Synthesis of optically pure 3-(1n.pi.\textsuperscript{•})-(1S,6R)-bicyclo[4.4.0]decane-3,8-dione, a molecule which is chiral in the excited state only
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Synthesis of Optically Pure
3-(1n*r*)-(1S,6R)-Bicyclo[4.4.0]decane-3,8-dione, a Molecule Which is Chiral in the Excited State Only


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Abstract: Low-temperature photooxygenation of (1S,6R,8S)-8-hydroxybicyclo[4.4.0]decan-3-one (6), prepared in 10 steps from 2,6-dimethoxynaphthalene (5), yields a mixture of four isomeric 1,2-dioxetanes (8a-d) with ee > 98%. Upon thermal decomposition, these 1,2-dioxetanes are all precursors for 3-(1n*r*)-(1S,6R)-bicyclo[4.4.0]decane-3,8-dione (1*), an optically active diketone in its locally excited 1n*r* state. The optical activity of this molecule is evidenced by the nonvanishing circular polarization in the chemiluminescence of 8a-d. The degree of polarization (g) at 420 nm equals (1.5 ± 0.3) × 10^{-3}, a value which is similar to that of the regular fluorescence of optically active (1S,6R,8S)-8-hydroxybicyclo[4.4.0]decane-3-one (6). This similarity implies the absence of substantial racemization in the excited state, whence one concludes that the rate constant for intramolecular 1n*r* energy transfer in 1* is ≤ 10^{9} s^{-1}. The chiroptical results show that localization of excitation energy at the carbonyl at the 3-position of 1* can be achieved by the synthetic route applied, yielding enantiomerically pure 3-(1n*r*)-(1S,6R)-bicyclo[4.4.0]decane-3,8-dione (1*), an optically active molecule whose chirality is due solely to the presence of localized electronic excitation energy.

Introduction

Molecules in which chirality is due solely to small differences between the discriminating groups have always fascinated stereochemists. Striking examples are chiral tetraalkylmethanes and fullerenes and molecules which are chiral due to isotopic substitution. One of the smallest deviations from achirality is found in systems in which the chirality is due solely to the presence of localized electronic excitation. This can arise in centrosymmetric or meso compounds with two remote enantiomeric chromophores, as shown in Figure 1 for 1, 1*, and related structures 2-4. In the ground state these diketones (R,S) are achiral, while in the excited state two enantiomeric forms (R*,S and S*,R*) are present, providing the excitation energy is localized.

The excited state can be formed by the irradiation of R,S with circularly polarized light. The difference in concentration of R*,S and S*,R* is then governed by the dissymmetry factor in absorption (g = ΔOD/OD), to which the resultant enantiomeric excess (ee) equals g/2. The optical activity of the excited-state species is evidenced by a nonvanishing degree of circular polarization of luminescence (CPL). Such excited-state chirality has experimentally been demonstrated in 1,7-diketone 2*.

In the case of the 1,5-diketone 3*, a zero CPL has been found which is ascribed to a fast racemization in the singlet excited state (lifetime τ<sub>r</sub> due to 1n*r* energy transfer. In the absence of energy transfer, the circular polarization, as measured in these experiments, equals g/2. Energy transfer reduces the ee, and thus the CPL signal, by a factor of (2k_{TR} + 1)^{-1}.

Since in photoselection experiments the ee is governed by g (which, for the n→π* band of ketones, will give an ee of at the most ~10%), a major improvement of selectivity has been foreseen by using chemixcitation to produce R*,S, potentially with an ee of 100%. According to this approach, singlet-excited-state

Figure 1. Meso diketones that contain two carbonyl moieties of opposite chirality. All structures are achiral in the ground state but chiral in the excited state, provided excitation energy is localized at one carbonyl group.

[Diagram of molecular structures]

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2 Leiden University.

0002-7863/94/1516-5129$04.50/0 © 1994 American Chemical Society
Scheme 1

2,4-adamantanedione ($4^*$) has been prepared by the thermolysis of the corresponding optically active 1,2-dioxetanes. These four-membered rings are known to dissociate into two carbonyl fragments accompanied with chemiluminescence. Upon thermal decomposition, one of the carbonyls is produced in its (singlet or triplet) excited state by a nonadiabatic process (chemiexcitation). The radiative transition from the singlet excited state to the ground state following chemiexcitation accounts then for the chemiluminescence. Despite the fact that the excitation is directed chemically to one of the carbonyls only, a vanishingly small circular polarization in chemiluminescence of the 1,2-dioxetanes has been detected. A complete loss of optical activity occurred within the lifetime of 2 ns of $4^*$; due to the close proximity of both carbonyls in $4$, energy transfer is extremely fast.

