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Stereoselective synthesis of γ-lactone fused cyclopentanoids

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ABSTRACT

The stereoselective synthesis of γ-lactone fused cyclopentanoids applying chemoenzymatic methods is described. *rac*-2-Hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene and *rac*-2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene were successfully resolved by *Candida rugosa* lipase (CRL), to afford enantiomerically enriched products with an ee of 94 and 97%, respectively. The enantiomerically enriched acetates were then subjected to ruthenium and/or cerium catalyzed oxidation to afford α-diketones and subsequent alkaline H_2O_2 mediated oxidative cleavage reaction of α-diketones, followed by CH_2N_2 esterification, gave enantiomerically enriched γ-lactone fused cyclopentanoids with known absolute configurations.

1. Introduction

Cyclopentanoids are important intermediates in the synthesis of many organic compounds and are amongst the most abundant substructures found in naturally occurring molecules. A cyclopentane ring *cis*-fused at the α,β-bond of the γ-lactone is the basic structural unit of many complex and challenging biologically active cyclopentanoid natural products[1] and also functions as the basic building block for the synthesis of a variety of cyclopentanoid natural products.[2] Various synthetic methods have been developed to prepare this important ring system.[3] Khan et al.[4] described an efficient synthetic methodology by employing catalytic $RuCl_3{\cdot}3H_2O$ and $NaIO_4$ as stoichiometric cooxidants to obtain α-diketones from the vicinal dihaloalkenes, which are known as masked α-diketones.[4] α-Diketones were cleaved using $Pb(OAc)_4$ or alkaline H_2O_2 to give γ-lactone-fused cyclopentane derivatives in their racemic form.[4a] The asymmetric synthesis of these compounds has gained further importance since they can be easily converted into biologically active precursors[5] and chiral ligands.[6]

Optically active norbornenes are key intermediates for the synthesis of biologically active prostaglandin endoperoxides such as PGH_2, PGG_2, and β-santalol as used by Corey[7] and Ogasawara.[8] The pursuit of novel approaches for enantiomerically pure compound syntheses is a major topic in modern organic synthesis.[9] A convenient method for obtaining enantiopure norbornene derivatives can involve enzyme-catalyzed acylation. In the literature, there are only been a few examples of the enzymatic resolution of hexa and tetrachlorinated norbornene and norbornadiene derivatives.[5,6,10,11] Recently, we reported the enzymatic resolution of *rac*-2-*endo*-hydroxymethyl and acetoxymethyl substituted hexachloronorbornene derivatives.[11c] Moreover, we documented the enzymatic resolution of compound *rac*-2-*endo*-hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene and conversion of the resulting enantiomerically enriched acetate derivative into novel carbasugar derivatives.[12] In connection to these biotransformations and Khan's methodology, we investigated the enzymatic resolution of polychlorinated norbornene systems and the stereoselective synthesis of γ-lactone fused cyclopentane derivatives by making use of the structural flexibility and stereochemical control offered by polychlorinated norbornene derivatives. Herein we report the highly efficient enantioselective resolution of *rac*-2-hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene *rac*-**1** and *rac*-2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene *rac*-**3** and conversion of the resulting enantiomerically enriched esters into γ-lactone fused cyclopentanoids.

2. Results and discussion

2.1. Enzymatic resolution of *rac*-1 and *rac*-3

The key substrates *rac*-**1** and *rac*-**3** were synthesized by Diels–Alder reactions of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and 1,2,3,4,5,5-hexachlorocyclo pentadiene with allyl alcohol, respectively, in their pure *endo* forms.[11c,12,13] Initially, the enantiomeric resolution of bicycloadduct *rac*-**1** was performed by using PPL and vinyl acetate as the acyl donor at 25 °C according to the literature.[12] The conversion was monitored by TLC and 38% conversion was achieved after 45 h. The reaction was carried out by using a substrate/enzyme ratio 1:0.1 (w/w) and afforded a relatively low ee value (64%) (Table 1, entry 1). We also decided to study the enzyme catalyzed resolution of the same substrate with the immobilized lipase from *Candida antarctica* lipase B (CAL-B,

