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Enantiomeric resolution of cyclobutanones and related derivatives by enzyme-catalyzed acylation and hydrolysis

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Abstract—A method for the regio- and enantioselective protection and deprotection of a number of cyclobutanone derivatives employing the isolated enzyme porcine pancreatic lipase (PPL) has been developed. PPL catalyzes the regioselective acylation or deacylation of the C-3 substituent in (2*S*,3*R*)-(+)-bis[hydroxymethyl]-1,1-dimethoxycyclobutanone and its enantiomer. Photochemical ring expansion of the corresponding cyclobutanones in methanol gave anomeric mixtures of the methyl furanosides with stereochemical retention of the ring substituents. The PPL-catalyzed hydrolysis of the acetal derived from (2*S*,3*R*)-bis[acetoxymethyl]cyclobutanone resulted in a regioselective reaction of the C-3 acetoxymethyl group. PPL exhibits no hydrolysis activity toward the acetal derived from the enantiomeric cyclobutanone diacetate.
Racemic 2-acetoxymethyl-3,3-dimethylcyclobutanone was converted to its enantiomerically enriched (*S*)-alcohol by PPL-catalyzed hydrolysis. The corresponding methyl furanoside obtained from the photochemical ring expansion of racemic 2-acetoxymethyl-3,3-dimethylcyclobutanone in methanol is not an effective substrate for PPL mediated hydrolysis.

1. Introduction

Cyclobutanes and cyclobutanones represent an important class of synthetic intermediates with diverse chemistry resulting from their ring strain.[1] With new enantioselective methods available for the construction of the four-carbon ring, their use in enantioselective synthesis has become increasingly popular. Cyclobutanones and cyclobutenones are the most readily available derivatives of cyclobutanes.[2] It is, therefore, rather surprising that whereas chiral cyclobutanes have been reported in the early 1900s,[3] the first optically active cyclobutanone was only reported in 1960,[4] even though cyclobutanones in their racemic forms were available much earlier.[5] Although a number of approaches to chiral cyclobutane derivatives have been developed,[6] the selective enzyme-catalyzed reactions of cyclobutanes have received scant attention. Our interest in cyclobutanones as synthetic intermediates to prepare nucleosides and oligosaccharides[7] prompted us to explore selective enzyme-catalyzed reactions to prepare optically active derivatives, which could serve as chiral precursors to these medicinally relevant compounds.

Enzyme-catalyzed hydrolysis and esterification are the most commonly exploited biotransformations. The lipases are enzymes, which catalyze the hydrolysis of lipids, specifically triglycerides, as their principle biological function. However, the fact that many lipases have the ability to hydrolyze a broad spectrum of esters other than those of triglycerides, makes them valuable catalysts in organic synthesis to perform regio- and stereoselective transformations. The reverse process of acetylation of the racemic or prochiral alcohols can be catalyzed by these same lipases using vinyl acetate in a transesterification reaction. The use of vinyl acetate for bioacetylations leads to the formation of vinyl alcohol, which rapidly tautomerizes to acetaldehyde. Acetaldehyde cannot take part in the reverse reaction allowing the forward reaction to go to completion. Unlike other enzymes, lipases can exhibit catalytic activity in biphasic media.[8] The neat substrate can be used as the organic phase, or it can be dissolved in a water immiscible organic solvent for reaction. This aspect also makes it possible to recover the enzyme after the reaction due to its insolubility in organic solvents. Of these lipases, pig liver esterase (PLE) and porcine pancreatic lipase (PPL) are commonly used for enantioselective hydrolysis and esterification.

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2. Results and discussion

Ketal **1** was prepared in its enantiomerically pure form following the literature method developed by Ahmad[9] using a key [2+2] cycloaddition of di-(−)-menthylfumarate with 1,1-dimethoxyethylene. A bioacetylation was performed on this diol employing PPL with vinyl acetate and toluene as solvent mixture. The lipase-catalyzed acetylation of diol **1** resulted in the regioselective acetylation of the C-3 hydroxymethyl group giving mono-acetate **2** in 94% yield (Table 1). The regiochemistry of **2** was determined by COSY NMR. The signal at δ 3.7 ppm assigned to protons H_a and H_b are only coupled to H_c (δ 2.3 ppm). The signal at δ 4.1 ppm assigned to protons H_e and H_f were only coupled to H_d (δ 2.2 ppm). The signals associated with the H_c and H_d protons are readily distinguished by the coupling pattern of H_d with the H_h and H_g protons (δ 2.4 and 1.8 ppm).

