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Enantiospecific Synthesis and Chiroptical Properties of Bicyclic Enones

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The enantiospecific synthesis of several bicyclic enones starting from enantiomerically pure (+)-(1*S*,5*S*)-bicyclo[3.3.1]-nonane-2,6-dione (**1**) was accomplished. The target enones **7**–**9** were obtained in high yield and purity by using a catalytic amount of benzeneselenic anhydride. (+)-(1*S*,5*R*)-bicyclo[3.3.1]nonane-2,3,6-trione was obtained from diketone **1** by α-hydroxylation involving the use of iodine under basic conditions. The reaction included a ring closure/reopening sequence via oxatricyclo[4.3.1.0^{3,8}]decane-10-one. It was shown that the latter triketone exists in enone/enol form. Chiroptical properties of the enantiomerically pure compounds were studied, and the sign of the Cotton effect was related to the absolute configuration of the enones. The positive Cotton effect in the bisignate CD curve is accounted for by the nonplanarity of the chromophore in enones (1*S*,5*R*)-**4** and (1*S*,5*S*)-**8**. The circular dichroism spectra provided evidence for interchromophoric interaction in dichromophoric bis(enone) **9**.

Introduction

A wide variety of natural products contain embedded in their frameworks bicyclic motifs possessing the enone functionality. This fragment is also essential in precursors for the synthesis of natural or biologically important compounds.[1] The majority of these compounds are chiral, as they have substituents at appropriate positions. Thus the question of establishing the absolute configuration of such molecules arises when isolating minor quantities of natural compounds and developing a range of methodologies for their assembly.

Bicyclo[3.3.1]nonenones have attracted attention as a synthetic goal, because polyfunctionalized derivatives of this skeleton are key intermediates in natural product synthesis.[2] We focused on the synthesis of chiral bicyclononane enones and the study of their chiroptical properties by circular dichroism (CD) spectroscopy.

CD spectroscopy today is a well-established technique in studies of stereochemistry.[3] Various chromophores have been investigated both experimentally and theoretically over the past decade in order to correlate the sign of the Cotton effects (CEs) to various sector and/or helicity rules. The enormous number of applications of electronic CD measurements led to the formulation of semiempirical rules for the correlation of the sign and magnitude of the observed CE with the absolute configuration of chiral molecules containing various chromophores.[4] The α,β-unsaturated ketone (enone) chromophore belongs to the group of chromophores that have been investigated quite extensively in recent years.[5] A number of sector and/or helicity rules have been proposed to correlate the sign of the CEs observed in the spectral region between 200 and 350 nm with the absolute configuration of α,β-enone molecules.[6] These rules are derived from the observation that the CD and UV spectra of enones are affected by substituents located close to this chromophore, which alter its electronic structure as well as spatial dimension.[7] Moreover, there is considerable interest in the chiroptical properties of molecules with several chromophores at appropriate positions and spatial arrangements in relevant molecules.

Therefore, well-designed molecules are needed for studying these phenomena in more detail. The chiral bicyclo[3.3.1]nonane and related tricyclic skeletons derived from this framework have been shown to be important structures for the study of chiroptical properties.[8] These molecules are structurally coherent and interconvertible by ring closure/reopening during chemical transformations, the appropriate chromophores could thus be introduced into a molecule by using relevant synthetic methods.[9] Enantiomerically pure compounds having this framework have been synthesized and employed as suitable models to study the effects of electronic interactions in the generation of rotational strength in electronic transitions.

In this work, we have accomplished the synthesis of several bicyclo[3.3.1]nonanes possessing an α,β-enone moiety, including a bicyclic triketone which was shown to exist in enone/enol form, from enantiomerically pure (+)-(1*S*,5*S*)-

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bicyclo[3.3.1]nonane-2,6-dione (**1**). The chiroptical properties of these molecules were studied in order to correlate the absolute configuration with the signs of the CD bands and to verify existing rules.