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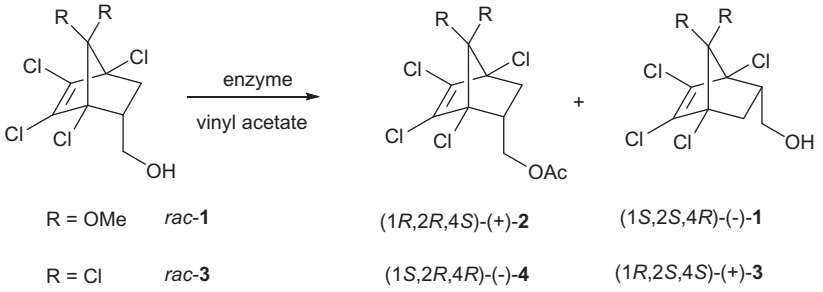
Table 1
Results of the enzyme catalyzed kinetic resolution of *rac*-**1** and *rac*-**3**

Entry[a]	Substrate	Enzyme	Substrate:enzyme	Time (h)	Esters[b] ee_p[c] (%)	c[d] (%)	E
1	*rac*-**1**	PPL	1:0.1	45	64	38	7
2	*rac*-**1**	*Novozym* 435	1:0.2	20	86	42	25
3	*rac*-**1**	CRL	1:0.1	68	94	39	60
4	*rac*-**3**	CRL	1:0.05	120	97	40	128
5	*rac*-**3**	PPL	1:0.05	40	94	47	85

[a] The reactions were carried out at 25 °C.
[b] The absolute configurations were found to be (*R*) according to the specific rotations reported in the literature.
[c] Determined by HPLC analysis employing a Diacel Chiralcel OD-H column.
[d] Yields (%) are given as the amount of isolated esters.



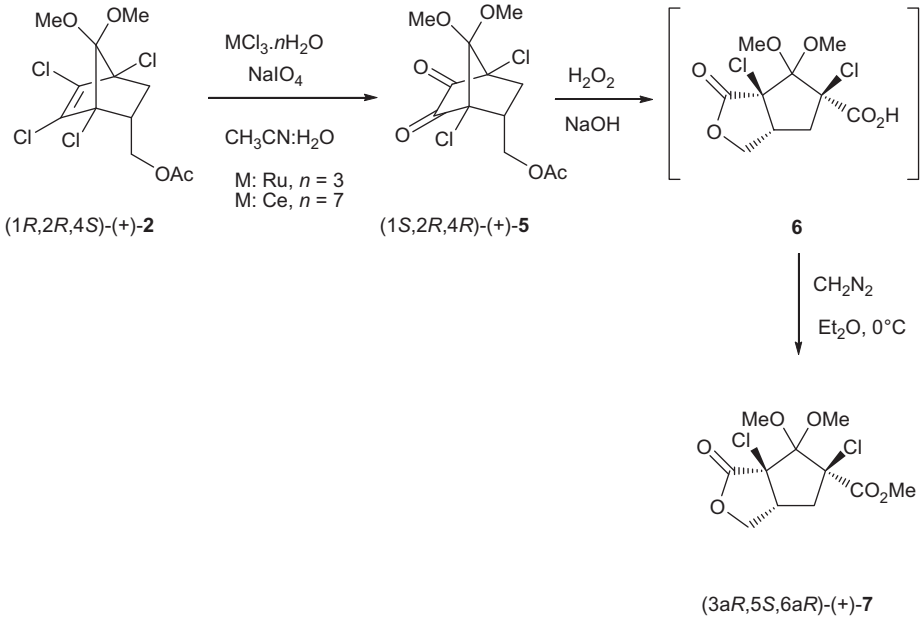
Scheme 1.

Novozym 435). A substantial increase was observed in the ee value (86%, entry 2). When substrate *rac*-**1** was subjected to CRL catalyzed acetylation under the same reaction conditions, excellent (Scheme 1) results were obtained in terms of enantioselectivity (94% ee, entry 3).

