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Synthesis and Absolute Configuration of Both Enantiomers of 4,5-Dihydroxy-3-(formyl)cyclopent-2-enone Acetonide as a New Chiral Building Block for Prostanoid Synthesis

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The synthesis of both enantiomers of 4,5-dihydroxy-3-(formyl)cyclopent-2-enone acetonide (**5**) was accomplished in five steps starting from *meso*-tartaric acid (**6**). The key steps involved preparation of the isopropylidene protected 3-[(dimethoxyphosphoryl)methyl]-4,5-dihydroxy-cyclopent-2-enone (**9**), resolution of the diastereoisomeric products **10** of the Horner reaction of racemic **9** with (*R*)-glyceraldehyde acetonide and final regioselective ozonolysis of the exocyclic carbon-carbon double bond of the separated dienones **10** leading to both enantiomeric title compounds **5**. The absolute configuration of both enantiomers was initially assigned based on the comparison of the chiroptical properties obtained from the DFT calculations with the experimental data and finally confirmed by X-ray analysis.

Introduction

Prostaglandins are naturally occurring metabolites derived from oxidation of polyunsaturated fatty acids. These hormone-like chemical messengers regulate a broad range of physiological activities in animals and man, including blood circulation, the contraction and relaxation of smooth muscle tissue, inflammatory and pain mediation, digestion and reproduction.[1] Moreover, prostaglandins of A and J series and their analogues characterized by the presence of a chemically reactive α,β-unsaturated carbonyl moiety show antineoplastic[2] and neuroprotective[3] activities. The complex structures of prostaglandins together with their broad spectrum of biological activity have stimulated the development of new methods of their synthesis for over 40 years.[4] Currently, the prostaglandins and their analogues are prepared by three main basic strategies. In the first one, the core cyclopentane bearing appropriate substituents is used as a precursor for further functionalization of α- and ω-chains. In the second strategy (a two-component coupling), a five-membered cyclic structure encompassing one of the two side chains is first synthesized and the second chain (either the α or the ω-chain) is introduced at a later stage. The third strategy (three-component coupling initiated and developed in Noyori's group), a one-pot procedure, involves a 1,4-addition of the ω-chain to the appropriate cyclopentenone, followed by in situ trapping with the required α-chain component as an electrophile.[5] All these strategies are based mainly on such chiral substrates like Corey's lactone and its derivatives **1**, 4-silyloxy- or 4-alkoxy derivatives of cyclopent-2-enone **2** and 4,5-dihydroxy cyclopent-2-enone acetonide **3** (Fig. 1). The syntheses of these cyclopentane and cyclopentene derivatives are often quite lengthy and based on the reagents which are expensive and/or hardly available.

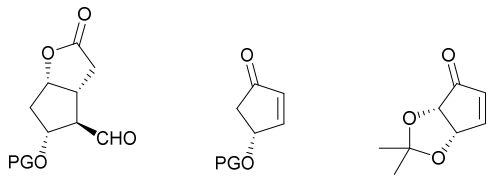

Fig. 1 The most frequently used intermediates in the prostaglandin synthesis.

As part of our research program aimed at the invention and development of general methods for the synthesis of bioactive cyclopentenones and cyclopentanones using phosphorus reagents,[6] the diastereoisomers of camphor protected 3-[(dimethoxyphosphoryl)methyl]-4,5-dihydroxycyclopent-2-enone **4** have been prepared[7] and proposed as new chiral building blocks in our strategy of the synthesis of various target compounds. Recently, their utility in the prostanoid synthesis has been demonstrated by the preparation of both enantiomers of anticancer cyclopentenone prostaglandin analogue TEI-9826.[8]

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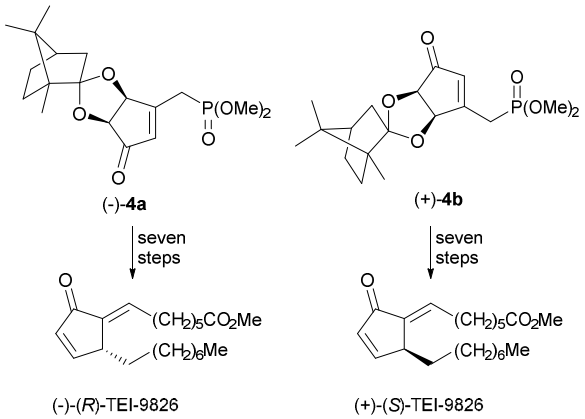

Scheme 1 Synthesis of both enantiomers of TEI-9826.

To gain further flexibility in functionalization of the cyclopentenone ring and to overcome some limitations in the use of the diastereoisomers of **4** (low diastereoselectivity of the cyclopentenone ring formation, tedious separation, steric bulk of the camphor protecting group), we decided to synthesize both enantiomers of compound **5** (Fig. 2) and use them as substrates in our planned syntheses of prostanoids. The presence of the formyl group at C3 allows to functionalize this position not only by the Wittig reaction, as reported by Durand and coworkers in their synthesis of phytoprostane B1 type I and II methyl esters,[9] but also by the Peterson reaction and Julia-Kocienski method. Some other reactions of the C3-formyl group may be utilized as well.

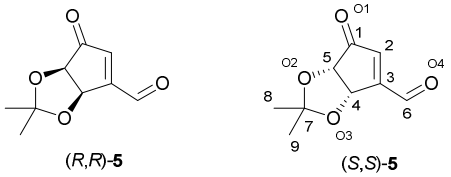

Fig. 2 Structures of both enantiomers of 4,5-dihydroxy-3-(formyl)cyclopent-2-enone acetonide **5**.

In this paper we report the synthesis of both enantiomers of the building block **5** and determination of their absolute configuration by two methods: (a) by DFT calculations of their chiroptical properties (optical rotation and electronic circular dichroism (ECD)) and (b) by X-ray structure determination of phenylhydrazone obtained from the dextrorotatory enantiomer of **5**.