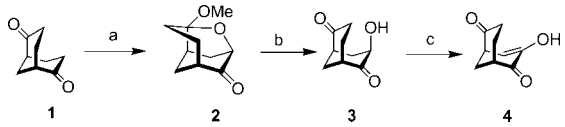
Results and Discussion

Synthesis of Bicyclo[3.3.1]nonenones

The synthesis of the enantiomerically pure target bicyclo[3.3.1]-nonane α,β-enones **4** and **7**–**9** was accomplished by using (+)-(1*S*,5*S*)-bicyclo[3.3.1]nonane-2,6-dione (**1**) as the starting compound. The kinetic resolution of racemic 2,6-dione **1** with baker's yeast reduced the (–)-(1*R*,5*R*)-enantiomer, thus enriching the mixture with (+)-(1*S*,5*S*)-**1**. A modification of the procedure reported by Hoffmann and Wiartalla[10] afforded the (+)-(1*S*,5*S*)-**1** enantiomer with >99% *ee* after repeated fermentations.

We developed a synthesis of triketone **4** by employing α-hydroxylation of the initial 2,6-diketone **1**, which involved a ring closure/reopening reaction sequence. A powerful method for the preparation of α-hydroxy carbonyl compounds from the parent carbonyl compound involves the hydroxylation of preformed enolates or enol ethers with a variety of oxidizing agents. However, the low stability of diketone **1** monoenolate makes these methods difficult to apply in our case and would necessitate the use of carbonyl protection-deprotection steps for selective monohydroxylation.

On the other hand, the α-hydroxylation of diketone **1** was successfully accomplished by following the reported procedure for the iodine-mediated α-hydroxylation of ketones and aldehydes to α-hydroxyketals under basic conditions in MeOH.[11] After treatment of (+)-**1** with iodine in basic methanol solution, tricyclic acetal **2** was formed in high yield instead of the expected α-hydroxyketone acetal (Scheme 1). This outcome can be explained by *exo*-selective iodination of the ketone in the first step and a subsequent cascade addition–cyclization reaction initiated by methoxide anion attack on the carbonyl group. This reaction can be regarded as analogous to a recently published synthesis of acetals under basic conditions.[12] The intramolecular acetal formation allowed us to obtain the monofunctionalized product without protecting the carbonyl group. The analogous ring closure/reopening reaction strategy was successfully used earlier with the bicyclo[3.3.1]nonane skeleton to effect carbonyl group transposition.[13] The tricyclic ring of **2** was readily converted to bicyclo[3.3.1]nonane by an acid-catalyzed transacetalization reaction with acetone, and subsequent Swern oxidation of the hydroxyketone **3** afforded the corresponding (+)-(1*S*,5*R*)-2,3,6-trione **4**. The predictable existence of triketone **4** in the enol form was confirmed by spectroscopic data. The intense band at ca. 3400 cm^{-1} in the IR spectrum clearly indicates O–H stretching. The signal observed at δ = 6.25 ppm in the ^1H NMR spectrum can also be readily assigned to the proton of the enol OH group, and carbon signals at δ = 150.0 and 117.0 ppm in the ^{13}C NMR spectrum confirm the presence of the unsaturated bond.



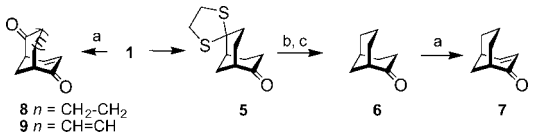
Scheme 1. Reagents and conditions: (a) I_2, KOH, MeOH, 0 °C; (b) $TsOH·H_2O$, acetone, room temp.; (c) DMSO, TFAA, TEA, CH_2Cl_2, –60 °C.

The above synthesis afforded the original dichromophoric enone/enol molecule, but related enones were required for a study of chiroptical properties. The synthesis of racemic enones **7** and **9** described in the literature involves multistep procedures. We have developed a simpler and higher-yielding synthesis of these enones.

The reported synthesis of bis(enone) **9** from diketone **1** comprises a bromination-debromination sequence; however, the purification of the product from the monoenone and brominated byproducts was very tedious because of the nonselective bromination step.[14] An acetal-protected diketone can be used for the same purpose; however, the synthesis requires many steps, and the overall yield is low.[13b] A challenge was to develop a practical, one-step synthesis of enones **7**–**9** in enantiomerically pure form. Recently, Nicolaou et al. reported unsaturation of aldehydes and ketones mediated by a stoichiometric amount of 2-iodoxybenzoic acid (IBX) in DMSO.[15] In our hands, this one-step synthesis of enones was quite successful with diketone **1**, providing bis(enone) **9** and enone **8** in 70% and 65% yield, respectively. Nevertheless, it required a large excess of expensive IBX (4–8 equiv.) and long reaction times (38–48 h) for complete conversion.