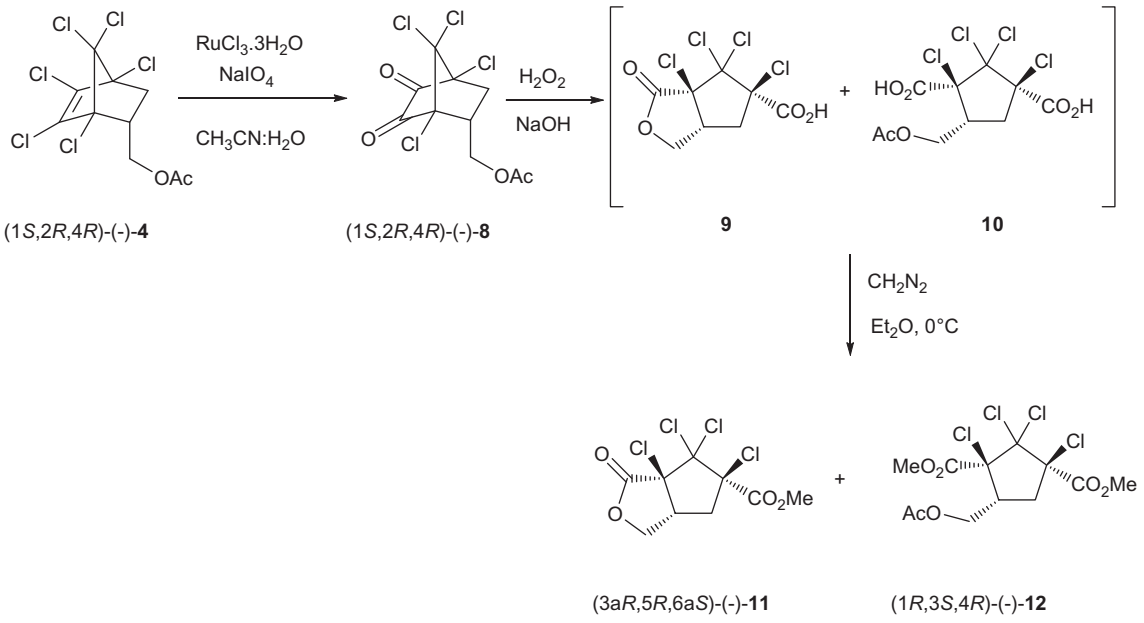
Next, the enzymatic kinetic resolution of alcohol *rac*-**3** was performed by CRL and PPL using the procedure given above.[11c] As can be seen in Table 1, *rac*-**3** was first tested with CRL in vinyl acetate as both the acyl donor and as the solvent by using a substrate/enzyme ratio 1:0.05 (w/w) to afford (−)-**4** in 97% ee with 40% conversion (entry 4); the PPL catalyzed kinetic resolution resulted in 94% ee with 47% conversion (entry 5). The absolute configurations of (+)-**2** and (−)-**4** were determined as (1*R*,2*R*,4*S*) and (1*S*,2*R*,4*R*), respectively, by comparing the specific rotation signs determined at equal concentrations in the same solvents, which have been reported in the literature.[12,11c]

2.2. Stereoselective synthesis of γ-lactone fused cyclopentanoids

After the successful enzymatic resolution and absolute configuration determination of the key compound (1*R*,2*R*,4*S*)-(+)-**2**, we turned our attention to the transformation of the dichloro substituted moiety into α-diketone. By applying Khan's procedure,[4b]



Scheme 2.



Scheme 3.

the acetylated derivative (1*R*,2*R*,4*S*)-(+)-**2** was subjected to an oxidation by using a catalytic amount of $RuCl_3{\cdot}3H_2O$ in the presence of $NaIO_4$ as a cooxidant and to afford α-diketone derivative (1*S*,2*R*,4*R*)-(+)-**5** in excellent yield (98%) as shown in Scheme 2. Over the course of this oxidation reaction, we also applied alternative catalysts such as $CeCl_3.7H_2O$ and $RhCl_3$. α-Diketone (1*S*,2*R*,4*R*)-(+)-**5** was obtained in 90% yield with the catalysis of $CeCl_3$. However, no product was observed in the case of $RhCl_3$. In the literature, $CeCl_3$ has been used as a cocatalyst in the ruthenium-catalyzed dihydroxylation reaction of dehalogenated alkene systems.[14] This is the first use of cerium in the oxidation of halogenated double bonds to α-diketones. It is environmentally friendly, softer and less expensive catalyst compared to ruthenium. Subsequent oxidative cleavage of α-diketone (+)-**5** with alkaline H_2O_2 gave non-isolable intermediate compound **6**, which was further subjected to an esterification reaction with CH_2N_2 in ether to overcome isolation problems. The resulting enantiomerically enriched γ-lactone fused cyclopentanoid methyl 5,6a-dichloro-6,6-dimethoxy-1-oxohexahydro-1*H*-cyclopenta[*c*]furan-5-carboxylate (+)-**7** was isolated with high chemical yield (90%) (Scheme 2). Since the transformation of α-diketone (+)-**5** into γ-lactone fused cyclopentanoid (+)-**7** has no effect on the stereocenters of the norbornane backbone, the absolute configuration of (+)-**7** was not altered during the transformation reactions. Thus the absolute configuration of (+)-**7** was determined as (3a*R*,5*S*,6a*R*).