Results and discussion

Synthesis of Enantiomeric 4,5-*cis*-dihydroxy-3-(formyl)cyclopent-2-enone acetonides (5)

The synthesis of both enantiomeric aldehydes **5** is outlined in Scheme 2. To have *cis*-arrangement of the two hydroxyl groups at C4 and C5 in the cyclopentenone ring, a commercially available, optically inactive, *meso*-tartaric acid (**6)** was used as a starting material. Its acid-catalyzed esterification with methanol gave the corresponding diester **7** which, in turn, was efficiently converted into acetal **8** upon treatment with 2,2-dimethoxypropane under acidic conditions. In the next step, the reaction of the protected diester **8** with an excess of lithium salt of dimethyl methanephosphonate produced 3-[(dimethoxyphosphoryl)methyl]-4,5-dihydroxycyclopent-2-enone acetonide (**9)** in moderate yield. This cyclopentenone was formally formed by the intramolecular Horner olefination of the bis(β-ketophosphonate) **A** as the first intermediate product of the above reaction. However, as we have showed earlier,[10] the reaction course is more complex since the kinetically controlled cyclopentenone **B** is initially formed from **A** as a result of the reversible Knoevenagel reaction. Addition of water under basic reaction conditions to **B** allows its irreversible transformation into **9** which is the thermodynamically controlled product of the condensation under discussion (Scheme 3). Therefore, the addition of **8** to the α-phosphonate carbanion was carried out at low temperature and then, after addition of water, the reaction mixture was stirred at room temperature for 18 h.

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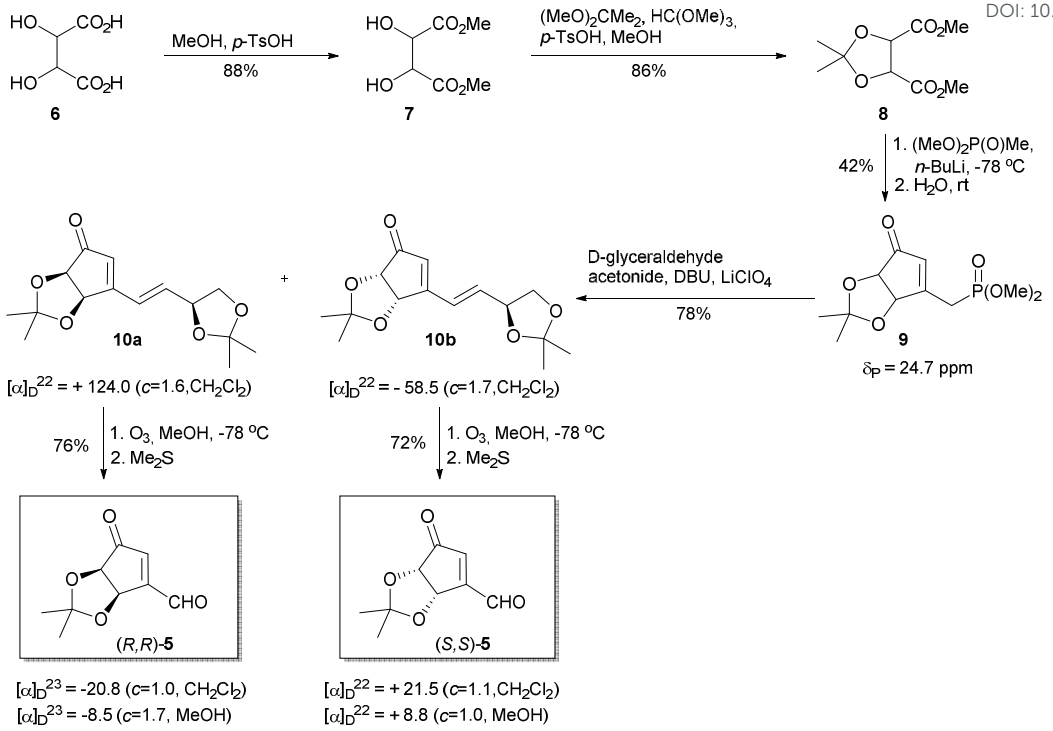
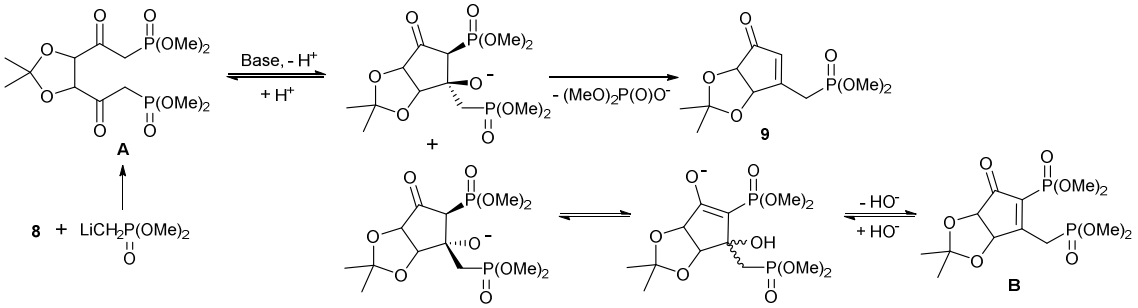


Scheme 2 Synthesis of (*R,R*)-**5** and (*S,S*)-**5**.



Scheme 3 The reaction course between diester **8** and α-phosphonate carbanion.

Our approach to the synthesis of both enantiomers of **5** involves separation of the diastereoisomeric dienones obtained in the Horner olefination reaction of **9** with a chiral aldehyde. With this in mind, D-(*R*)-gliceraldehyde acetonide, easily available from D-mannitol by a bisacetalization/glycol cleavage sequence,[11] has been chosen. The Horner reaction of **9** with D-(*R*)-gliceraldehyde acetonide in the presence of DBU and lithium perchlorate afforded an equimolar mixture of diastereoisomeric dienones **10a** and **10b** in a high yield. They were easily separated by column chromatography. In the final step, as expected, selective ozonolysis of a more reactive exocyclic carbon-carbon double bond in the diastereoisomers **10a** and **10b** carried out with one equivalent of ozone in methanol at -78 °C gave rise to both enantiomers of aldehyde **5** in a good yield.

Theoretical Calculations of Chiroptical Properties of (*R,R*)-5

To assign absolute configuration of both enantiomers of aldehyde **5**, theoretical calculations of their optical rotation and electronic circular dichroism (ECD) were conducted. The principle of this approach is based on the comparison of the calculated chiroptical properties with the experimental data. If the two data sets are very similar to each other, then highly reliable assignment can be made. During the last several years numerous examples of a successful application of this methodology in the determination of absolute configuration of a broad range of chiral species have been reported.[12-15]

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To calculate chiroptical properties of aldehyde **5**, conformational search on an arbitrarily chosen enantiomer (*R,R*)-**5** was carried out employing MM+ force field.[16] The obtained structures were fully optimized with the global-hybrid functional B3LYP[17] in conjunction with the split-valence double-zeta polarized Pople 6-31G(d) basis set.[18] These DFT calculations[19] showed that in the energy range of 4 kcal/mole there are four stable conformers, **5a-d**, in equilibrium at room temperature, as a result of different orientation of the formyl group (s-*cis* or s-*trans*) and the flap position of the acetal carbon atom in adopted envelope conformation of the dioxolane ring (Fig. 3).