Another widely used method for introducing unsaturation in carbonyl compounds is based on selenoxide elimination.[16] The reaction between diketone (+)-**1** and phenylselenyl chloride under various conditions failed to give the diselenyl derivative in high yield. This could be explained by unfavourable steric interactions between phenylselenyl groups in positions 3 and 7 of the bicyclononane skeleton. We reasoned that introducing selenium in its higher oxidation state would ensure immediate selenoxide elimination, thus avoiding steric interactions between substituents in the 3- and 7-positions.

The Barton dehydrogenation procedure seemed very attractive and was thus subsequently examined, as benzeneselenic anhydride is generated in the reaction in situ from a catalytic amount of diphenyl diselenide by using iodoxybenzene as stoichiometric oxidant.[17] The unsaturation of diketone (+)-**1** under these conditions by using an excess of iodoxybenzene indeed afforded bis(enone) **9** in high yield (90%). The monounsaturation was achieved directly by using 2 equiv. of iodoxybenzene giving enone **8** in 60% yield. By analogy, enone **7** was synthesized in 95% yield from monoketone **6**, which was obtained by protection of one carbonyl group in diketone **1** with a slight modification of the reported procedure (Scheme 2).[18]



Scheme 2. (a) $PhIO_2$, PhSeSePh, TsOH (cat.), toluene, reflux; (b) Ra-Ni, EtOH, reflux; (c) Jones reagent, room temp.

Table 1.Specific rotation and λ_{max} for compounds **4** and **7**–**9**.

Compound	$[\alpha]_{546}$, °cm^{2}g^{-1}	CD, λ_{max}, nm ($\Delta\varepsilon$, dm^{3}mol^{-1}cm^{-1})
(+)-(1*S*,5*R*)-**4**	+350 (EtOH, *c* = 3.1, 20 °C)	314 (+0.40), 273 (–0.37)
(+)-(1*S*,5*S*)-**7**	+115 (EtOH, *c* = 0.76, 20 °C)	341 (+0.95)
(+)-(1*S*,5*S*)-**8**	+1569 (EtOH, *c* = 0.0204, 20 °C)	313 (+5.4), 254 (–2.4)
(+)-(1*S*,5*S*)-**9**	+2260 (EtOH, *c* = 0.37, 20 °C)	342 (+10.2)

CD Analysis

The synthesized compounds possess enone chromophores, and among them compounds **4**, **8** and **9** are dichromophoric. The CD spectra of enones usually have two CD bands in the range 220 to 350 nm. The third short-wavelength CD band, which is found in the 200 to 220 nm spectral region, is of very small absorption intensity and is likely to be due to a π→π* transition, though this assignment is not unequivocal.[19] The long-wavelength band is due to an n→π* transition which appears around 350 nm. The second band, which appears between 230–260 nm, is due to a π→π* transition polarized approximately along the line connecting the oxygen and the most remote carbon atom of the C=C bond.

The bands of the n→π* transition in the CD spectra of the studied enones are observed at ca. 340 nm for enone **7** and bis(enone) **9**, and at ca. 310 nm for ketoenone **8** and triketone **4** (Figure 1). The λ_{max} and specific rotation of these enones are presented in Table 1. The CD spectra of all compounds exhibited a positive Cotton effect. Enone **7**, containing the single chromophore, could be regarded as a reference compound for this transition.

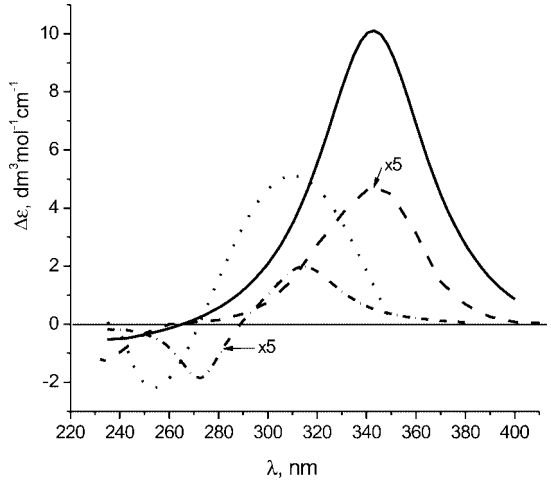


Figure 1. CD spectra of triketone (1*S*,5*R*)-**4** (–·–), ketoenone (1*S*,5*S*)-**8** (···), enone (1*S*, 5*S*)-**7** (– –), and bis(enone) (1*S*,5*S*)-**9** (—) in ethanol.

