chromatographed on silica gel (hexane-ethyl acetate, 10:1) to give (*S*)-**24** (42 mg, 35%), mp 72-73 °C (pentane). $[\alpha]_D^{19}$ +26.0 (*c* 2.36, $CHCl_3$) [lit.[19] $[\alpha]_D$ +28.6 (*c* 2.05, $CHCl_3$)].

Following the above procedure, (*R*)-**24** was obtained from (*S*)-**23** in 66% yield, mp 72-73 °C (pentane). $[\alpha]_D^{22}$ -22.6 (*c* 1.00, $CHCl_3$)

8-Methylene-2-oxo-3,5-dioxabicyclo[4.2.0]octane-4-spirocyclohexane (30). A solution of **17** (3.36 g. 20 mmol) and allene (*ca.* 0.5 mol) in a mixture of benzene (40 ml) and ethyl acetate (280 ml) was irradiated for 5 h under the conditions B. The product thus obtained was chromatographed on a short column of silica gel (hexane-ethyl acetate, 5:1) to give a mixture of the photoadducts (**30** and **31**) as a solid. Recrystallization from hexane gave **30** (2.2 g, 53 %), mp 54-56 °C (hexane). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.94; H, 7.74. IR ($CHCl_3$): 1730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.36-1.90 (10H, m, cyclohexyl), 2.74 (1H, dddd, *J*=2.0, 3.0, 6.0, and 17.0 Hz, C_7-H_{endo}), 3.07 (1H, ddt, *J*=3.0, 6.0, 17.0 Hz, C_7-H_{exo}), 3.745 (1H, dq, *J*=3.0, 6.0 Hz, C_1-H), 4.705 (1H, dt, *J*=2.0, 6.0 Hz, C_6-H), 5.09 (1H, m, =CH), 5.376 (1H, m, =CH).

The mother liquor was chromatographed on silica gel (hexane-ethyl acetate, 5:1) to give additional **30** (300 mg, 7%) and then **31** (240 mg, 6%), mp 80-81 °C (pentane). *Anal.* Calcd for $C_{12}H_{16}O_3$; C, 69.23; H, 7.69. Found: C, 69.34; H, 7.93. IR

($CHCl_3$): 1730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.40-1.90 (10H, m, cyclohexyl), 3.10-3.21 (3H, m, C_1-, C_8-H), 4.95 (1H, m, C_6-H), 5.09 (1H, m, =CH), 5.28 (1H, m, =CH).

***endo*-8-Methyl-2-oxo-3,5-dioxabicyclo[4.2.0]octane-4-spirocyclohexane (32).** Compound **30** (416 mg, 2 mmol) was hydrogenated with 10% Pd-C (100 mg) in ethyl acetate (20 ml) under 1 atm. at room temperature. A usual work-up followed by chromatography on silica gel (hexane-ethyl acetate, 5:1) gave **32** (420 mg, quant.) as an oil. High-resolution MS *m/z* Calcd $C_{12}H_{18}O_3$ (M^+): 210.1256. Found: 210.1245. IR ($CHCl_3$): 1725 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.242 (3H, d, *J*=7.0 Hz, Me), 1.36-1.88 (10H, m, cyclohexyl), 2.582 (2H, ddd, *J*=7.0, 9.0, 14.0 Hz, C_7-H), 2.82 (1H, m, C_8-H), 3.27 (1H, dd, *J*=6.0, 10.0 Hz, C_1-H), 4.567 (1H, m, C_6-H).

(1*R,2*S**,4*R**)-4-methyl-2-*tert*-Butyldimethylsiloxycyclobutanecarboxylic acid (34).** A solution of **32** (710 mg, 3.38 mmol) in a mixture of water (5 ml) and THF (10 ml) was warmed at 50 °C for 3 h. Evaporation of solvents *in vacuo* at room temperature gave crude **33** as an oil. To a solution of this oil, *tert*-butylchlorodimethylsilane (2.55 g, 16.9 mml) and imidazole (1.84 g, 27 mmol) in DMF (4 ml) were added and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with water and extracted with ether. To a solution of the crude silyl ester thus obtained in methanol (10 ml) was added finely powdered K_2CO_3 (1.0 g) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water, acidified with 1M aq. $KHSO_4$, and extracted with ether. The extract was chromatographed on silica gel (hexane-ethyl acetate, 10:1) to give **34** (825 mg, quant. based on **32**), mp 71-72 °C (pentane). High-resolution MS *m/z* Calcd $C_{12}H_{25}O_3Si$ (M^++H): 245.1537. Found: 245.1561. IR ($CHCl_3$): 3200-2600, 1745 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.06 (6H, s, $Si(Me)_2$), 0.91 (9H, s, *tert*-Bu), 1.167 (3H, d, *J*=6.0 Hz, Me), 1.5-2.67 (3H, m, C_3-, C_4-H), 3.1-3.5 (1H, m, C_1-H), 4.1-4.6 (1H, m, C_2-H).