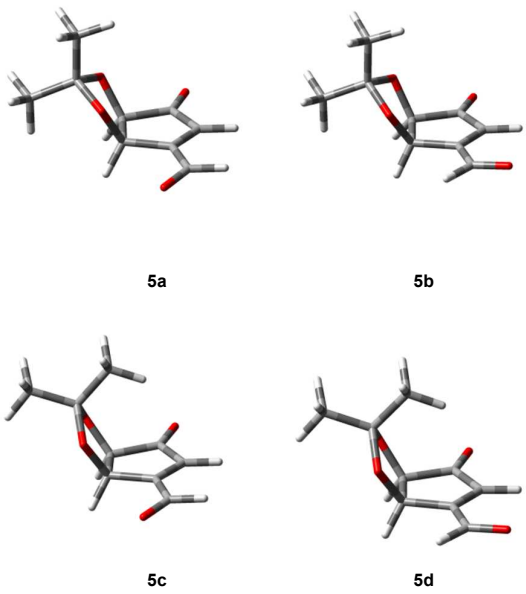

Fig. 3 Geometries of the stable conformers of (*R,R*)-**5** calculated at the B3LYP/6-31G(d) level.

To include solvent effects in calculations of chiroptical properties, conformers **5 a-d** were reoptimized at the B3LYP/6-311++G(2d,2p)[20] level applying the integral equation formalism of the polarizable continuum model (IEFPCM)[21] for methanol and dichloromethane (DCM). The harmonic vibrational frequencies of each conformation were calculated at the same level to confirm their stability (no imaginary frequencies observed), and to evaluate the corresponding free energies. Because the knowledge of the correct conformer populations is crucial for the proper prediction of the molecular chiroptical properties, for all conformers more accurate single-point energy calculations applying the double-hybrid density functional with long-range dispersion correction B2PLYP-D[22] and Dunning's correlation-consistent polarized triple-zeta with diffusion functions aug-cc-pVTZ[23] were performed to obtain a reliable Boltzmann distribution.

Based on the results of geometry optimizations single-point optical rotation calculations of conformers **5a-d** were conducted at either 589.3 nm (sodium D line) and 546 nm wavelengths of incident light in methanol and dichloromethane applying the four density functionals differing in the amount of Hartree-Fock (HF) exchange: the global-hybrid meta-GGA M062X functional[24] with 54% of HF exchange; the long range corrected CAM-B3LYP functional[25] using the Coulomb-attenuating method (19-65% of HF exchange); the range-separated hybrid ωB97XD[26] functional with dispersion correction (22.2-100% of HF exchange) and the global-hybrid GGA B3LYP[17] functional (20% of HF exchange). The main goal of conducting these calculations with the four functionals and under different conditions was to reach a higher level of confidence in the assignment of absolute configuration of both enantiomers of aldehyde **5**. Moreover, we also were interested in comparison of the accuracy of the modern M062X, CAM-B3LYP and ωB97XD functionals with respect to the B3LYP functional, which is still most popular in most areas of quantum chemistry despite its known shortcomings. The theoretical specific rotation values were obtained as averages weighted on the Boltzmann population of conformers **5a-d** estimated on the basis of free energies ($P_{\Delta G}$) and on single-point energies with thermal correction to free energy ($P_{\Delta E}$) (Table 1 and Table 2).

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Table 1. Experimental ((-)-**5**) and theoretical optical rotations of (*R,R*)-**5** calculated in MeOH at the IEFPCM DFT/6-311++G(2d,2p) level at 598.3 and 546 nm wavelengths.

Conformer	$P_{\Delta G}$ [%][a]	$P_{\Delta E}$ [%][b]	$[\alpha]_D$				$[\alpha]_{546}$			
			B3LYP	CAM-B3LYP	M062X	ωB97XD	B3LYP	CAM-B3LYP	M062X	ωB97XD
5a	65.9	53.2	+16.9	+33.6	+35.0	+30.3	+25.6	+44.8	+48.4	+41.2
5b	9.7	6.8	-115.9	-89.8	-79.8	-97.3	-102.5	-92.1	-75.3	-100.7
5c	21.7	36.3	-73.9	-43.6	-41.2	-38.9	-77.6	-48.8	-45.2	-41.6
5d	2.6	3.7	-341.0	-256.6	-243.9	-256.3	-379.3	-299.9	-280.3	-298.3
Boltzmann-averaged [α][c]			-25.3 (-38.3)	-2.9 (-13.5)	-0.1 (-10.7)	-4.7 (-14.1)	-20.0 (-35.5)	+2.0 (-11.2)	+7.3 (-6.1)	+0.4 (-11.0)
Experimental [α]			-8.5 (c=1.7)				-3.8 (c=1.7)			

[a] Populations based on ΔG values at 298 K. [b] Population based on single-point energy calculations at the B2PLYP-D/aug-cc-pVTZ level with thermal correction to free energy. [c] Based on populations calculated on ΔG and ΔE (in parentheses) values.

Table 2. Experimental ((-)-**5**) and theoretical optical rotations of (*R,R*)-**5** calculated in dichloromethane at the IEFPCM DFT/6-311++G(2d,2p) level at 598.3 and 546 nm wavelengths.

Conformer	$P_{\Delta G}$ [%][a]	$P_{\Delta E}$ [%][b]	$[\alpha]_D$				$[\alpha]_{546}$			
			B3LYP	CAM-B3LYP	M062X	ωB97XD	B3LYP	CAM-B3LYP	M062X	ωB97XD
5a	65.6	53.4	-3.8	+18.0	+17.5	+14.3	-0.4	+25.9	+26.5	+21.7
5b	11.3	8.2	-44.4	-52.0	-35.7	-57.1	+1.6	-42.4	-16.4	-47.8
5c	19.8	33.7	-109.5	-63.2	-62.9	-58.7	-129.7	-74.1	-73.8	-67.2
5d	3.3	4.7	-324.6	-245.7	-230.6	-244.2	-353.2	-285.0	-261.8	-281.8
Boltzmann-averaged [α][c]			-39.9 (-57.8)	-14.7 (-37.0)	-12.7 (-25.6)	-16.7 (-28.2)	-37.4 (-60.3)	-11.9 (-27.9)	-7.7 (-24.3)	-13.8 (-28.1)
Experimental [α]			-20.8 (c=1)				-18.7 (c=1.0)			

[a] Populations based on ΔG values at 298 K. [b] Population based on single-point energy calculations at the B2PLYP-D/aug-cc-pVTZ level with thermal correction to free energy. [c] Based on populations calculated on ΔG and ΔE (in parentheses) values.