Conformational analysis by molecular mechanics and B3LYP/6-31G* calculations revealed that the cyclohexenone ring of enones **4** and **8** exists in a distorted flattened chair conformation.

The enone functionality is nonplanar, and the torsional angles were found to be 4° and 5°, respectively, in minimized structures. The sector and/or helicity rules correlating the sign of the CEs that are observed in the spectral region between 200 and 350 nm with the absolute configuration of α,β-enone molecules have to be applied with caution. Recently a study on the chiroptical properties of *cisoid* enones showed that, in general, the positive (negative) sign of the CE associated with the n→π* transition reflects the positive (negative) enone helicity.[20] The sign of the torsional angles in enones **4** and **8** correlates with the long-wavelength sign of the CE in the bisignate CD curve (Figure 1).[21] The sign of the shorter-wavelength band is opposite to that of the longer-wavelength band.

Compound **4** possesses one band in the UV region between 200 and 360 nm (Figure 3b). The CD maximum is shifted to a shorter wavelength relative to that of the UV absorption of **4**. The hypsochromic shift of the n→π* transition in triketone **4** and ketoenone **8** is associated with the effect of neighbouring substituents. The marked difference in intensity of this transition is accounted for by the electronic effects of the carbonyl group in the next six-membered ring of ketoenone **8**, and more substantially, of the hydroxy group attached directly to the enone double bond in triketone **4**.

The intensity of the CD bands of enone **4** are ten times weaker than those of ketoenone **8**. This is due to the magnitude of the dipoles, although their orientation is nearly the same in both molecules (Figure 2a). We calculated the angle between the planes containing chromophores to be ca. 60° for both compounds by the B3LYP/6-31G* method. However, the dipole moment is substantially smaller in molecule **4** because of the electronic effects of the hydroxy group at the enone double bond, which decreases the electron density. The positive mesomeric effect of the hydroxy group

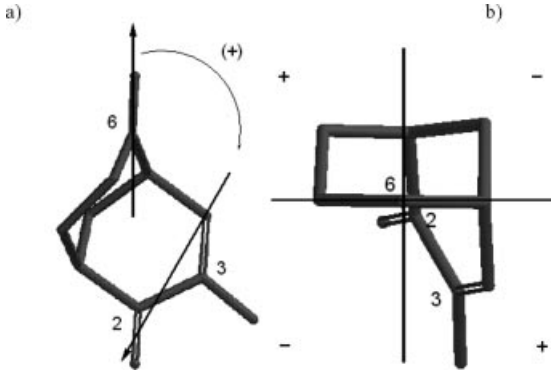


Figure 2. (a) Distorted cyclohexenone chair conformation (in front) and angle between planes containing chromophores in triketone **4**; (b) Division of the C-6 carbonyl group in triketone (+)-**4** into octants.

and the intramolecular hydrogen bonding of the latter with the enone carbonyl group (cf. the case of 1,2-cyclohexanedione)[22] considerably reduce the charge separation between the carbonyl oxygen atom and the terminal carbon atom of the enone double bond, thus affecting the value of the chromophore dipole moment in compound **4**. This conclusion is strongly supported by the ^{1}H NMR signals of the corresponding ethylene protons in molecules **4** and **8**, 6.17 ppm and 7.12 ppm, respectively, which demonstrates the strong deshielding of the enone double bond in **8**. Accordingly, the bathochromic shift of the shorter-wavelength band in the CD spectrum of compound **4** relative to that of ketoenone **8** (Figure 1) is accounted for by the resulting dipole as well.

We next examined the applicability of the octant rule for the correlation of the sign of the observed Cotton effect with the absolute configuration of enones containing a carbonyl chromophore in the next six-membered ring. The band of an n→π* transition is ascribed to the carbonyl chromophore. In order to apply the octant rule, the triketone molecule **4** was divided into octants. The cyclohexanone ring with the carbonyl group is in a conformationally defined chair form in this molecule, and dividing it into octants is straightforward. Figure 2b shows the division of the minimized structure (1*S*,5*R*)-**4** into octants. The hydroxy group of the enone functional group, the C-2 carbon atom of the carbonyl group in the cyclohexenone ring and the C-8 carbon atom of the next six-membered ring are located in positive octants, while the enone carbonyl group is close to the nodal surfaces. Thus the major input in the top left and the bottom right positive octants leads to a positive CE, which is in accordance with the experimental data. An analogous unambiguous conclusion can be reached by dividing the carbonyl groups of ketoenone (1*S*,5*S*)-**8** into octants.