(1*S*,2*R*,4*R*)-(−)-1,4,5,6,7,7-Hexachlorobicyclo[2.2.1]hept-5-en-2yl methyl acetate (−)-**4** can also serve as a potential precursor for the synthesis of enantiomerically enriched cyclopentane derivatives, since two geminal chloride atoms can be easily transformed into many functional groups. The hexachlorinated acetate derivative (1*S*,2*R*,4*R*)-(−)-**4** resolved by CRL was exposed to the ruthenium catalyzed oxidation, since cerium did not give any of the desired oxidation product. The resultant α-diketone (1*S*,2*R*,4*R*)-(−)-**8** was further subjected to oxidative cleavage by alkaline H_2O_2 followed by methylation of non-isolable intermediate compounds **9** and **10** with CH_2N_2 to afford a mixture of cyclopentanoid derivatives, (−)-**11** and (−)-**12** in a ratio of 1:4 (Scheme 3). Similar to the transformation of α-diketone (+)-**5** into γ-lactone fused cyclopentanoid (+)-**7**, the synthetic route applied has no effect on the stereocenters of the norbornane backbone. Therefore, the absolute configurations of (−)-**11** and (−)-**12** were determined as (3a*R*,5*R*,6a*S*) and (1*R*,3*S*,4*R*), respectively.

3. Conclusion

In conclusion, we have described the stereoselective synthesis of γ-lactone fused cyclopentanoids by applying chemoenzymatic methods. The 2-hydroxymethyl substituted tetra- and hexachlorinated norbornene derivatives were successfully resolved by CRL with high enantioselectivities of 94% and 97%, respectively. Using a synthetic route which has no effect on the stereocenters of the norbornane backbone, we have presented an effective transformation of the dichloro-substituted alkene moiety into α-diketones by applying $RuCl_3$ and/or $CeCl_3$ catalyzed oxidation and then subsequent oxidative cleavage with alkaline H_2O_2 to afford enantiomerically enriched and highly functionalized cyclopentaannulated γ-lactone fused cyclopentanoids, which are potential building blocks in organic synthesis. The geminal dimethoxy and dichloro units are open to various further transformations. Furthermore, $CeCl_3$ was used for the first time for the transformation of vicinal dihaloalkenes into α-diketones as an alternative to $RuCl_3$.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Advance DPX 400 spectrometer. ^1H (400 MHz) and ^{13}C NMR were recorded in $CDCl_3$ and the chemical shifts are expressed in ppm relative to $CDCl_3$ (δ 7.26 and 77.0 for ^1H and ^{13}C NMR, respectively) as the internal standard. Standard COSY, HETCOR, and DEPT experiments were performed to establish NMR assignments. Infrared spectra were obtained from KBr pellets on a Varian 1000 FT-IR spectrophotometer and are reported in cm^{-1}. HRMS data were obtained via LC–MS analysis performed with a Waters Synapt mass spectrometer at Central Laboratory of Middle East Technical University. Optical rotations were measured a 1 dm cell using a Rudolph research analytical, Autopol III automatic polarimeter. HPLC measurements were performed with a Thermo Separa-

tion Products, Inc., P1500-SN-4000-UV2000 instrument using a Chiralcel OD-H analytical column (250 × 4.60 mm). Flash column chromatography was performed on silica gel (60-mesh, Merck). The reactions were monitored by thin layer chromatography using Merck 0.2 mm silica gel 60 F_{254} analytical aluminium plates. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. CRL (*Candida rugosa* lipase) and PPL (lipase, type II, from porcine pancreas) were purchased from Aldrich. Novazyme 435 was donated by Novo Nordisk AS, Bagsverd, Denmark.