All the four methods agree that the individual conformers exhibit substantially different specific rotation regarding their sign and magnitude. Thus, for example, the specific optical rotations of the conformers **5a** and **5d** calculated with the B3LYP functional in methanol at the 589.3 nm wavelength were +16.9 and -341.0, respectively. It shows that although the population of conformer **5d** is relatively low (4.7-2.6% depending on the calculation methods and conditions) it has a great impact on averaged optical rotation of (*R,R*)-**5** which makes of special importance the proper estimation of conformers distribution for accurate computations. In contrast to the B3LYP functional, which has a small HF exchange and does not have asymptotic correction, Boltzmann-averaged optical rotations calculated by the use of the M062X, CAM-B3LYP and ωB97X-D functionals were close to the experimental values obtained for (-)-**5**.

The geometries of conformers **5a-d** optimized at the IEFPCM-B3LYP/6-311++G(2d,2p) level in methanol were also employed as the input geometries for the simulations of the ECD spectra by the TD-DFT method. Excitation energies and rotatory strengths for the lowest 20 states have been calculated for each conformer with the 6-311++G(2d,2p) basis set and the B3LYP, M062X, CAM-B3LYP and ωB97XD functionals applying IEFPCM solvent model for methanol. The theoretical ECD spectra of (*R,R*)-**5** were obtained by applying a 0.4 eV Gaussian shaped line width for each transition and taking into account conformer populations based the on ΔE values.[27] In the ECD spectrum of (-)-**5** recorded in methanol, a strong negative Cotton effect is visible at 224 nm and a very broad weak positive band at 341 nm (Fig. 4). The calculated ECD spectra of (*R,R*)-**5** with the M062X, CAM-B3LYP and ωB97XD functionals reproduce well the experimental spectrum of (-)-**5** in term of the shape as well as the sequence of the negative/positive Cotton effects (Fig. 5). Both the (–/+) pattern are clearly visible however, the peaks show a redshift to higher wavelengths and lower intensity with respect to the experimental spectrum. The agreement is especially good when employing the M062X functional. In contrast, the B3LYP functional does not give the right prediction of the sign and magnitude of the positive Cotton effect visible in the experimental spectrum of (-)-**5**.

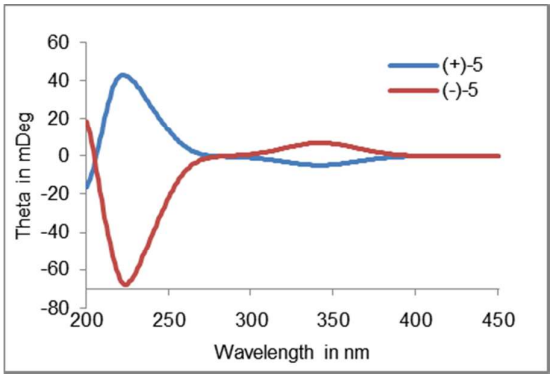

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Fig. 4 Experimental ECD spectra of (+)-**5** and (-)-**5** recorded in methanol.

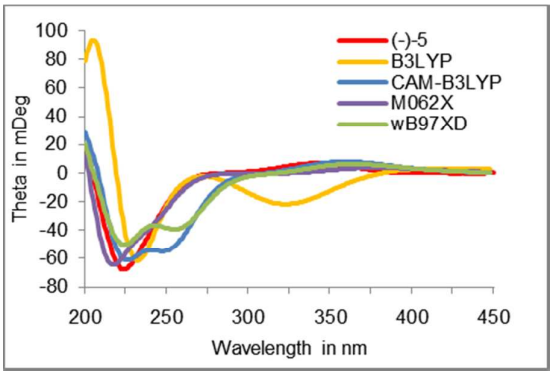
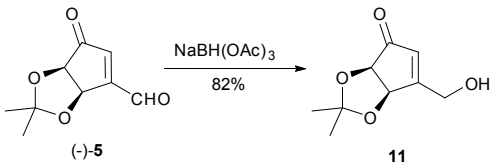


Fig. 5 ECD spectrum of (-)-**5** and simulated spectra of (*R,R*)-**5** calculated at the IEFPCM TD-DFT/6-311++G(2d,2p) level in methanol. The simulated spectra have been red-shifted by 16 nm in order to match the experimental trace.

Because the calculated chiroptical properties were in such a close agreement with the experimental results, it allowed us to assign *R,R* absolute configuration to the levorotary enantiomer of **5** and *S,S* to the opposite one.

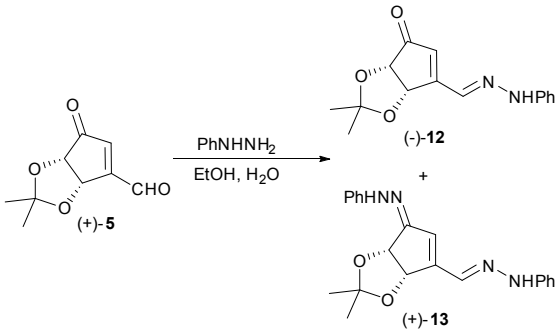
X-Ray Analysis

To give definite proof of the right assignment of absolute configuration based on the theoretical calculations, (-)-**5** was selectively reduced with sodium triacetoxyborohydride to allyl alcohol **11** with the hope of obtaining suitable crystals for X-ray diffraction analysis (Scheme 4).



Scheme 4 Preparation of allyl alcohol **11**.

In fact, alcohol **11** turned out to be solid, however, our attempts to obtain the good quality crystals failed. In our second approach aldehyde (+)-**5** was reacted with phenylhydrazine to give crystalline hydrazone **12** and dihydrazone **13** in the yield of 38% and 35%, respectively (Scheme 5).



Scheme 5 Synthesis of hydrazone **12**.