The intensities of the n→π* transition bands of compounds **4** and **7**–**9** are significantly different. For bis(enone) **9** the absorption of this transition is enhanced by an order of magnitude in comparison to enone **7**. This originates from a transannular orbital interaction of chromophores in dichromophoric bis(enone) **9**.

The transannular interaction of enone chromophores in this compound has been demonstrated earlier by photoelectron spectroscopy[18] in comparison to enone **7** as well as by their chemical reactivity leading to intramolecular ring closure.[23] In addition, the molecular structure of **9** has a slightly nonplanar arrangement of chromophores (calculated torsional angle 2°), and this helicity contributes to the intensity of the CD absorption. In bis(enone) **9** the intensity of the n→π* transition band is significantly higher as a result of the orientation of dipoles which are nearly parallel (Figure 3a). Compound **9** possesses two bands in the UV region, maxima occurring at 350 and 230 nm (Figure 3b). The CD maximum corresponds to the absorption maximum in the UV spectrum. Interestingly, the polarimetric rotation angle of the bis(enone) **9** is remarkably large.

The second band between 230 and 260 nm arises from a π→π* transition polarized approximately along the line

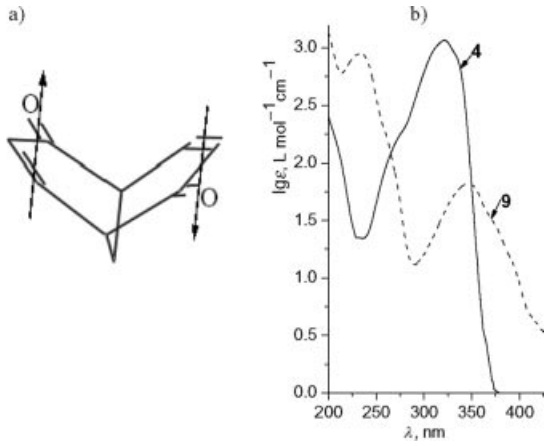


Figure 3. (a) The orientation of dipoles in the minimized structure of bis(enone) **9**; (b) UV spectra of triketone **4** (−) and bis(enone) **9** (---).

connecting the oxygen atom and the most remote carbon atom of the C–C double bond, and is observed for enones **4** and **8** (Figure 1). Interestingly, though the exciton chirality rule is not applicable to enones **4** and **8**, a positive CD couplet could be linked to a positive angle between planes containing transition dipoles (Figure 2a) and vice-versa,[24] thus relating positive chirality with the positive first and negative second Cotton effects.

Conclusions

The synthesis of bicyclo[3.3.1]nonenones in enantiomerically pure form afforded a series of novel derivatives of this framework in high yield. A CD study of the molecules possessing the α,β-enone chromophore was performed. The positive Cotton effect in the bisignate CD curve is accounted for by the nonplanarity of the enone chromophore in enones (1*S*,5*R*)-**4** and (1*S*,5*S*)-**8**. The octant rule was applied to both enones. The hypsochromic shift of the transition in ketoenone **8** and triketone **4** is associated with the effect of neighbouring substituents. The marked difference in intensity of this transition for ketoenone **8** is accounted for by the electronic effects of the carbonyl group in the next six-membered ring. The more substantial changes observed in triketone **4** are attributed to the hydroxy group attached directly to the enone double bond and the orientation of planes where transition dipoles are located. The significant increase in the n→π* transition intensity in bis(enone) **9** relative to enone **7** is attributed to a transannular orbital interaction of chromophores in the bis(enone).

Experimental Section

General: Melting points were determined with a Gallencamp melting apparatus in capillary tubes and are not corrected. IR spectra were recorded in KBr pellets with a Perkin–Elmer Spectrum BX spectrometer. NMR spectra were recorded with a Varian Inova 300 spectrometer in $CDCl_3$. Chemical shifts are given in parts per mil-

lion relative to TMS by using the residual solvent peak as internal standard.

Mass spectra were run with a Hewlett–Packard 6980 instrument having the mass selective detector 5975 inert XL and a Supelcowax capillary column (30 m × 0.25 μm). Chiral GC analysis was carried out with a Perkin–Elmer Autosystem instrument by using a Beta-Dex 120 fused silica capillary column.