4.2. General procedure for the enzymatic resolution of alcohols

To a stirred solution of *rac*-**1** or *rac*-**3** (500 mg) in vinyl acetate (5 mL), enzyme (as shown in Table 1) was added in one portion and the reaction mixture stirred at 25 °C (TLC monitoring). The reaction mixture was filtered and vinyl acetate was evaporated under reduced pressure. The products were purified by flash column chromatography (EtOAc/hexane, 1:4).

4.2.1. ((1*S*,2*S*,4*R*)-1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-yl) methanol (−)-1

This was obtained as a white solid; Mp: 83.5–84 °C; $[\alpha]_D^{20} = -15.1$ (*c* 1.8, MeOH).

4.2.2. ((1*R*,2*R*,4*S*)-1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-yl)methyl acetate (+)-2

This was obtained as a colorless oil; (0.22 g, 39% yield); $[\alpha]_D^{20} = +11.4$ (*c* 1.8, MeOH) for 94% ee.[12] The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/*i*-PrOH 99:1, flow rate = 0.3 mL min^{-1}, λ = 230 nm, t_R = 19.8 min (minor), t_R = 21.3 min (major) in comparison with the racemic sample. ^{1}H NMR: δ 4.13 (dd, 1H, CH_2O, *J* = 11.6 and 5.3 Hz), 3.86 (dd, 1H, CH_2O, *J* = 11.6 and 7.2 Hz), 3.61 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 2.99–2.92 (m, 1H, C*H*), 2.50 (dd, 1H, *exo* CH_2, *J* = 11.7 and 9.2 Hz), 2.04 (s, 3H, CH_3), 1.67 (dd, 1H, *endo* CH_2, *J* = 11.9 and 4.1 Hz). ^{13}C NMR: δ 170.6, 130.2, 128.3, 111.9, 77.0, 74.3, 62.6, 52.7, 51.6, 45.8, 39.1, 20.7.

4.2.3. ((1*R*,2*S*,4*S*)-1,4,5,6,7,7-Hexachlorobicyclo[2.2.1]hept-5-en-2-yl)methanol (+)-3

This was obtained as a white solid; Mp: 166–167 °C; $[\alpha]_D^{20} = +35.1$ (*c* 1.5, MeOH).

4.2.4. ((1*S*,2*R*,4*R*)-1,4,5,6,7,7-Hexachlorobicyclo[2.2.1]hept-5-en-2-yl)methyl acetate (−)-4

This was obtained as a colorless oil; (0.25 g, 40% yield); $[\alpha]_D^{20} = -1.5$ (*c* 1.53, MeOH) for 97% ee.[11c] The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/i-PrOH 98:2, flow rate = 1.0 mL min^{-1}, λ = 254 nm, t_R = 6.3 min (minor), t_R = 6.8 min (major) in comparison with the racemic sample. ^{1}H NMR: δ 1.86 (dd, 1H, *endo* CH_2, *J* = 4.2 and 12.6 Hz), 1.99 (s, 3H, CH_3), 2.60 (dd, 1H, *exo* CH_2, *J* = 8.9 and 12.6 Hz), 3.00–3.13 (m, 1H, C*H*), 3.92 (dd, 1H, CH_2O, *J* = 6.7 and 11.7 Hz), 4.08 (dd, 1H, CH_2O, *J* = 5.8 and 11.7 Hz). ^{13}C NMR: δ 21.1, 38.6, 46.4, 62.7, 79.0, 81.3, 102.9, 130.5, 132.3, 170.8.

4.3. Ruthenium catalyzed oxidation of (1*R*,2*R*,4*S*)-(+)-2 and (1*S*,2*R*,4*R*)-(−)-4

To a stirred solution of dihaloalkene (1*R*,2*R*,4*S*)-(+)-**2** (0.20 g, 0.55 mmol) or (1*S*,2*R*,4*R*) (-)-**4** (1.0 g, 2.7 mmol) in acetonitrile (6 mL) at 0 °C was added a solution of $RuCl_3{\cdot}3H_2O$ (0.038 mmol or 0.19 mmol) and $NaIO_4$ (0.82 mmol or 4.02 mmol) in water (1 mL). The mixture was stirred and monitored by TLC. The resulting suspension was filtered through a thin pad of silica gel followed by concentration of the filtrate under vacuum. The crude product was purified by flash column chromatography using EtOAc/hexane (1:2) as eluent to afford (+)-**5**[15] and (−)-**8**.