(1*S,2*S**, 3*R**)-2-(*tert*-Butyldiphenylsiloxymethyl)-3-methylcyclobutanol (37).** To a stirred solution of **34** (800 mg, 3.28 mmol) in dry THF (10 ml) was added a solution of BH_3 in THF (1M, 6.6 ml) under ice-cooling. The solution was stirred at ice-cooling temperature for 30 min, then at room temperature for 3.5 h. The solution was diluted with ether and successively washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 25:1) to give **35** (460 mg, 61%) as an oil. A solution of compound **35** (380 mg, 1.62 mmol), *tert*-butylchlorodiphenylsilane (1.34 g, 4.86 mmol) and imidazole (661 mg, 9.72 mmol) in DMF (5 ml) was stirred at room temperature for 12 h. The mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 100:1) to give **36** (737 mg, 95%). A solution of **36** in a mixture of THF (5 ml), AcOH (7 ml), and water (7 ml) was warmed at 50 °C for 12 h. The solution was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and then with brine. The residue obtained after evaporation of the solvent was

chromatographed on silica gel (hexane-ethyl acetate, 10:1) to give **37** (513 mg, 92%) as an oil. High-resolution MS *m/z* Calcd $C_{18}H_{21}O_2Si$ (M^+-*tert*-Bu): 297.1311. Found: 297.1333. IR ($CHCl_3$): 3615-3200 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.93 (3H, d, *J*=7 Hz, Me), 1.05 (9H, s, *tert*-Bu), 1.225 (1H, br s, OH), 1.82 (1H, dt, *J*=8, 10 Hz, C_4-H), 2.055 (1H, m, C_3-H), 2.492 (1H, m, C_4-H), 2.615 (1H, m, C_2-H), 3.945 (1H, dd, *J*=4, 12 Hz, CHOSi), 4.14 (1H, dd, *J*=8, 12 Hz, CHOSi), 4.338 (1H, m, C_1-H), 7.34-7.74 (10H, m, 2 x Ph).

(1*S*,2*S*,3*R*)-37 and (1*R*,2*R*,3*S*)-38. A mixture of **37** (400 mg, 0.112 mmol), Lipase PS (400 mg), vinyl acetate (1.93 g, 22.4 mmol), and hexane (70 ml) was shaken at 28 °C for 24 h. The mixture was filtered and evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 10:1). The acetate [(1*R*,2*R*,3*S*)-**38**, 220 mg (49%)] was eluted first as an oil. $[\alpha]_D^{16}$ +8.6 (*c* 2.05, $CHCl_3$). The alcohol [(1*S*,2*S*,3*R*)-**37**, 198 mg (49.5%)] was eluted next as an oil. The spectral data were identical with those of racemic **37**. $[\alpha]_D^{22}$ +10.9 (*c* 2.17, $CHCl_3$). The e.e.s were determined to be 98% for **38** and 94% for **37** by ^1H NMR (500 MHz) analysis of the corresponding (*R*)-MTPA esters.

(1*R*,2*R*,3*S*)-37. A mixture of (1*R*,2*R*,3*S*)-**38** (210 mg, 0.53 mmol), K_2CO_3 (400 mg, 24 mmol), and methanol (30 ml) was stirred at room temperature for 4 h. The solvent was evaporated off *in vacuo*. The residue was dissolved in ether and washed with water. The organic layer was dried over $MgSO_4$, evaporated, and then chromatographed on silica gel (hexane-ethyl acetate, 10:1) to give the alcohol (160 mg, 86%) as an oil. $[\alpha]_D^{18}$ -10.55 (*c* 4.9, $CHCl_3$). The e.e. of this sample was determined to be 98% by ^1H NMR (500 MHz) analysis of the (*R*)-MTPA ester.