Thin-layer chromatography was carried out on Kieselgel 60 F254 (Merck) sheets coated with silica gel. Column chromatography was performed on silica gel (0.040–0.063 mm, Merck). The CD spectra were recorded with a Jasco Model J-500A spectropolarimeter at 20 °C in 0.1-cm or 1.0-cm cells using spectral grade ethanol (99.5%). The CD spectra were measured in millidegrees and normalized into the units $dm^3 mol^{-1} cm^{-1}$ for $\Delta\varepsilon_{max}$ and nm for λ. Optical rotations were measured with a Polamat-A (Carl Zeiss) instrument at 546 nm. $[a]_{546}^{20}$ values are given in 10^{-1} °$cm^2 g^{-1}$, and concentrations are given in units of g/100 cm^3.

The lowest energy conformational search was performed by using the molecular mechanics MMFF94 force field, and the energy of conformers was refined with ab initio B3LYP/6-31G* calculations using the program package SPARTAN '06 for Windows Version 1.0.2.[25]

(+)-(1*S*,5*S*)-Bicyclo[3.3.1]nonane-2,6-dione (1): Baker's yeast (65 g) and saccharose (100 g) were added to a preheated (36–38 °C) suspension of racemic bicyclo[3.3.1]nonane-2,6-dione **2** (20.2 g, 0.13 mol) in water (500 mL). The mixture was kept at the same temperature for 6 d without stirring with daily addition of saccharose (50 g). After this time, the yeast was centrifuged off, and the resulting mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to dryness. The residue was subjected to a second fermentation for an additional 6 d, the products were then separated as above and purified by flash chromatography ($CHCl_3$) to yield 6 g (59%) of (+)-(1*S*,5*S*)-diketone **1**, *ee* >99% (GC).

(+)-(1*R*,3*R*,6*S*,8*R*)-3-Methoxy-2-oxatricyclo[4.3.1.0^{3,8}]decane-10-one (2): A solution of **1** (52 mg, 0.34 mmol) in methanol (5 mL) was cooled to 0 °C, and solid KOH (0.19 g, 3.4 mmol) was added. After stirring the mixture for 5–10 min, a solution of I_2 (0.17 g, 0.68 mmol) in MeOH (3 mL) was added dropwise over 30 min. The reaction mixture was stirred for 1 h and then quenched by addition of conc. $Na_2S_2O_3$ and HCl (2 M). The aqueous phase was extracted with CH_2Cl_2, which was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography ($CHCl_3$) to afford 50 mg (81%) of **2** as a yellowish oil: $[a]_{546}^{20}$ = +81 (*c* 2.0, EtOH). ^{1}H NMR: δ = 4.33 (d, 1 H), 3.35 (s, 3 H, OMe), 1.73–2.65 (m, 10 H) ppm. ^{13}C NMR: δ = 211.2 (C-10), 109.7 (C-3), 83.3 (C-1), 49.7, 44.8, 40.5, 38.3, 31.4, 26.6, 24.0 ppm. IR: $\tilde{\nu}$ = 1727 (C=O), 1045 (O–C–O) cm^{-1}. MS: *m*/*z* (%) = 182 (10) $[M]^+$, 151 (100) $[M - CH_3O]^+$, 123 (20) $[M - CH_3O - CO]^+$.

(–)-(1*S*,3*R*,5*R*)-3-Hydroxybicyclo[3.3.1]nonane-2,6-dione (3): To a solution of **2** (50 mg, 0.27 mmol) in acetone (10 mL) was added TsOH·H_2O (60 mg, 0.32 mmol).The reaction mixture was stirred under argon for 2 h at room temperature, then quenched with solid $NaHCO_3$, filtered and concentrated to dryness. The residue was purified by column chromatography (chloroform/acetone, 9:1) to afford 40 mg (90%) of **3** as a yellowish oil: $[a]_{546}^{20}$ = –22 (*c* 1.35, EtOH). ^{1}H NMR: δ = 4.35 (dd, *J* = 6.3, 1.4 Hz, 1 H), 3.94 (br. s, 1 H, OH), 2.97 (m, 1 H), 2.80–1.68 (m, 9 H) ppm. ^{13}C NMR: δ = 211.5 (C-6), 211.3 (C-2), 77.1 (C-3), 48.7 (C-5), 42.4 (C-1), 36.7, 35.9, 32.7, 24.9 ppm. IR: $\tilde{\nu}$ = 3400 (OH), 1705 (6-C=O), 1714 (2-C=O) cm^{-1}.