The enzyme-catalyzed hydrolysis was performed on diacetate **3**, which was obtained from the bis-acetylation of diol **1** with acetyl chloride in pyridine. The bioconversion resulted in selective hydrolysis of the C-3 acetoxymethyl group leaving the C-2 acetoxymethyl intact to yield mono-acetate **4** in 97% yield (Table 1). The regiochemistry was confirmed using COSY NMR analysis in a similar fashion to mono-acetate **2**. The observed regioselectivity of the PPL acetylation of diol **1** and the hydrolysis of diacetate **3** is in accordance with the active site model for PPL catalysis.[10] According to this model the substrate fit for the hydrolysis of an ester possessing a chiral alcohol moiety is depicted in Figure 1, where the L_H site represents a large and hydrophobic group and the S_p site accommodates small polar or hydrophilic groups of up to CH_2OAc in size. Small, non-polar groups, such as methyl or methylene, are also tolerated. In the hydrolysis reaction it is the ring methylene group, which is accommodated in the S_p-site, while the remaining ring substituents are located in the L_H-site. If the hydrolysis of the C-2 acetoxymethyl were to occur, the ketal carbon $C(OCH_3)_2$ would have to be directed to the S_p-site (see Fig. 2). According to Jones and Hultin, this group would exceed the size limitation for the small polar pocket.[10]

Ketals **2**–**4** were transformed to their corresponding cyclobutanones **5**–**7**, respectively, using acid hydrolysis

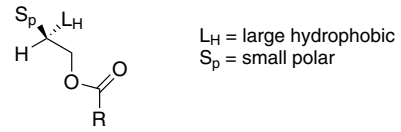


Figure 1. Active site model for PPL-catalyzed hydrolysis.

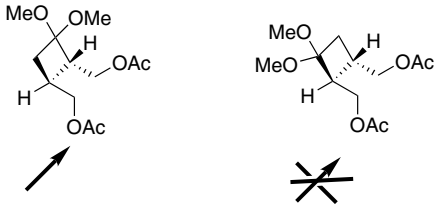
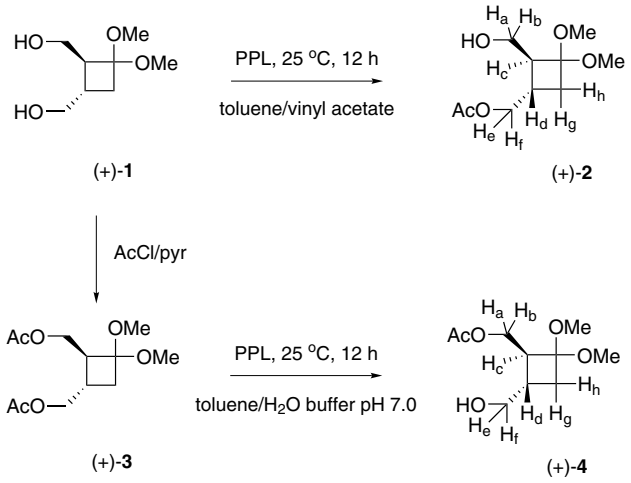


Figure 2. Regioselectivity for PPL hydrolysis of diacetate **3**.

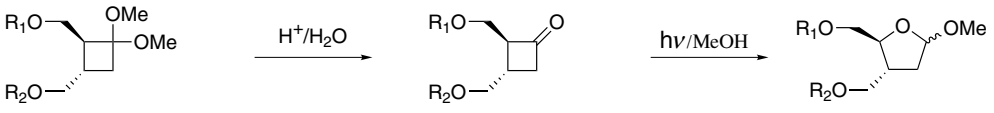


with 0.2 M sulfuric acid. Under these relatively mild acid conditions, the acetyl groups were not cleaved. Ketones **5**–**7** were subjected to a photochemical ring-enlargement reaction in the presence of methanol in acetonitrile. UV radiation of ketones **5**–**7** resulted in anomeric mixtures of methyl furanosides **8**–**10**, in yields ranging from 48 to 59%, derived from α-cleavage at the more substituted carbon, along with corresponding cycloelimination products. Diacetate **9** was subjected to PPL-catalyzed hydrolysis resulting in a regioselective transformation of the C-3 acetoxymethyl group to the alcohol mono-

Table 1. Product yields and % ee for PPL-catalyzed reactions[a]