(2*S*,3*R*)- and (2*R*,3*S*)-2-(*tert*-Butyldiphenylsiloxymethyl)-3-methylcyclobutanones [(2*S*,3*R*)- and (2*R*,3*S*)-39]. A mixture of (1*S*,2*S*,3*R*)-**37** (166 mg, 0.512 mmol), pyridinium chlorochromate (221 mg, 1.024 mmol), and molecular sieves 4A (160 mg) in CH_2Cl_2 (10 ml) was stirred at room temperature for 5 h. The organic layer was passed through a short column of silica gel and then evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 10:1) to give (2*S*,3*R*)-**39** (136 mg, 82%), mp 47-48 °C (pentane). *Anal.* Calcd for $C_{22}H_{28}O_2Si$;.C, 75.0; H, 7.95. Found; C, 74.84; H, 7.82. IR ($CHCl_3$): 1780 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.037 (9H, s, *tert*-Bu), 1.31 (3H, d, *J*=7 Hz, Me), 2.595 (1H, ddd, *J*=17, 6, 2.5 Hz, C_4-H), 2.705 (1H, m, C_3-H), 3.184 (1H, ddd, *J*=17, 9, 3.5 Hz, C_4-H), 3.828 (1H, dd, *J*=11, 4 Hz, CH-OSi), 3.903 (1H, dd, *J*=11, 7 Hz, CH-OSi), 7.36-7.68 (10H, m, 2 x Ph). $[\alpha]_D^{22}$ -9.05 (*c* 6.11, $CHCl_3$).

Following the above procedure, (1*R*,2*R*,3*S*)-**37** was oxidized to give (2*R*,3*S*)-**39** in 83% yield, mp 47-48 °C. The spectral data were identical with those of (2*S*,3*R*)-**39**. $[\alpha]_D^{18}$ +9.2 (*c* 2.68, $CHCl_3$).

Racemic alcohol (**37**) was also oxidized in the same manner to give racemic **39** in 85% yield, mp 47-48 °C.

(4*R*,5*S*)- and (4*S*,5*R*)-Dihydro-5-(*tert*-butyldiphenylsiloxymethyl)-4-methyl-2(3*H*)-furanone [(4*R*,5*S*)-40 and (4*S*,5*R*)-40]. A mixture of (2*R*,3*S*)-**39** (134 mg, 0.38 mmol), *m*-chloroperbenzoic acid (100 mg, 0.58 mmol), and sodium phosphate (monobasic, dihydrate,120 mg, 0.76 mmol) in CH_2Cl_2 (7 ml) was stirred at room temperature for 12 h. The mixture was filtered through Celite. The filtrate was washed with aq. sodium thiosulphate, aq. sodium bicarbonate, and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 7:1) to give (4*S*,5*R*)-**40** (126 mg, 90%), mp 90-91 °C (hexane-ether). *Anal.* Calcd for $C_{22}H_{28}O_3Si$: C, 71.74; H, 7.61. Found: C, 71.95; H, 7.79. IR ($CHCl_3$): 1780 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.047 (9H, s, *tert*-Bu), 1.22 (3H, d, *J*=7 Hz, Me), 2.515 (1H, dd, *J*=17, 10 Hz, C_3-H), 2.606 (1H, dd, *J*=17, 8 Hz, C_3-H), 2.78 (1H, m, C_4-H), 3,781 (1H, dd, *J*=12, 3 Hz, CHOSi), 3.868 (1H, dd, *J*=12, 3 Hz, CHOSi), 4.454 (1H, dt, *J*=3, 8 Hz, C_5-H), 7.36-7.68 (10H, m, 2 x Ph). $[\alpha]_D^{24}$ -52.0 (*c* 1.28, $CHCl_3$).

Following the above procedure, (2*S*,3*R*)-**39** was converted to (4*R*,5*S*)-**40** in a quantitative yield, mp 90-91 °C. The spectral data were identical with those of (4*S*,5*R*)-**40**. $[\alpha]_D^{23}$ +47.2 (*c* 5.7, $CHCl_3$).

The racemic **40** (mp 90-91 °C) was also obtained from the racemic **39** (quant.).