4.3.1. ((1*S*,2*R*,4*R*)-1,4-Dichloro-7,7-dimethoxy-5,6-dioxobicyclo-[2.2.1]heptan-2-yl)methyl acetate (+)-5

This was obtained as a yellow liquid. (0.17 g, 98%). $[\alpha]_D^{20} = +24.6$ (*c* 3.7, MeOH). ^{1}H NMR: δ 4.17 (dd, 1H, CH_2O, *J* = 12.0 and 1.7 Hz), 3.98 (dd, 1H, CH_2O, *J* = 12.1 and 3.1 Hz), 3.67 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 2.96–2.92 (m, 1H, C*H*), 2.68 (t, 1H, *exo* CH_2, *J* = 12.6 Hz), 2.10 (dd, 1H, *endo* CH_2, *J* = 13.1 and 4.8 Hz), 1.84 (s, 3H, CH_3). ^{13}C NMR: δ 187.5, 186.3, 168.6, 101.4, 77.5, 73.7, 58.7, 51.7, 50.6, 42.0, 32.8, 18.9. IR (KBr): 2900, 1785, 1720, 1440, 1200 cm^{-1}.

4.3.2. ((1*S*,2*R*,4*R*)-1,4,7,7-Tetrachloro-5,6-dioxobicyclo[2.2.1]-heptan-2-yl)methyl acetate (−)-8

This was obtained as a yellow liquid. (0.16 g, 90%). $[\alpha]_D^{20} = -46.0$ (*c* 1.0, MeOH). ^{1}H NMR: δ 4.31 (dd, 1H, CH_2O, *J* = 12.3 and 1.8 Hz), 4.12 (dd, 1H, CH_2O, *J* = 12.5 and 3.5 Hz), 3.14–3.09 (m, 1H, C*H*), 2.84 (t, 1H, *exo* CH_2, *J* = 12.7 Hz), 2.36 (dd, 1H, *endo* CH_2O, *J* = 13.6 and 4.9 Hz), 1.93 (s, 3H, COCH_3); ^{13}C NMR: δ 185.2, 184.3, 169.3, 92.9, 82.5, 78.9, 59.2, 44.1, 34.4, 19.8. IR (KBr): 2880, 1780, 1715, 1443, 1206 cm^{-1}. HRMS, Calcd [M+H]$^+$, 331.9177, Measured [M+H]$^+$ 331.9173.

4.4. Cerium catalyzed oxidation of (1*R*,2*R*,4*S*)-(+)-2

To a stirred solution of dihaloalkene (1*R*,2*R*,4*S*)-(+)-**2** (0.18 g, 0.50 mmol) in acetonitrile (6 mL) at 0 °C was added a solution of $CeCl_3{\cdot}7H_2O$ (0.05 mmol) and $NaIO_4$ (0.16 g, 0.75 mmol) in water (1 mL). The mixture was stirred and monitored by TLC. The crude product was purified by flash column chromatography to afford α-diketone (+)-**5**[15] (0.15 g, 90%).

4.5. Oxidative cleavage of α-diketones (1*S*,2*R*,4*R*)-(+)-5 and (1*S*,2*R*,4*R*)-(−)-8

To a stirred solution of α-diketone (**+**)-**5** (0.13 g, 0.40 mmol) or acetate (−)-**8** (0.8 g, 2.4 mmol) in methanol (3 ml) was added 30% H_2O_2 (0.30 mL) followed by the slow addition of 6 M NaOH solution (0.15 mL). The mixture was stirred at room temperature for 1 h and then, 5% HCl (10 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 10) mL. The combined organic layer was washed with water (3 × 10 mL) and brine (2 × 10 mL), and dried over $MgSO_4$. The solvent was evaporated and the crude carboxylic acids **6**, **9**, and **10** were obtained without any further isolation.