Substrate	Product	Reaction time (h)	Chemical yield (%)[b]	% ee or de
(+)-**1**	(+)-**2**	12	94	100[c]
(+)-**3**	(+)-**4**	12	97	100[c]
(+)-**9**	(+)-**10**	12	77	100[c]
(−)-**1**	(−)-**2**	24	41	100[c]
(−)-**3**	(−)-**4**	24	46	100[c]
(−)-**9**	(−)-**10**	24	0[d]	—
(±)-**1**	(+)-**12**	18	34	80 ± 5

[a] Acetylations carried out in toluene–vinyl acetate (15:1), hydrolysis with toluene–aq buffer pH 7 (1:1).
[b] Isolated yields.
[c] Single regio-isomer produced from optically pure substrate.
[d] Only starting material recovered.



(+)-**2** R_1 = H, R_2 = Ac
(+)-**3** R_1 = R_2 = Ac
(+)-**4** R_1 = Ac, R_2 = H

(+)-**5** R_1 = H, R_2 = Ac
(+)-**6** R_1 = R_2 = Ac
(+)-**7** R_1 = Ac, R_2 = H

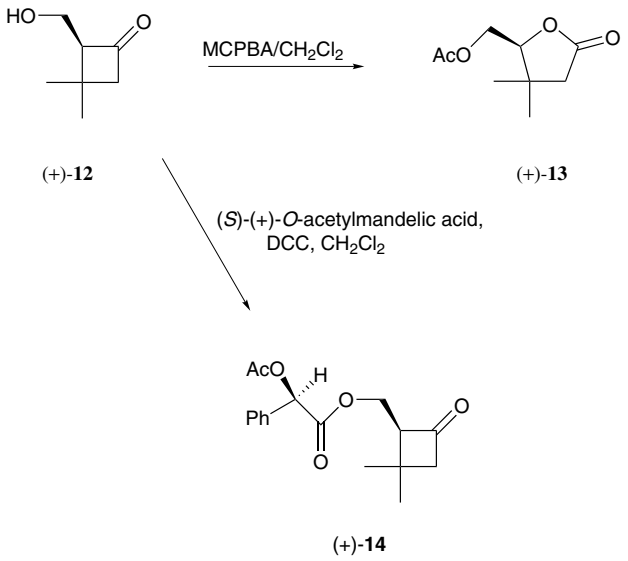
(+)-**8** R_1 = H, R_2 = Ac
(+)-**9** R_1 = R_2 = Ac
(+)-**10** R_1 = Ac, R_2 = H

acetate **10** with a yield of 77% (Table 1). The identity of this product was confirmed by comparison with the photoproduct obtained from ketone **7** under identical conditions. This observation is again consistent with that predicted by the PPL active site model, with the ring CH_2 group located in the S_p site and the remaining groups directed to the L_H-site.

To further explore the enantio- and regioselectvity of PPL catalysis, the enantiomeric diol (−)-**1** was prepared following Ahmad's procedure[9] employing di-(+)-menthyl fumarate cycloaddition with 1,1-dimethoxyethylene. (2*R*,3*S*)-Bishydroxymethyl-1,1-dimethoxycyclobutane ((−)-**1**), and its diacetylated derivative (−)-**3** was individually subjected to biotransformation using PPL. Reaction of diol (−)-**1** with vinyl acetate under PPL catalysis as previously described, except for a doubling of reaction times, formed hydroxyester (−)-**2** in 41% yield, while hydrolysis of diacetate (−)-**3** yielded hydroxyester (−)-**4** in 46% yield (Table 1). The ^{1}H NMR spectra of the products were identical to that of the corresponding enantiomeric products (+)-**2** and (+)-**4**. The lower yields and longer reaction times (24 h compared to 12 h) for the unexpected biotransformations of (−)-**1** and (−)-**3** indicate that the (+)-cyclobutanes are better substrates for PPL catalysis. Cyclobutanones (−)-**5**, (−)-**6**, and (−)-**7** were prepared from their corresponding ketals (−)-**2**, (−)-**3**, and (−)-**4**, respectively, by aqueous acid hydrolysis. Photolysis of these cyclobutanones produced anomeric mixtures of acetals (−)-**8**, (−)-**9**, and (−)-**10** in yields of 55%, 53%, and 57%, respectively, along with cycloelimination products. Ketal (−)-**9** was subjected to PPL catalysis with no detectable transformation as would be expected from the active site model.