(4*R*,5*S*)- and (4*S*,5*R*)-Dihydro-5-hydroxymethyl-4-methyl-2(3*H*)-furanone [(4*R*,5*S*)- and (4*S*,5*R*)-41]. A solution of tetrabutylammonium fluoride (0.6 ml of 1M THF solution) was added to a solution of (4*R*,5*S*)-**40** (120 mg, 0.33 mmol) in THF (4 ml) with stirring. The whole was stirred at ice-cooling temperature for 30 min and then at room temperature for 2.5 h. The residue obtained after evapoation of THF was diluted with CH_2Cl_2 and the solution was washed with brine. The organic layer was dried over $MgSO_4$ and then evaporated. The residue was chromatographed on silica gel (ether) to give (4*R*,5*S*)-**41** (27 mg, 63%) as an oil. High-resolution MS *m/z* Calcd $C_6H_{10}O_3$ (M^+): 130.0630, Found: 130.0654. IR ($CHCl_3$): 3500, 1780 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.155 (3H, d, *J*=7 Hz, Me), 1.695 (1H, br s, OH), 2.365 (1H, dd, *J*=8, 17 Hz, C_3-H), 2.64 (1H, dd, *J*=9, 17 Hz, C_3-H), 2.763 (1H, dddd, *J*=7, 7.5, 8, 9 Hz, C_4-H), 3.857 (2H, m, CH_2OH), 4.54 (1H, ddd, *J*=3.5, 5, 7.5 Hz, C_5-H). $[\alpha]_D^{25}$ +60.0 (*c* 0.6, $CHCl_3$).

Following the above procedure, (4*S*, 5*R*)-**40** was deprotected to give (4*S*,5*R*)-**41** in 59% yield. $[\alpha]_D^{24}$ -63.0 (*c* 0.86, $CHCl_3$).

Photoaddition of 17 to propargyl alcohol. A solution of dioxinone **17** (58 mg, 0.35 mmol) and propargyl alcohol (392 mg, 7 mmol) in ethyl acetate (30 ml) was irradiated (condition A) under argon atmosphere for 15 h. The residue obtained after evaporation of the solvent was chromatographed on silica gel (hexane-ethyl acetate, 1:1). The H-H adduct [**45**: 15 mg (19%)] was eluted first as an oil. High-resolution MS *m/z* Calcd $C_{12}H_{16}O_4$ (M^+): 224.1048. Found: 224.1087. IR ($CHCl_3$): 3400,1715, 1638 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.38-2.02 (10H, m, cyclohexyl), 3.729-3.750 (1H, m, C_1-H), 4.286, 4.338 (each 2H, d, *J*=15.2 Hz, $C\underline{H}_2OH$), 4.913 (1H, m, C_6-H), 6.15(1H, br s, C_7-H).

The H-T adduct [**44**, 23 mg (30%)] was eluted next as an oil. High-resolution MS *m/z* Calcd $C_{12}H_{14}O_3$ (M^+-H_2O): 206.0942. Found: 206.0960. IR ($CHCl_3$): 3400, 1710, 1642 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.38-1.95 (10H, m, cyclohexyl), 3.560-3.585 (1H, m, C_1-H), 4.255 (2H, br q, *J*=15.2 Hz, CH_2OH), 4.995 (1H, dd, *J*=7.2, 3.0 Hz, C_6-H), 6.220-6.238 (1H, m, C_8-H).

Synthesis of 47. According to the general synthetic method reported previously,[18] compound **47** was synthesized from allyl 4-oxopentanoate and formylated Meldrum's acid as follows. To a refluxing solution of allyl 4-oxopentanoate (3.12 g, 20 mmol) in toluene (100 ml) was added formylated Meldrum's acid[28] (1.72 g, 10 mmol) for a period of 15 min. After the addition was completed, the mixture was further reluxed for 90 min. The residue obtained after evaporation of the solvent was chromatographed over sillica gel (hexane-ethyl acetate, 5:1) to give **47** [1.40 g (62%)] as an oil. High-resolution MS *m/z* Calcd $C_{11}H_{14}O_5$ (M^+): 226.0840. Found: 226.0831. IR ($CHCl_3$): 1740, 1625 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.70 (3H, s, Me), 2.31-2.83 (4H, m, C_2-,C_3-H), 4.62 (2H, d *J*=5.0 Hz, $CH_2CH=CH_2$), 5.08-6.33 (3H, m, $CH=CH_2$), 5.43 (1H, d, J=6.0 Hz, C_5-H), 7.15 (1H, d, J=6.0 Hz, C_6-H).