(+)-(1*S*,5*R*)-Bicyclo[3.3.1]nonane-2,3,6-trione (4): TFAA (0.14 mL, 1.0 mmol) was added dropwise to a stirred solution of dimethyl sulfoxide (0.10 mL, 1.4 mmol) in dry CH_2Cl_2 (5 mL) under argon at –60 °C. The resulting colourless, clear solution was stirred at –60 °C for 10 min, and a solution of **3** (40 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was then added dropwise. The mixture was stirred at –60 °C for 1.5 h and triethylamine (0.28 mL, 2.0 mmol) was added dropwise. The light yellow reaction mixture was stirred for 1.5 h at –60 °C, warmed to 5 °C, poured into water and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$) to afford 30 mg (80%) of **4** as a yellowish waxy solid: $[a]_{546}^{20}$ = +350 ° (*c* 3.1, EtOH). CD: λ_{max} ($\Delta\varepsilon$/$dm^3 mol^{-1} cm^{-1}$) = 314 (+0.40), 273 (–0.37) nm. UV: λ_{max} (lgε) = 275 (sh 2.26), 321 (3.06) nm. ^{1}H NMR: δ = 6.25 (s, 1 H, enol-OH), 6.17 (dd, *J* = 7.2, 1.5 Hz, 1 H), 3.25–3,22 (m, 1 H), 2.96–2.89 (m, 2 H), 2.70 (ddd, *J* = 13.2, 6.3, 3.1 Hz, 1 H), 2.35–2.08 (m, 5 H) ppm. ^{13}C NMR: δ = 207.8 (C-6), 197.1 (C-2), 150.0 (C-4), 117.0 (C-3), 47.6 (C-5), 40.4 (C-1), 35.4 (C-9), 33.8 (C-7), 28.8 (C-8) ppm. IR: $\tilde{\nu}$ = 3407 (OH), 1712 (6-C=O), 1676 (2-C=O), 1650 (C=C) cm^{-1}. MS of the acetyl derivative: *m*/*z* (%) = 166 (100) $[M - CH_3CO]^+$, 148 (1), 138 (30), 111 (100).

(+)-(1*S*,5*S*)-Bicyclo[3.3.1]nonane-2-one (6): The Lightner procedure[18] of monothioketalization was followed with 0.30 g of diketone **1** to afford 0.38 g (83%) of **5**.

Freshly prepared Ra-Ni (4.2 g) was added to a solution of monothioketal **5** (0.38 g, 1.7 mmol) in EtOH (25 mL). The mixture was heated under reflux for 0.5 h, cooled to room temperature and filtered through Celite (**CAUTION**: Do not let the pyrophoric Raney nickel get dry. The filter cake is washed several times with ethanol and then destroyed with dilute hydrochloric acid). The filtrate was concentrated under reduced pressure. The crude mixture, consisting of monoketone **6** and the corresponding alcohol, was dissolved in acetone (30 mL), and Jones reagent was added dropwise at room temperature until the orange colour remained. After stirring for an additional 30 min at room temperature, 2-propanol was added to destroy excess Jones reagent. The mixture was filtered through a short plug of silica gel and concentrated under reduced pressure. The remaining solid was purified by flash chromatography (petroleum ether/ethyl acetate, 15:1) to afford 0.17 g (74%) of **6** as a white waxy solid. ^{1}H NMR: δ = 1.48–2.61 (m, 14 H) ppm. ^{13}C NMR: δ = 20.0 (C-7), 26.1 (C-6), 27.4 (C-4), 29.7 (C-8), 31.9 (C-5), 32.5 (C-9), 38.9 (C-3), 45.0 (C-1), 216.9 (C-2) ppm.