To further exploit the catalytic activity of PPL, we attempted a kinetic resolution of a racemic cyclobutanone. (±)-Cyclobutanone **11** was prepared by the cycloaddition of dichloroketene with 1-acetoxy-3-methyl-2-butene (Scheme 1).

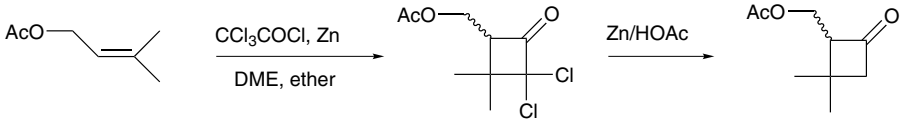
Racemic ketoacetate (±)-**11** was subjected to a PPL-catalyzed hydrolysis resulting in the production of (*S*)-(+)-hydroxyketone **12** in 34% yield with an ee of 80 ± 5% (Table 1). The absolute stereochemistry of (+)-**12** was assigned based on its conversion to the known lactone (+)-**13**[11] by a Baeyer–Villiger oxidation (Scheme 2). Under these conditions, ring-enlargement proceeds both regio- and stereospecifically.[12] The sign of the specific rotation of (+)-**13** indicated an (*S*)-configuration for (+)-**12**.



(+)-**14**

Scheme 2.

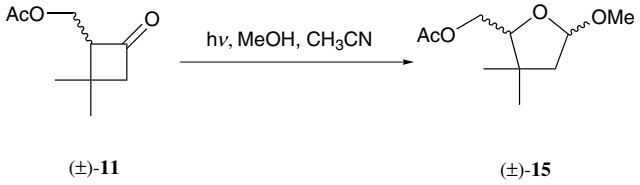
The enantiomeric excess of (+)-**12** was determined by its esterification with (*S*)-(+)-*O*-acetylmandelic acid to (+)-**14** and comparison of its ^{1}H NMR spectrum with that obtained from racemic **12** in the methyl proton region of the spectrum. Each methyl signal was cleanly resolved for the pair of diastereomeric esters **14**, whereas ester (+)-**14** obtained from (+)-**12** showed an enhancement of two of the methyl signals by a factor of 8. The enantiomeric excess of alcohol **12** could be improved upon by employing a second enzymatic resolution using a bioacetylation forming (+)-**11**.



(±)-**11**

Scheme 1.

UV irradiation of racemic **11** produced an anomeric mixture of **15** in 45% yield (Scheme 3) and some cycloelimination product. The mixture consisted of about equal amounts of the two inseparable anomers as evident from the doubling of the signals in the acetal proton region δ 4.8–5.2 ppm. Methyl furanoside **15** was subjected to an enzyme-catalyzed hydrolysis with PPL, but showed no activity as a substrate.



(±)-**11** (±)-**15**

Scheme 3.

2.1. Control experiments and effect of temperature

In no case was hydrolysis or acetylation observed in the absence of PPL. Variation in the temperature between 20 and 27 °C did not affect the reaction rate, regioselectivity, or enantiomeric excess for products (+)-**2**, (+)-**4**, (+)-**10**, (−)-**2**, (−)-**4**, and (+)-**12**. In contrast, the reaction rate at 39 °C became very slow and at 0 °C, no reaction took place. These temperature effects could be due to a change in the enzyme secondary and/or tertiary structure rendering in certain instances complete loss of activity. An increase in the enzyme concentration resulted in an acceleration of the reaction rate with the consequence that, at high enzyme concentration and long reaction times, the enantiomeric excess of (+)-**12** decreased. It was also determined that benzoate esters of alcohols (+)-**1**, (−)-**1**, and (+)-**12** are not suitable substrates for PPL catalysis. Other solvents, including hexane, dichloromethane, chloroform, and acetone all resulted in lower yields of reaction when compared with toluene. All reactions were repeated with three different commercial batches of PPL at different times and showed the same selectivity and rates, which demonstrate the reproducibility of these catalyzed reactions.

3. Conclusion

In summary, it was demonstrated that PPL can be used in catalyzing regio- and enantioselective esterification and hydrolysis of cyclobutane alcohols and esters, respectively. The regioselectivity for enzymatic hydrolysis of diesters, and acetylation of diols is identical as would be expected by the principle of microscopic reversibility[16] involving the same substrate–enzyme complex. These chiral cyclobutanes are considered useful intermediates in the synthesis of chiral products such as nucleosides and oligosaccharides.