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The suitable for X-ray analysis crystal of **12** was obtained by slow crystallization from ethanol. X-ray analysis of hydrazone **12** strongly suggested *S* absolute configuration of the stereogenic C4 and C5 carbon atoms which was in a full agreement with the conclusions drawn from the theoretical calculations (Fig. 6). The determination of the absolute configuration of compound **12** based on the analysis of the Friedel opposites[28] required a precise diffraction experiment. There were 979 Friedel pairs out of total possible 1238 (for that data resolution), meaning that the Flack test should be meaningful. Random errors in the data increased standard deviation of the Flack parameter, which in our refinement was -0.3(3) for the given configuration and 1.2(3) for the opposite one, but in overall the determined absolute configuration of **12** is highly probable. Hydrazone **12** crystallized in $P2_12_12_1$ group which is one of the most popular groups for chiral compounds. The shape of the molecule is reflected in the unit cell dimensions with one short axis and two other approximately three times longer (Fig. 7). The molecule of **12** has four possible proton acceptor groups and only one strong hydrogen donor from the hydrazone moiety. The intermolecular hydrogen bonds are responsible for the crystal packing. The deficiency of strong donors was compensated by carbon hydrogens. There are three hydrogen bonds in the crystal lattice: the first N2-H2N···O1 with the distance 2.12(1)Å, the second C6-H61...O2 with the distance 2.45(1)Å, and third C12-H121···O1 with the distance 2.56(1)Å. The fourth contact with O3 as an acceptor is much weaker and the distance C14-H141···O3 is 2.99(1) Å. The closest contact to the acceptor atoms N1 is from hydrogen H151 connected to C15; this intermolecular hydrogen contact is 2.51(1) Å but the angle C15-H151···N1 is only 97.6(1) what reduces its strength.

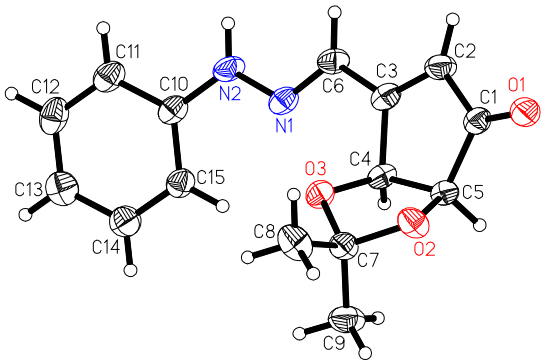

Fig. 6 X-ray ORTEP plot of hydrazone **12**. Displacement ellipsoids are shown at 50% probability level.

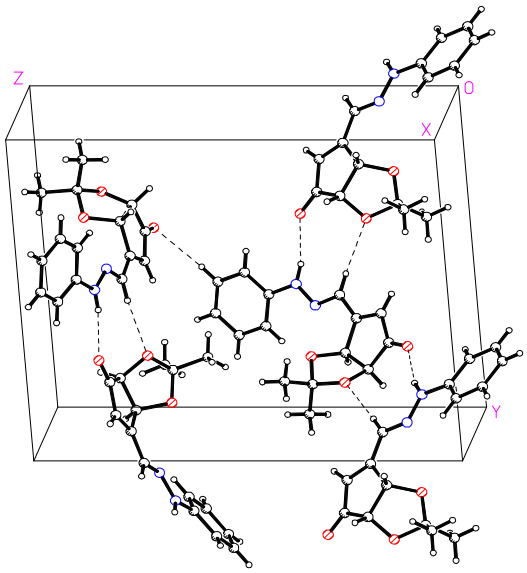

Fig. 7 X-ray structure of **12** showing intermolecular interactions.

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Conclusions

In conclusion, the short synthesis of both enantiomers of 4,5-dihydroxy-3-(formyl)cyclopent-2-enone acetonide (**5**) was developed based on commercially available *meso*-tartaric acid (**6**) as a starting material. The absolute configuration of aldehyde **5** was assigned on the basis of the theoretical calculations of the optical rotation and electronic circular dichroism and confirmed by X-ray analysis of hydrazone derivative of (+)-**5**. Calculations were conducted with four functionals under different conditions. The best agreement of the theoretically calculated chiroptical properties with the experimental data was observed for the M062X functional while the B3LYP functional did not give satisfactory results.

Experimental

General: Unless stated otherwise, all air and water sensitive reactions were carried out under an argon atmosphere using freshly distilled dry solvents. All glassware was dried prior to use by heating under vacuum. Commercial grade reagents and solvents were used without further purification except as indicated below. THF and diethyl ether were distilled over Na/benzophenone prior to use. Ozone was generated using Fisher Ozone Generator 500. Thin layer chromatography (TLC) was conducted on Silica Gel 60 F_{254} TLC purchased from Merck. Column chromatography was performed using Merck silica gel (70-230 mesh). NMR spectra were recorded on Bruker AV 200, Bruker DRX 500 or Bruker Avance III 600 spectrometers. ^{1}H, ^{13}C and ^{31}P chemical shifts are reported relative to the residual proton resonance in the deuterated solvents or referred to an 85% aqueous solution of H_3PO_4, respectively. All chemical shifts (δ) are given in ppm and the coupling constants (J) in Hz. HRMS were recorded on Finnigan MAT 95 apparatus. Optical rotations were measured using a Perkin-Elmer MC 241 photopolarimeter. Melting and boiling points are uncorrected.

ECD Spectra Recording: ECD spectra were recorded on a CD6 dichrograph (Jobin-Yvon, Longjumeau, France) at room temperature using cells with 0.1 mm path length, 2 nm bandwidth, and 1-2 s integration time. Each spectrum was smoothed with a 24-point algorithm (included in the manufacturer's software, version 2.2.1) after averaging at least three scans. Spectra of (-)-**5** and (+)-**5** were recorded in methanol at concentration of 17.6 mM and 17.56 mM, respectively.

X-Ray Crystal Structure Determination: The crystal data were recorded on an Oxford Xcalibur Onyx Nova single-crystal diffractometer with Cu Kα radiation (λ = 1.5418 Å). To obtain the high resolution data with a good redundancy the 16 runs under different theta and kappa angles were collected. Data collection, cell refinement and data reduction were performed using the *CrysAlis PRO* program (Oxford Diffraction). The structure was solved by direct methods (*OLEX2*)[29] and refined using full-matrix least-squares difference Fourier techniques *SHELX97*[30]. The carbon hydrogens were set geometrically and refined as riding, the hydrogen atom connected with nitrogen was found on the difference Fourier map and refined with geometrical restrains. The anisotropic thermal parameters were applied for all the non-hydrogen atoms and isotropic for hydrogens, equal to 1.2 of the thermal parameter of their parental atoms. The absolute configuration was assigned based on Flack parameters.