(+)-(1*S*,5*S*)-Bicyclo[3.3.1]non-3-en-2-one (7): A mixture of ketone **6** (60 mg, 0.43 mmol), $PhIO_2$ (0.28 g, 1.18 mmol), PhSeSePh (14 mg, 0.045 mmol) and a catalytic amount of TsOH in dry toluene (10 mL) was heated under reflux for 3 h. The mixture was cooled to room temperature, filtered, washed with saturated $NaHCO_3$ and brine and dried with $MgSO_4$. After concentration under reduced pressure, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 7:1) to afford 56 mg (95%) of **7** as a white waxy solid: $[a]_{546}^{20}$ = +115 (*c* 0.76, EtOH). CD: λ_{max} ($\Delta\varepsilon$/$dm^3 mol^{-1} cm^{-1}$) = 341 (+0.95) nm. ^{1}H NMR: δ = 1.50–1.70 (m, 6 H), 1.60–1.80 (m, 1 H), 2.17–2.26 (m, 1 H), 2.45–2.54 (m, 1 H), 2.57–2.68 (m, 1 H), 6.17–6.21 (d, *J* = 9.9 Hz, 1 H), 6.92–6.98 (ddd, *J* = 9.9, 6.5, 1.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 203.3 (C-2), 152.8 (C-4), 132.0 (C-3), 42.9, 34.2, 30.9, 28.2, 25.2, 17.5 ppm.

(+)-(1*S*,5*S*)-Bicyclo[3.3.1]non-3-ene-2,6-dione (8): A mixture of diketone **1** (0.1 g, 0.66 mmol), $PhIO_2$ (0.34 g, 1.31 mmol), PhSeSePh (5 mg, 0.00165 mmol) and a catalytic amount of TsOH in dry toluene (10 mL) was heated under reflux for 3–4 h. The mixture was

cooled to room temperature, filtered, washed with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). After concentration under reduced pressure, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 7:1) to afford 58 mg (60%) of **9** as a white solid, m.p. 80 °C (transition at 70 °C): $[\alpha]_{546}^{20}$ = +1569 (*c* 0.204, EtOH). CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) = 313 (+5.4), 254 (–2.4) nm. ^{1}H NMR: δ = 7.12–7.05 (ddd, *J* = 9.9, 6.8, 2.1 Hz, 1 H), 6.32 (d, *J* = 9.9 Hz, 1 H), 3.40–3.30 (ddd, *J* = 6.8, *J* = 3.1 Hz, 1 H), 2.39–2.77 (m, 2 H), 2.71–2.63 (ddd, *J* = 13.2, 3.1 Hz, 1 H), 2.37–2.11 (m, 4 H) ppm. ^{13}C NMR: δ = 207 (C-6), 200.8 (C-2), 148.6 (C-4), 133.1 (C-3), 49.9 (C-5), 41.9 (C-1), 35.2 (C-7), 34.3 (C-9), 29.3 (C-8) ppm. IR: $\tilde{\nu}$ = 3048 (=C–H), 1711 (C=O), 1673 (C=O), 1608 (C=C) cm^{-1}. $C_9H_{10}O_2$ (150.17): calcd. C 71.79, H 6.75; found C 71.98, H 6.71.

(+)-(1*S*,5*S*)-Bicyclo[3.3.1]nona-3,7-diene-2,6-dione (9): A mixture of diketone **1** (50 mg, 0.33 mmol), $PhIO_2$ (0.39 g, 1.64 mmol), PhSeSePh (5 mg, 0.0016 mmol) and a catalytic amount of TsOH in dry toluene (10 mL) was heated under reflux for 3 h. The mixture was cooled to room temperature, filtered, washed with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). After concentration under reduced pressure the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to afford 44 mg (90%) of **9** as a yellowish solid, m.p. 105 °C (transition at 98 °C), ref.[13] m.p. 81–84 °C (for the racemate). $[\alpha]_{546}^{20}$ = +2260 (*c* 0.37, EtOH). CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) = 342 (+10.2) nm. UV: λ_{max} (lg ε) = 233 (2.95), 260 (sh 2.23), 346 (1.82) nm. ^{1}H NMR: δ = 7.03–6.98 (dd, *J* = 9.9, 6.75 Hz, 2 H), 5.88 (d, *J* = 9.9 Hz, 2 H), 3.36–3.32 (ddd, *J* = 6.75, 3 Hz, 2 H), 2.77 (t, *J* = 3 Hz, 2 H) ppm. ^{13}C NMR: δ = 193.8 (C-2, C-6), 146.7 (C-4, C-8), 126.4 (C-3, C-7), 45.9 (C-1, C-5), 34.6 (C9) ppm. IR: $\tilde{\nu}$ = 3040 (=C–H), 1676 (C=O), 1607 (C=C) cm^{-1}.

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