4. Experimental

All commercial chemicals were used without further purification. Porcine Pancreatic Lipase (containing 160 U/mg solid, using olive oil as substrate) was purchased from Sigma and used as received. NMR spectra were recorded on a Bruker ARX 400 (400 MHz) spectrometer in $CDCl_3$ solution containing 1% TMS. Low resolution mass spectra were recorded at 70 eV on a Kratos Profile mass spectrometer. High resolution mass spectra (HRMS) were provided by the McMaster Regional Centre for Mass Spectrometry using a VG ZAB-E instrument in the electron impact (EI) mode at 70 eV. Photolyses were carried out using a Hanovia 450 W medium-pressure mercury arc lamp in a water-cooled Pyrex immersion well. Pyrex tubes containing the samples were strapped around this well and the assembly immersed in an ice-water bath. The samples were purged with argon for 30 min prior to irradiation. All solvents used in these reactions were dried and distilled. Optical rotations were measured using a Perkin–Elmer 241 polarimeter at 22 °C employing a sodium lamp. FT-IR spectra were recorded on a Pye Unicam SP3-200 spectrometer using thin films. Elemental analyses were performed by Guelph Chemical Laboratories Ltd. Analytical TLC was performed on commercial silica gel 60F 254 coated plastic sheets. Preparative TLC was performed using silica gel 60F 254 precoated glass plates. For column chromatography, flash chromatography grade, 20–45 μm silica gel was used.

4.1. (+)-((1*S*,2*S*)-2-(Hydroxymethyl)-3,3-dimethoxycyclobutyl)methyl acetate 2

A mixture of ketal (+)-**1**[9] (80 mg, 0.45 mmol) and PPL (170 mg) in toluene–vinyl acetate (15:1 vv, 16 mL) was vigorously stirred for 12 h at room temperature. The insoluble enzyme was filtered and washed with ethyl acetate. The combined filtrates were evaporated to dryness under reduced pressure and the residue chromatographed by preparative TLC (ethyl acetate–hexane, 1:1) to give **2** (93 mg, 94%) as a colorless oil. ^{1}H NMR: δ 4.11–4.06 (m, 2H), 3.72–3.67 (m, 2H), 3.17 (s, 6H), 2.56 (s, 1H), 2.36–2.33 (m, 2H), 2.27–2.24 (m, 1H), 2.02 (s, 3H), 1.81–1.78 (m, 1H); ^{13}C NMR: δ 171.0, 102.0, 67.0 61.8, 48.6, 48.5, 48.3, 32.2, 26.3, 20.8; MS m/z 187 (M^+-OCH_3); $[\alpha]_D = +18.7$ (c 0.05, $CHCl_3$); Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.44; H, 8.75.

4.2. (+)-((1*S*,2*S*)-3,3-Dimethoxycyclobutane-1,2-diyl)-bis(methylene) diacetate 3

To a solution of ketal **1** (1 g, 5.67 mmol) in 56.7 mL of pyridine at 5 °C under argon, was added acetyl chloride (0.97 mL, 13.6 mmol) over a period of 30 min. The mixture was allowed to warm to room temperature and stirred for 3 h. After this time, the reaction was quenched with 10 mL water and stirred for 30 min. The resulting solution was diluted with 100 mL EtOAc and then treated sequentially with: 100 mL H_2O, 3 × 100 mL 3% HCl, 3 × 100 mL satd $NaHCO_3$ solution, 100 mL H_2O, and 100 mL brine solution. The organic layer was dried over $MgSO_4$ and evaporated to give the crude diester (+)-**3**. The residue was chromatographed on a column (hexane–ethyl acetate 4:1) to give (+)-**3** (1.28 g, 87%) as a pale yellow oil. ^{1}H NMR: δ 4.28–4.11 (m, 4H), 3.19

(s, 6H), 2.48–2.40 (m, 1H), 2.38–2.35 (m, 1H), 2.11–2.09 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 1.79–1.76 (m, 1H); ^{13}C NMR: δ 170.9, 170.7, 100.1, 66.9, 62.6, 48.8, 48.4, 46.5, 32.0, 28.5, 25.2, 20.8; MS m/z 229 (M^+-OCH_3); $[\alpha]_D = +22.0$ (c 0.06, $CHCl_3$); Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.88; H, 7.71.