Irradiation of 47: formation of the parallel and cross adducts. A solution of **47** (200 mg, 0.88 mmol) in ethyl acetate (200 ml) was irradiated for 3 h under argon atmosphere. After evaporation of the solvent, the residue was chromatographed on sillica gel (hexane-ethyl acetate, 10:1). The parallel adduct [**48**: 160 mg (80%)] was eluted first, mp 93-95 °C (ether-CH_2Cl_2). High-resolution MS *m/z* Calcd $C_{11}H_{14}O_5$ (M^+): 226.0840. Found: 226.0898. IR ($CHCl_3$): 1731 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.53 (3H, s, Me), 2.075-2.120 (2H, m, C_6-H), 2.344 (1H, dt, *J*=12.0, 3.8 Hz, C_5-H), 2.485 (1H, dt, *J*=12.0, 6.0 Hz, C_{11}-H), 2.562-2.630 (1H, m, C_1-H), 2.684-2.760 (2H, m, C_5- and C_{11}-H), 3.231 (1H, dddd, *J*=11.0, 8.0, 5.5, 1.0 Hz, C_{10}-H), 3.763 (1H, br d, *J*=12.5 Hz, C_2-H), 5.059 (1H, t, *J*=8.0 Hz, C_{12}-H), 5.268 (1H, dd, *J*=13.0, 3.5 Hz, C_2-H).

The cross adduct (29 mg, 15%) was eluted next, mp 143-144 °C dec (ether-CH_2Cl_2). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.26; H, 6.22. IR ($CHCl_3$): 1731 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ:1.549 (3H, s, Me), 2.049 (1H, ddd, *J*=13.5, 2.5, 1.0 Hz, C_{11}-H), 2.160-2.342 (3H, m, C_5- and C_6-H), 2.609 (1H, ddd, *J*=13.5, 1.0, 5.0 Hz, C_{11}-H), 2.700-2.790 (1H, m, C_5-H), 3.172-3.241 (1H, m, C_1-H), 3.337 (1H, br dd, *J*=10.0, 4.5 Hz, C_{10}-H), 3.915 (1H, dd, *J*=12.0, 6.0 Hz, C_2-H), 4.528 (1H, ddd, *J*=5.0, 4.5, 2.5 Hz, C_{12}-H), 5.065 (1H, d, *J*=12.0 Hz, C_2-H).

***tert*-Butyldiphenylsilyl (1*R**,2*S**,3*R**)-2-(*tert*-butyldiphenylsiloxy)-3-(4-oxopentanoyloxymethyl)cyclobutane-1-carboxylate (49).** A solution of **48** (452 mg, 2 mmol) in a mixture (5 ml) of water and acetonitrile (2:1) was kept at 50 °C for 8 h. After evaporation of the solvent, DMF (5 ml) was added to the residue and then, *tert*-butylchlorodiphenylsilane (688 mg, 2.5 mmol) and imidazole (340 mg, 5 mmol) were added and the mixture was stirred for 2 d. After addition of water, the product was extracted with ether and dried over $MgSO_4$. The residue thus

obtained was chromatographed on silica gel (hexane-ethyl acetate, 2:1) to give **49** (1.368 g, 95%) as an oil. High-resolution MS *m/z* Calcd $C_{39}H_{43}O_6Si_2$ (M^+-*tert*-Bu): 663.2596. Found: 663.2562. IR ($CHCl_3$): 1725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00, 1.13 (each 9H, s, *tert*-Bu), 1.85-2.85 (7H, m), 2.32 (3H, s, Ac), 3.18-3.85 (1H, m, C_1-H), 4.30-4.63 (2H, m, OCH_2), 4.80 (1H, br t, *J*=8.0 Hz, C_2-H), 7.10-7.97 (20H, m, Ph).

***cis*-2-(*tert*-Butyldiphenylsiloxy)-1,3-bishydroxymethylcyclobutane (50).** The product **49** (943 mg, 1.09 mmol) obtained as above was dissolved in dry THF (30 ml). To this solution was added 1 M Super-Hydride-THF solution (15 ml) dropwise under ice-cooling (argon atmosphere). After removing of the ice-bath, the mixture was stirred for 3 h at room temperature. After decomposing an excess of the reducing reagent by addition of ice, the solvent was evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 4:3) to give **50** (403 mg, quant.), mp 96-97 °C (pentane-ether). *Anal.* Calcd for $C_{22}H_{30}O_3Si$: C, 71.32; H, 8.16. Found: C, 71.20; H, 7.99. IR ($CHCl_3$): 3601 cm-1. ^1H NMR ($CDCl_3$) δ: 1.13 (9H, s, *tert*-Bu), 1.57-2.07 (4H, m, C_4-H, OH), 2.13-2.97 (2H, m, C_1- and C_3-H), 3.63-4.00 (4H, m, 2 x $C\underline{H}_2OH$), 4.87 (1H, br t, *J*=7.8 Hz, C_2-H), 7.20-7.87 (10H, m, Ph).