4.6. Esterification of carboxylic acids 6, 9 and 10

At first, KOH (0.56 g, 10.0 mmol) was dissolved in water (1.2 mL) and cooled in an ice-bath. Then cold diethyl ether (10 mL) was added. When the temperature was 0 °C, *N*-methyl-*N*-nitrosourea was slowly added. After the gas evolution was complete, the ether phase was separated and dried over KOH, then filtered and cooled to 0 °C. Next, carboxylic acid **6** or the mixture of **9** and **10** (0.40 mmol) in ether were added dropwise. After the temperature reached 20 °C, the ether was evaporated. The crude product was purified by flash column chromatography (EtOAc/hexane 1:3) to afford (+)-**7**[15] or (−)-**11** and (−)-**12**.

4.6.1. (3a*R*,5*S*,6a*R*)-Methyl 5,6a-dichloro-6,6-dimethoxy-1-oxo-hexahydro-1*H*-cyclopenta[*c*]furan-5-carboxylate (+)-7

This was obtained as a colorless solid. (0.11 g, 90%). $[\alpha]_D^{20} = +7.2$ (*c* 0.6, MeOH). Mp: 118–120 °C. ^{1}H NMR: δ 4.61 (t, 1H, CH_2O, *J* = 9.0 Hz), 4.14 (dd, 1H, CH_2O, *J* = 9.3 and 3.6 Hz), 3.86 (s, 3H,

OCH_3), 3.78 (s, 3H, OCH_3), 3.49 (dtd, 1H, C*H*, *J* = 9.0, 9.0 and 3.6 Hz), 3.32 (s, 3H, CH_3), 2.82 (dd, 1H, CH_2, *J* = 14.5 and 9.0 Hz), 2.66 (dd, 1H, CH_2, *J* = 14.5 and 9.0 Hz). ^{13}C NMR: δ 171.1, 167.7, 110.0, 74.0, 73.8, 70.6, 54.3, 53.5, 51.6, 46.4, 41.9. IR (KBr): 2850, 1740 (br), 1180 cm^{-1}.

4.6.2. (3a*R*,5*R*,6a*S*)-Methyl 5,6,6,6a-tetrachloro-1-oxohexahydro-1*H*-cyclopenta[*c*]furan-5-carboxylate (−)-11

This was obtained as a colorless oil. (0.11 g, 15% yield). $[\alpha]_D^{20} = -8.3$ (*c* 0.6, MeOH). ^{1}H NMR: δ 4.72 (t, 1H, CH_2O, *J* = 9.4 Hz), 4.15 (dd, 1H, CH_2O, *J* = 9.4 and 4.6 Hz), 3.92 (s, 3H, CO_2CH_3), 3.79–3.70 (m, 1H, C*H*), 3.00–2.98 (m, 2H, CH_2); ^{13}C NMR: δ 168.3, 165.4, 92.8, 78.9, 70.9, 61.2, 54.0, 46.1, 42.5. HRMS, Calcd $[M+H]^+$, 319.9177, Measured $[M+H]^+$ 319.91779. IR (KBr): 2870, 1737 (br), 1183 cm^{-1}.

4.6.3. (1*R*,3*S*,4*R*)-Dimethyl 4-(acetoxymethyl)-1,2,2,3-tetrachlorocyclopentane-1,3-dicarboxylate (−)-12

This was obtained as a colorless oil. (0.58 g, 61% yield). $[\alpha]_D^{20} = -17.4$ (*c* 2.5, MeOH). ^{1}H NMR: δ 4.71 (dd, 1H, CH_2O, *J* = 11.1 and 5.4 Hz), 4.48 (dd, 1H, CH_2O, *J* = 11.1, 8.7 Hz), 3.90 (s, 3H, CO_2CH_3), 3.85 (s, 3H, CO_2CH_3), 3.57–3.49 (m, 1H, C*H*), 2.92 (dd, 1H, CH_2, *J* = 15.0 and 11.8 Hz), 2.68 (dd, 1H, CH_2, *J* = 15.0 and 8.0 Hz), 2.06 (s, 3H, $COCH_3$). ^{13}C NMR: δ 170.4, 165.8, 165.3, 95.0, 78.3, 76.5, 63.6, 53.6, 53.4, 49.3, 39.5, 20.7. HRMS, Calcd $[M+H]^+$, 393.9544, Measured $[M+H]^+$ 393.9539.

Acknowledgements

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15. The spectroscopic data of diketone (+)-**5** and γ-lactone-fused cyclopentanoid (+)-**7** are all in accordance with the literature values of the corresponding racemic forms reported in Ref. 4b,a, respectively.