4.3. (+)-((1*S*,4*S*)-4-(Hydroxymethyl)-2,2-dimethoxycyclobutyl)methyl acetate 4

A mixture of diacetate **3** (117 mg, 0.45 mmol), PPL (170 mg) in toluene–phosphate buffer solution (pH 7.0) (20 mL, 1:1 vv) was vigorously stirred for 12 h at room temperature. The solution was then treated with 3×20 mL CH_2Cl_2 and the combined organic layers dried over $MgSO_4$. The solution was evaporated to dryness under reduced pressure and the residue chromatographed by preparative TLC (ethyl acetate–hexane, 1:1) to give a colorless oil (96 mg, 97%). ^{1}H NMR: δ 4.30–4.15 (m, 2H), 3.64–3.59 (m, 2H), 3.19 (s, 6H), 2.44–2.40 (m, 1H), 2.34–2.29 (m, 1H), 2.07 (s, 3H), 1.96–1.91 (m, 1H), 1.72–1.67 (m, 1H), 1.58 (s, 1H); ^{13}C NMR: δ 171.0, 100.3, 66.0, 63.2, 48.8, 48.4, 46.8, 32.0, 31.5, 28.5, 21.0; MS m/z 187 (M^+-OCH_3); $[\alpha]_D = +15.7$ (c 0.08, $CHCl_3$); Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.10; H, 8.02.

4.4. Preparation of cyclobutanones 5–7, general procedure

To a solution containing ketal (2.5 mmol in 25 mL of acetonitrile) was added 10 mL of 0.2 M sulfuric acid (4 mL/mmol of ketal). The mixture was stirred for 72 h at room temperature and monitored by TLC. The reaction mixture was diluted with 50 mL of ethyl acetate, and washed with water (2×20 mL) and brine solution (1×20 mL). The organic solution was dried over $MgSO_4$ and evaporated to give the cyclobutanone, which was further purified.

4.5. (+)-((1*S*,2*S*)-2-(Hydroxymethyl)-3-oxocyclobutyl)methyl acetate 5

Preparative TLC (ethyl acetate–hexane, 1:1) gave pure **5** as an oil (0.35 g, 81%). ^{1}H NMR: δ 4.35–4.30 (m, 2H), 3.96–3.76 (m, 2H), 3.33–3.32 (m, 1H), 2.92–2.91 (m, 1H), 2.78–2.76 (m, 1H), 2.11 (s, 3H), 1.73 (m, 1H), 1.58 (s, 1H); ^{13}C NMR: δ 207.5, 171.0, 66.4, 65.0, 59.5, 48.0, 26.5, 20.8; MS m/z 172 (M^+); $[\alpha]_D = +29.0$ (c 0.06, $CHCl_3$); Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.02. Found: C, 55.95; H, 7.41.

4.6. (+)-((1*S*,2*S*)-3-Oxocyclobutane-1,2-diyl)bis(methylene) diacetate 6

Preparative TLC (ethyl acetate–hexane, 1:4) gave pure **6** as an oil (0.45 g, 84%). ^{1}H NMR: δ 4.35–4.23 (m, 4H), 3.41–3.40 (m, 1H), 3.14–3.08 (m, 1H), 2.95–2.91 (m, 1H), 2.73–2.69 (m, 1H), 2.11 (s, 3H), 2.08 (s, 3H); FT-IR (neat) 1785, 1739 cm^{-1}; MS m/z 215 (M^++H); $[\alpha]_D = +20.3$ (c 0.04, $CHCl_3$); HRMS calcd for $C_{10}H_{15}O_5$, 215.092 (M^++H); found 215.094 ± 0.005.

4.7. (+)-((1*S*,2*S*)-2-(Hydroxymethyl)-4-oxocyclobutyl)methyl acetate 7

Preparative TLC (ethyl acetate–hexane, 1:4) gave pure **7** as an oil (0.37 g, 85%). ^{1}H NMR: δ 4.30–4.29 (m, 2H), 3.94–3.81 (m, 2H), 3.44 (m, 1H), 2.96–2.90 (m, 1H), 2.58–2.55 (m, 1H), 2.09 (s, 3H), 1.69 (s, 1H); FT-IR (neat) 1779, 1733 cm^{-1}; MS m/z 172 (M^+); $[\alpha]_D = +25.1$ (c 0.06, $CHCl_3$); HRMS calcd for $C_8H_{12}O_4$, 172.074 (M^++H); found 172.074 ± 0.005.