(1*R*,2*R*,3*S*)-1-Acetoxymethyl-2-(*tert*-butyldiphenylsiloxy)-3-hydroxymethylcyclobutane (51). According to the procedure of the resolution of **20** into (1*S*,2*S*)-**21** and (1*R*,2*R*)-**22**, **50** (250 mg, 0.68 mmol) was treated with Lipase MY (Meito Industries, Inc.) (250 mg x 3) for 3 d. After chromatography on silica gel (hexane-ethyl acetate, 20:1), (+)-**51** was obtained (266 mg, 96%) as an oil. $[\alpha]_D^{23}$ +32.9 (*c* 2.56, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{20}H_{23}O_4Si$ (M^+-*tert*-Bu): 355.1364. Found: 355.1327. IR ($CHCl_3$): 3600, 1738 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.12 (9H, s, *tert*-Bu), 1.50-2.20 (3H, m, C_4-H, OH), 1.95 (3H, s, Ac), 2.29-2.91 (2H, m, C_1- and C_3-H), 3.55-3.85 (2H, m, $C\underline{H}_2OH$), 4.23 (2H, br d, *J*=7.8 Hz, $AcOC\underline{H}_2$), 4.76 (1H, br t, *J*=7.8 Hz, C_2-H), 7.17-7.87 (10H, m, Ph).

(1*R*,2*S*,3*R*)-3-Acetoxymethyl-2-(*tert*-butyldiphenylsiloxy)cyclobutanal (52). According to the procedure for the formation of **23** from **21**, compound **51** (88 mg, 0.21 mmol) was oxidized to give **52** (88 mg, quant.) as an oil. $[\alpha]_D^{19}$ -26.1 (*c* 1.38, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{20}H_{21}O_4Si$ (M^+-*tert*-Bu): 353.1208. Found: 353.1192. IR ($CHCl_3$): 1702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.10 (9H, s, *tert*-Bu), 1.63-3.40 (4H, m, C_1-, C_3-, and C_4-H), 1.97 (3H, s, Ac), 3.90-4.40 (2H, m, $AcOC\underline{H}_2$), 4.90 (1H, br t, *J*=8.0 Hz, C_2-H), 7.13-7.93 (10H, m, 2 x Ph), 9.71 (1H, d, *J*=2.0 Hz, CHO).

(1*R*,2*R*)-1-Acetoxymethyl-2-(*tert*-butyldiphenylsiloxy)cyclobutane (53). To a refluxing solution of compound **52** (75 mg, 0.18 mmol) in benzene (10 ml) was added slowly tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst, 169 mg, 0.18 mmol) in benzene (10 ml). After 2 h, the same amount of the complex was added and the mixture was refluxed for further 2 h. After the reaction, the mixture was passed through short column of Florisil (2 g). The residue obtained after evaporation of the solvent was chromatographed on silica gel (hexane-ethyl acetate: 20:1) to give **53** (27 mg, 39%) as an oil. $[\alpha]_D^{21}$ +35.9 (*c* 2.63, $CHCl_3$). High-

resolution MS *m/z* $C_{19}H_{21}O_3Si$ (M^+-*tert*-Bu): 325.1259. Found: 325.0299. IR ($CHCl_3$): 1725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.07 (9H, s, *tert*-Bu), 1.40-1.83 (2H, m), 1.90-3.03 (3H, m), 2.00 (3H, s, Ac), 4.17-4.80 (3H, m, $AcOCH_2$, C_2-H), 7.23-7.93 (10H, m, 2 x Ph).

(1*R*,2*R*)-2-Hydroxymethylcyclobutan-1-ol (54). To a solution of **53** (22 mg, 0.058 mmol) in THF (1 ml) was added 1M tetrabutyl ammonium fluoride-THF solution (0.29 ml) under ice-cooling. After the addition, the mixture was kept standing for 2 h at room temperature. The residue obtained after evaporation of the solvent was extracted by ether, and the organic layer was washed with water and evaporated. The residue thus obtained was dissolved in methanol (1 ml). To this solution was added K_2CO_3 (40 mg, 0.29 mmol) in water (0.5 ml) and the mixture was kept standing for 30 min. The residue obtained after neutralization by addition of aq. 1M $KHSO_4$ followed by evaporation was chromatographed on silica gel (ethyl acetate) to give **54** as an oil. $[\alpha]_D^{23}$ -27.6 (*c* 0.37, $CHCl_3$).

The silylation of **54** with *tert*-butylchlorodipenylsilane according to the procedure for the formation of **39** from **37** gave the monosilylation product, whose specific rotation as well as spectral data were identical with those of (1*R*,2*R*)-**21**.

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