Computational Details: The preliminary conformational search was carried out on an arbitrarily chosen enantiomer (*R,R*)-**5** using HyperChem[16] and the MM+ molecular mechanics force field. All DFT and TD-DFT calculations were performed using the ultrafine ("99,590") Lebedev grid and tight convergence criteria of the Gaussian 09[19] program. For all conformers **5a-d** optimized at the B3LYP/6-311++G(2d,2p) level in methanol and dichloromethane (IEFPCM solvent model) more accurate IEFPCM B2PLYP-D/aug-cc-pVTZ single-point energy calculations were performed to obtain a reliable Boltzmann distribution. Calculations of chiroptical properties was carried out with the four density functionals (B3LYP, CAM-B3LYP, M062X, ωB97XD) in conjunction with the 6-311++G(2d,2p) basis set. The theoretical specific rotation values and ECD spectra were obtained as averages weighted on the Boltzmann population of conformers **5a-d**.

Dimethyl *meso*-tartrate (7): A mixture of *meso*-tartaric acid (**6**) (315.0 g, 2.1 mol), methanol (100 mL), benzene (1000 mL) and *p*-toluenesulfonic acid monohydrate (1.5 g, 7.88 mmol) was refluxed for 20 h. The water formed was distilled off as an azeotrope with benzene and methanol which was successively added (8 x 50 mL). Then, methanol (200 mL) was added and the solution was cooled to room temperature. Anhydrous potassium carbonate (3 g) was added and the mixture was stirred for 15 minutes. The solution was filtered and the solvents were evaporated to afford **7** (305.5 g, 88%) as a colorless solid. mp 113-114 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.57 (s, 2 H, C*H*), 3.80 (s, 6 H, CH_3), 3.37 (s, 2 H, O*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.36 (*C*OOCH$_3$), 72.91 (*C*H), 52.92 (OCH$_3$). $C_6H_{10}O_6$ (178.14): calcd. C 40.45, H 5.66; found C 40.32, H 5.71.

Dimethyl *O,O*-isopropylidenetartrate (8): A mixture of dimethyl *meso*-tartrate (**7**) (20.0 g, 0.112 mol), 2,2-dimethoxypropane (25.5 g, 0.244 mol), dry methanol (9 mL) and *p*-toluenesulfonic acid monohydrate (0.18 g, 1 mmol) was heated at 70 °C under an argon atmosphere for 1 h. The dark red solution was cooled to room temperature and dry cyclohexane (45 mL) was added. Methanol and acetone were removed under gentle reflux (c.a. 37 mL). Next, 2,2-dimethoxypropane (5.1 g, 0.049 mol) and dry cyclohexane (10 mL) were added and the solution was refluxed for 2 h. After cooling down to room temperature anhydrous potassium carbonate (1 g) was added. The solution was filtered and the crude product was purified by distillation under reduced pressure (78 °C, 0.1 mmHg) to give **8** (21.1 g, 86%) as a colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.84 (s, 2 H, C*H*), 3.75 (s, 6 H, OCH_3), 1.65 (s, 3 H, C-CH_3), 1.41 (s, 3 H, C-CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.60 (*C*OOCH$_3$), 113.08 (O-*C*-O), 76.29 (*C*H), 52.51 (OCH$_3$), 26.59 (*C*H$_3$C), 25.75 (*C*H$_3$C). HRMS (EI) calcd. for $C_8H_{11}O_6$ [M - CH_3]$^+$ 203.0556, found 203.0554. $C_9H_{14}O_6$ (218.20): calcd. C 49.54, H 6.47; found C 49.68, H 6.55.

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4,5-Dihydroxy-3-[(dimethoxyphosphoryl)methyl]cyclopent-2-enone acetonide (9): To a stirred solution of dimethyl methanephosphonate (15.3 g, 123.7 mmol) in THF (400 mL) at -78 °C *n*-BuLi (49.9 mL, 2.37 M in hexane, 118 mmol) was added. Stirring was continued for 0.5 h and dimethyl *O,O*-isopropylidenetartrate (**8**) (6.0 g, 27.5 mmol) in THF (20 mL) was added. After 1 h the cooling bath was removed, and the mixture was allowed to warm to room temperature. Then, THF was evaporated under reduced pressure, water (200 mL) was added and the resulting solution was stirred for 18 h. The mixture was neutralized with an aqueous solution of 5% hydrochloric acid and extracted with $CHCl_3$ (4 x 150 mL). The organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated, and the crude product was purified by column chromatography (petroleum ether/acetone 3:1) to yield **9** (5.9 g, 42%) as a colorless oil. ^{31}P NMR (243 MHz, $CDCl_3$): δ 24.72. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.10 (d, J_{PH} = 4.3, 1 H, C(O)-C*H*=C), 5.23 (dd, J_{HH} = 5.4, J_{PH} = 3.0, 1 H, C(O)-CH-C*H*-O), 4.48 (d, J_{HH} = 5.5, 1H, C(O)-C*H*-O), 3.79 (d, J_{PH} = 11.2, 3 H, OCH_3), 3.80 (d, J_{PH} = 11.1, 3 H, OCH_3), 3.15-3.00 (m, 2 H, CH_2), 1.40 (s, 3 H, CH_3C), 1.37 (s, 3 H, CH_3C). ^{13}C NMR (151 MHz, $CDCl_3$): δ 201.29 (d, J_{PC} = 2.9, *C*=O), 166.89 (d, J_{PC} = 10.2, C(O)-CH=*C*), 132.16 (d, J_{PC} = 9.1, C(O)-*C*H=C), 115.44 (s, O-*C*-O), 80.05 (d, J_{PC} = 4.0, C(O)-CH-*C*H-O), 77.55 (s, C(O)-*C*H-O), 53.19 (d, J_{PC} = 6.7, *C*H_3O), 52.99 (d, J_{PC} = 6.6, *C*H_3O), 27.62 (d, J_{PC} = 137.4, *C*H_2-P), 27.30 (s, *C*H_3C), 26.17 (s, *C*H_3C). HRMS (EI) calcd. for $C_{10}H_{14}O_6P$ [M - CH_3]$^+$ 261.0528, found 261.0528. $C_{11}H_{14}O_6P$ (276.22): calcd. C 47.83, H 6.20; found C 48.02, H 6.19.