4.8. Photolysis of cyclobutanones 5–7, general procedure

A solution containing 0.3 mmol of ketone in 20 mL of methanol and 40 mL of acetonitrile was purged with argon for 30 min. Irradiation of the sample was carried out for 12 h in an ice-water bath. Evaporation of the solvent under reduced pressure gave the crude methyl furanoside, which was further purified.

4.9. ((2*S*,3*R*)-2-(Hydroxymethyl)-5-methoxytetrahydrofuran-3-yl)methyl acetate 8

Preparative TLC (ethyl acetate–hexane, 2:1) of the photomixture from ketone **5** gave pure **8** as an oil (0.36 g, 59%). ^{1}H NMR: δ 5.05–4.99 (two d, 1H, $J = 5.2$, 5.2 Hz), 4.18–4.01 (m, 3H), 3.79–3.56 (m, 2H), 3.38–3.33 (two s, 3H), 2.63–2.60 (m, 1H), 2.41 (s, 1H), 2.37–2.28 (m, 1H), 2.10–2.09 (s, 3H), 1.90–1.81 (m, 1H); MS m/z 203 (M^+-H); $[\alpha]_D = +14.0$ (c 0.05, $CHCl_3$); Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.89. Found: C, 52.87; H, 8.29.

4.10. ((2*S*,3*R*)-5-Methoxytetrahydrofuran-2,3-diyl)bis-(methylene) diacetate 9

Preparative TLC (ethyl acetate–hexane, 1:3) of the photomixture from ketone **6** gave pure **9** as an oil (0.40 g, 54%). ^{1}H NMR: δ 5.07–5.00 (two d, 1H, $J = 4.8$, 4.8 Hz), 4.27–4.03 (m, 5H), 3.34–3.33 (two s, 3H), 2.61–2.59 (m, 1H), 2.23–2.19 (m, 1H), 2.11 (s, 3H), 2.06 (s, 3H), 1.79–1.75 (m, 1H); MS m/z 245 (M^+-H); $[\alpha]_D = +16.1$ (c 0.08, $CHCl_3$).

4.11. ((2*S*,3*R*)-3-(Hydroxymethyl)-5-methoxytetrahydrofuran-2-yl)methyl acetate 8

Preparative TLC (ethyl acetate–hexane, 2:1) of the photomixture from ketone **7** gave pure **10** as an oil (0.84 g, 48%). ^{1}H NMR: δ 5.06–4.98 (two d, 1H, $J = 3.6$, 4.4 Hz), 4.28–4.08 (m, 3H), 3.72–3.61 (m, 2H), 3.36–3.33 (two s, 3H), 2.42–2.38 (m, 1H), 2.26–2.18 (m, 1H), 2.10–2.03 (s, 3H), 1.83–1.75 (m, 1H), 1.66 (s, 1H); MS m/z 203 (M^+-H); $[\alpha]_D = +13.7$ (c 0.06, $CHCl_3$); Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.89. Found: C, 52.51; H, 8.05.

4.12. (±)-2,2-(Dimethyl-4-oxocyclobutyl)methyl acetate 11

A two-neck round bottomed flask, equipped with a magnetic stirrer, dropping funnel and argon inlet, was charged with activated zinc[13] (16.32 g, 4 equiv) and

3-methyl-2-butenyl acetate[14] (8 g, 62.42 mmol, 1 equiv) in anhydrous ether (125 mL, 2 mL/mmol of olefin). To this vigorously stirred suspension was added dropwise a mixture of trichloroacetyl chloride (13.93 mL, 2 equiv), 1,2-dimethoxyethane (12.96 mL, 2 equiv) in anhydrous ether (62.42 mL, 1 mL/mmol of olefin) over a period of 30 min. The mixture was stirred overnight at room temperature. Hexane (50 mL) was added and the suspension was stirred for 10 min to precipitate the zinc salts. The solution was filtered and washed sequentially with 100 mL H_2O, 3×100 mL aqueous satd $NaHCO_3$, 100 mL brine, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude material in glacial acetic acid (10 mL/equiv of olefin) was slowly added to a suspension of zinc powder (20.4 g, 0.31 mol) and glacial acetic acid solution (7.5 mL, 1.5 mL/equiv of zinc) and stirred for 2 h at room temperature. The reaction mixture was then diluted with 100 mL ether and the zinc powder filtered off. The filtrate was then washed with 5×100 mL satd $NaHCO_3$, 100 mL H_2O, and 100 mL of brine solution. After drying over $MgSO_4$, the solution was concentrated and applied on a silica gel column (hexane–ethyl acetate, 5:1) to give pure ketone **11** as an oil (5.4 g, 51%). ^{1}H NMR: δ 4.30–4.17 (m, 2H), 3.30–3.27 (m, 1H), 3.33–3.32 (m, 1H), 2.94–2.89 (dd, 1H, $J = 2.0$, 2.4 Hz), 2.68–2.64 (dd, 1H, $J = 16.8$, 0.8 Hz), 2.07 (s, 3H), 1.46 (s, 3H), 1.24 (s, 3H); ^{13}C NMR: δ 205.7, 170.6, 65.9, 59.2, 58.4, 29.8, 29.4, 22.6, 20.7; FTIR (neat): 1781, 1741 cm^{-1}; MS m/z 170 (M^+); Anal. Calcd for $C_{10}H_{18}O_5$: C, 63.51; H 8.29; O 28.19 found C, 62.96; H 8.65; O 28.49.