Synthesis of diastereoisomers 10a and 10b: Phosphonate **9** (1.5 g, 5.43 mmol) and lithium perchlorate (0.628 g, 5.89 mmol) were dissolved in THF (5 mL) and cooled to 0 °C. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU, 0.9 g, 5.89 mmol) was added and the mixture was stirred for 15 min. (*R*)-glyceraldehyde acetonide (0.893 g, 6.86 mmol) in THF (1.5 mL) was added and the resulting solution was stirred at 0-5 °C for 3 h. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography (petroleum ether: diethyl ether – 1.3:1) affording **10a** (0.61 g, 40%) and **10b** (0.58 g, 38%) as yellowish oils. **10a** (less polar)**:** $[\alpha]_D^{22}$ +124 (*c* 1.6 in CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.75 (d, *J* = 15.8, 1 H, C(O)-CH=C-C*H*=CH), 6.56 (dd, *J* = 15.8, *J* = 6.1, 1 H, C(O)-CH=C-CH=CH), 6.00 (s, 1 H, C(O)-C*H*), 5.32 (d, *J* = 5.7, 1 H, C(O)-C*H*-O), 4.71 (q, *J* = 6.4, 1 H, CH_2-C*H*-CH), 4.52 (d, *J* = 5.7, 1 H, C(O)-CH-C*H*-O), 4.21 (dd, *J* = 8.2, *J* = 6.6, 1 H, CH_AH$_X$), 3.72 (t, *J* = 7.7, 1 H, CH$_A$*H*$_X$), 1.47 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 202.26 (*C*=O), 167.13 (C(O)-CH=*C*), 140.08 (C(O)-CH=C-CH=*C*H), 129.65 (C(O)-*C*H), 125.55 (C(O)-CH=C-*C*H=CH), 115.21 (C(O)-CH-O-*C*(CH$_3$)$_2$-O), 110.13 (CH$_2$-O-*C*(CH$_3$)$_2$-O), 77.89 (C(O)-CH-*C*H-O), 77.53 (C(O)-*C*H-O) , 75.93 (CH$_2$-*C*H-O), 69.03 (O-*C*H$_2$), 27.29 (*C*H$_3$), 26.53 (*C*H$_3$), 26.08 (*C*H$_3$), 25.68 (*C*H$_3$). $C_{15}H_{20}O_5$ (280.32): calcd. C 64.27, H 7.19; found C 64.05, H 7.29. **10b:** $[\alpha]_D^{22}$ - 58,5 (*c* 1.7 in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 (d, *J* = 15.9, 1 H, C(O)-CH=C-C*H*=CH), 6.60 (dd, *J* = 15.8, *J* = 5.7, 1 H, C(O)-CH=C-CH=C*H*), 6.01 (s, 1 H, O=C-C*H*=C, C(O)-C*H*), 5.31 (d, *J* = 5.7, 1 H, O-C*H*-C=O), 4.72 (q, *J* = 6.5, 1 H, CH$_2$-C*H*-CH), 4.52 (d, *J* = 5.7, 1 H, C(O)-CH-C*H*-O), 4.21 (dd, *J* = 8.1, *J* = 6.5, 1 H, CH_AH$_X$-O), 3.71 (t, *J* = 7.8, 1 H, CH$_A$*H*$_X$-O), 1.49 (s, 3 H, CH_3), 1.43 (s, 6 H, CH_3), 1.37 (s, 3 H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.27 (*C*=O), 167.26 (C(O)-CH=*C*), 140.11 (C(O)-CH=C-CH=*C*H), 129.55 (C(O)-*C*H), 125.09 (C(O)-CH=C-*C*H=CH), 115.27 (C(O)-CH-O-*C*(CH$_3$)$_2$-O), 110.13 (CH$_2$-O-*C*(CH$_3$)$_2$-O), 77.90, 77.63, 75.86 (CH$_2$-*C*H-O), 69.12 (*C*H$_2$O), 27.34 (*C*H$_3$), 26.53 (*C*H$_3$), 26.16 (*C*H$_3$), 25.76 (*C*H$_3$). $C_{15}H_{20}O_5$ (280.32): calcd. C 64.27, H 7.19; found C 64.03, H 7.14.

(*S*,*S*)-(+)-4,5-Dihydroxy-3-(formyl)cyclopent-2-enone acetonide ((*S*,*S*)-5): A solution of dienone **10b** (0.148 g, 0.528 mmol) in anhydrous methanol (15 mL) was cooled to -78 °C and ozone (0.025 g, 0.528mmol) stream was passed through a reaction mixture. Dimethyl sulfide (0.109 g, 1.71 mmol) was added, the cooling bath was removed and the solution was allowed to warm to room temperature. After 2 h the solvent was removed *in vacuo* and the crude product was purified by column chromatography (petroleum ether: acetone – 20:3.5) to yield (*S*,*S*)-**5** (69 mg, 72%) as a light yellow oil. $[\alpha]_D^{22}$ +21.5 (*c* 1.1 in CH_2Cl_2). $[\alpha]_D^{22}$ +8,8 (*c* 1 in MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.23 (s, 1 H, C*H*O), 6.75 (s, 1 H, C=C*H*), 5.49 (d, *J* = 5.6, 1 H, O-C*H*-C=O), 4.61 (d, *J* = 5.6, 1 H, O-C*H*-C-CHO), 1.43 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.34 (*C*O), 189.13 (*C*HO), 162.36 (*C*-CHO), 140.03(C=*C*H), 116.37((CH$_3$)$_2$*C*), 77.80 (O-*C*H-C-CHO) , 75.26 (O-*C*H-C=O), 27.05 (*C*H$_3$), 25.61 (*C*H$_3$). HRMS (EI) calcd. for $C_9H_{10}O_4$ 182.0579, found 182.0576.

(*R*,*R*)-(-)-4,5-Dihydroxy-3-(formyl)cyclopent-2-enone acetonide ((*R*,*R*)-5): According to the procedure described above, **10a** (0.124 g, 0.442 mmol) was transformed into aldehyde (*R*,*R*)-**5** (0.061 g, 76%). Pale yellow oil. $[\alpha]_D^{23}$ -20.8 (*c* 1 in CH_2Cl_2). $[\alpha]_D^{23}$ -8,5 (*c* 1.7 in MeOH). HRMS (EI) calcd. for $C_9H_{10}O_4$ 182.0579, found 182.0577.

(*R*,*R*)-(-)-4,5-Dihydroxy-3-(hydroxymethyl)cyclopent-2-enone acetonide (11): To a stirred suspension of sodium borohydride (0.301 g, 7.9 mmol) in dry benzene (40 mL) acetic acid (1.551 g, 0.026 mol) in dry benzene (5 mL) was slowly added. The mixture was refluxed for 0.5 h and transferred to a solution of aldehyde (*R*,*R*)-**5** (0.181 g, 0.994 mmol) in dry benzene (2 mL). After 5 min of gentle heating the reaction mixture was cooled down to room temperature and filtered through a silica gel pad. The solvent was evaporated and a crude mixture was purified by column chromatography (petroleum ether : acetone - 2:1) to give **11** (0.141 g, 82%) as a colorless solid. mp 63-64 °C. $[\alpha]_D^{25}$ -22.9 (*c* 1 in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.15 (s, 1 H, C=C*H*), 5.11 (d, *J* = 5.0, 1 H, O-C*H*-C=O), 4.68 (d, *J* = 18.5, 1 H, C*H*$_2$OH), 4.52 (d, *J* = 18.5, 1 H, C*H*$_2$OH), 4.49 (d, *J* = 5.0, 1 H, O-C*H*-C-CH$_2$), 2.63 (s, 1 H, O*H*), 1.38 (s, 6 H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.97 (*C*O), 176.74 (C=*C*-CH$_2$), 127.46 (C=*C*H), 115.59 ((CH$_3$)$_2$*C*), 77.89 (O-*C*H-C-CH$_2$), 77.79 (O-*C*H-C=O), 60.94 (*C*H$_2$), 27.28 (*C*H$_3$), 26.01 (*C*H$_3$). HRMS (EI) calcd. for $C_9H_{12}O_4$ 184.0736, found 184.0729. $C_9H_{12}O_4$ (184.19): calcd. C 58.69, H 6.57; found C 58.73, H 6.61.

(*S*,*S*)-(-)-4,5-Dihydroxy-3-[(phenylhydrazyl)methyl]cyclopent-2-enone acetonide (12): To a stirred suspension of phenylhydrazine hydrochloride (0.087 g, 0.605 mmol) in ethanol (2 mL) was added sodium acetate (0.116 g, 1.414 mmol) in water (0.5 mL). To a clear, pale yellow solution was added aldehyde (*S*,*S*)-**5** (0.092 g, 0.504 mmol) in ethanol (1 mL), and the reaction mixture was stirred for 0.5 h. Then, the solvents were evaporated, water (5 mL) was added, and the mixture was

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extracted with $CHCl_3$ (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated, and a mixture was purified by flash chromatography (chloroform:ethyl acetate – 100:1) to afford hydrazone (*S,S*)-**12** (52 mg, 38%) as a reddish-orange solid and dihydrazone **13** (64 mg, 35%) as a yellowish-orange solid. The suitable for X-ray diffraction analysis single crystal of **12** was obtained by its slow crystallization from ethanol. **12** (more polar): mp 187-189 °C. $[\alpha]_D^{23}$ -23.2 (*c* 0.9 in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (s, 1 H, N*H*), 7.68 (s, 1 H, C*H*=N), 7.32 (t, *J* = 7.9, 2 H, C_{Ar}-*H*), 7.17 (d, *J* = 7.7, 2 H, C_{Ar}-*H*), 7.00 (t, *J* = 7.4, 1 H, C_{Ar}-*H*), 6.08 (s, 1 H, C=C*H*), 5.63 (d, *J* = 5.7, 1 H, O-C*H*-C=O), 4.57 (d, *J* = 5.7, 1 H, O-C*H*-C-CH=N), 1.49 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.61 (*C*=O), 165.59 (*C*-CH=N), 142.43 (NH-C_{Ar}), 130.38 (*C*H=N), 129.42 (C_{Ar}-H), 126.96 (C=*C*H), 122.52 (C_{Ar}-H), 114.88 ((CH_3)$_2$*C*), 113.93 (C_{Ar}-H), 78.03 (O-*C*H-C), 76.91 (O-*C*H-C=O), 27.44 (*C*H$_3$), 26.17 (*C*H$_3$). HRMS (EI) calcd. for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1164. **13**: mp 201-202 °C. $[\alpha]_D^{23}$ +697.6 (c 0,6 in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1 H, N*H*-Ph), 7.82 (s, 1 H, N*H*-Ph), 7.56 (s, 1 H, C*H*=N), 7.28-7.23 (m, 4 H, C_{Ar}-*H*), 7.09 (d, *J* = 7.7, 2 H, C_{Ar}-*H*), 7.07 (d, *J* = 7.7, 2 H, C_{Ar}-*H*), 6.87 (t, *J* = 7.3, 2 H, C_{Ar}-*H*), 6.37 (s, 1 H, C=C*H*), 5.61 (d, *J* = 6.2, 1 H, O-C*H*-C=O), 5.20 (d, *J* = 6.2, 1 H, O-C*H*-C-CH=N), 1.51 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.06 (N=*C*), 145.21 (NH-C_{Ar}), 144.46 (NH-C_{Ar}), 143.67 (C_{Ar}-H), 132.98 (*C*H=N), 130,04 (C=*C*H), 129.24 (C_{Ar}-H), 129.22 (C_{Ar}-H), 120.73 (C_{Ar}-H), 120.39 (C_{Ar}-H), 114.06 ((CH_3)$_2$*C*), 113.09 (C_{Ar}-H), 113.00 (C_{Ar}-H), 80.03 (O-*C*H-C=N), 75.22 (O-*C*H-C-CH=N), 27.55 (*C*H$_3$C), 27.40 (*C*H$_3$C). HRMS (EI) calcd. for $C_{21}H_{22}N_4O_2$ 362.1743, found 362.1742.

Crystal data of 12: orthorhombic, $C_{15}H_{16}N_2O_3$, space group $P2_12_12_1$, a =5.6153(1) Å, b = 14.7472(3) Å, c = 16.9257(4) Å, V = 1401.71(5) Å^3, Z = 4, Dcalcd = 1.290 g/cm^3, μ = 0.747 mm^{-1}, and F(000) = 576. Crystal size: 0.34 × 0.23 × 0.18 mm. Independent reflections: 2722 [Rint = 0.0881]. The final indices were R1 = 0.0566, wR2 = 0.1588 for 2432 reflections with I > 2σ(I) and R1 = 0.0615, wR2 = 0.1745 for all reflections. The asymmetric unit contains one molecule of **12**. The Flack parameter is -0.3(3) for **12**, and 1.2(3) for the reverse model in *SHELX97*. Crystallographic data of (-)-**12** have been deposited with the Cambridge Crystallographic Data Centre. CCDC-1011113 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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