4.13. (*S*)-(+)-2-(Hydroxymethyl)-3,3-dimethylcyclobutanone 12

A mixture of acetate (±)-**11** (0.076 g, 0.45 mmol), PPL (170 mg) in toluene–phosphate buffer (pH 7) (20 mL, 1:1 v) was vigorously stirred for 18 h at room temperature. The solution was then treated with 3×20 mL CH_2Cl_2 and the combined organic layers dried over $MgSO_4$. The organic solution was evaporated to dryness under reduced pressure and the residue purified by preparative TLC (hexane–ethyl acetate, 2:1) to give **12** as a colorless oil. $[\alpha]_D = +45.0$ (*c* 0.08 $CHCl_3$). The spectral data of this material were identical to those reported in the literature for the racemic compound.[15] FT-IR (neat) 3410, 1774 cm^{-1}; ^{1}H NMR: δ 4.52 (br s, 1H), 3.83–3.79 (m, 1H), 3.73–3.70 (m, 1H), 3.18–3.15 (m, 1H), 2.87–2.82 (dd, 1H, $J = 2.7$, 16.9 Hz), 2.66–2.62 (dd, 1H, $J = 1.7$, 16.8 Hz), 1.45 (s, 3H), 1.26 (s, 3H); ^{13}C NMR: δ 209.4, 69.3, 58.5, 58.2, 30.2, 29.3, 22.6; MS m/z 128 (M^+), 110, 95, 85, 71 (base peak), 56, 41, 28; Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.40; H, 9.60.

4.14. (+)-(*S*)-5-(Hydroxymethyl)-4,4-dimethyldihydrofuran-2-(3*H*)-one 13

To a solution of alcohol (+)-**12** (0.012 g, 0.1 mmol) in chloroform (30 mL) at 5 °C were added *m*-chloroperbenzoic acid (0.0259 g, 0.15 mmol) and $NaHCO_3$ (0.012 g, 0.15 mmol). The mixture was stirred under reflux for 3 h after which time it was washed with 10 mL 10% aqueous Na_2SO_3, 10 mL $NaHCO_3$, 10 mL saturated NaCl solution, and dried over $MgSO_4$. After evaporation the residue was subjected to preparative TLC (hexane–ethyl acetate, 1:1) to give the title compound as an oil (10 mg, 72%). $[\alpha]_D = +42.2$ (*c* 0.08, $CHCl_3$). The spectral data matched those reported in the literature for the same compound.[11]

4.15. (±)-(5-Methoxy-3,3-dimethyltetrahydrofuran-2-yl)-methyl acetate 15

A solution containing 0.3 mmol of (±)-**11** in 20 mL of methanol and 50 mL of acetonitrile was purged with argon for 30 min. The solution was irradiated for 12 h in an ice bath. Evaporation of the solvent under reduced pressure gave a residue, which was purified by preparative TLC (hexane–ethyl acetate, 4:1) to give the title compound as an oil (27 mg, 45%). ^{1}H NMR: δ 5.05–5.00 (two d, 1H, $J = 4.8$, 4.8 Hz), 4.26–4.02 (m, 2H), 3.89–3.81 (m, 1H), 3.39–3.37 (two s, 3H), 2.11 (s, 3H), 2.08–2.01 (m, 1H), 1.82–1.76 (m, 1H), 1.15 (s, 3H), 1.13 (s, 3H); MS m/z 201 ($M^+ - H$).

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