In this paper we describe the synthesis and the circular polarization of the chemiluminescence of optically pure 3-(1$^a$)- (1S,6R)-bicyclo[4.4.0]decane-3,8-dione (1$^a$), a diketone in which both carbonyls are more remote. The synthetic route is based on our previous work for the chemiexcitation of $4$. Via thermal decomposition of the optically active 1,2-dioxetanes 8a-d, enantiomerically pure $1^a$ is obtained together with ground-state methyl formate (Scheme 1). 

Results and Discussion

Synthesis. The optically active precursor of $1^a$ is synthesized starting from 2,6-dimethoxynaphthalene (5), as outlined in Scheme 2. In six steps and an overall yield of 15%, 5 has been transformed into optically pure (ee $> 98\%$) (1S,6R,8S)-8-hydroxybicyclo[4.4.0]decane-3,8-dione (6) using in the last step the HLADH-reduction of 1 as pioneered by Jones et al. The conversion of 6 into (1S,6R)-3-(E,Z)-methoxymethylenebicyclo[4.4.0]decane-8-one (7) is achieved in a four-step procedure. Protection of the alcohol with an acetyl group followed by the Wittig reaction with 1.1 equiv of (methoxymethylene)phosphorane will be transformed into optically pure (ee $= 92\%$) 1,2-dioxetanes 8a-d, for model compounds. 

The thermolysis of the optically active 1,2-dioxetanes during thermolysis in diglyme at 80 °C. The circular anisotropy $g_0$ is detected at optimal wavelength $\lambda = 430$ nm. In the inset, the decay of chemiluminescence at 80 °C is shown.

The four isomeric (1S,6R)-1,2-dioxetanes 8a-d are formed in approximately equal amounts by the $1^2O_2$ attack of

(7) To obtain as much consistency as possible, numbers in IUPAC nomenclature for the bicyclo compounds are assigned as in $1^a$, in which priority is given to the carbonyl which is in the 1$^a$ state.


Figure 2. $^1H$ NMR analysis of the decomposition at 60 °C in toluene-$d_6$ of the four isomeric 1,2-dioxetanes 8a-d by monitoring the intensities of the characteristic protons of the four-membered ring. The upper lines represent the methoxy protons, whereas the lower lines represent the olefinic protons. It should be noted that two proton chemical shifts do coincide (line in the middle).

Figure 3. Emission spectrum of the optically active 1,2-dioxetanes during thermolysis in diglyme at 80 °C. The circular anisotropy $g_0$ is detected at optimal wavelength $\lambda = 430$ nm. In the inset, the decay of chemiluminescence at 80 °C is shown.

Figure 4. CD data for 1 and 2, showing a negative residual CD at 295 nm. The CD data for the optically active 1,2-dioxetanes are presented as a function of time. The decay of chemiluminescence at 80 °C is shown.

both enol ethers at both sides of the molecule, as is concluded from NMR spectra.

Thermolysis and Chiroptical Properties. In order to investigate the rates of decomposition of the four individual isomeric 1,2-dioxetanes, we have monitored the thermolysis of 8a-d with $^1H$ NMR spectroscopy. First-order rate constants of $k_1 = 9.6 \times 10^4$ s$^{-1}$ and $k_2 = 6.5 \times 10^4$ s$^{-1}$ for two pairs of 1,2-dioxetanes are estimated from kinetic studies at 60 °C in toluene-$d_6$ (Figure 2).

The unequal rate constants give rise to a nonexponential decay of the chemiluminescence intensity (Figure 3) as well as the circular dichroism signal at 295 nm (Figure 4). The $CD$ data have been taken on a dilute sample of (1S,6R)-8a-d in bis(2-methoxyethyl) ether (diglyme). After thermolysis at 80 °C, only a trace amount of optically active impurity (probably a trace of one product) gives rise to a small negative residual $CD$ of 8a-d at $\lambda_{max} = 295$ nm.

The thermolysis of 8a-d in diglyme at 80 °C is accompanied with chemiluminescent emission, the spectrum of which (Figure 3) closely resembles the fluorescence spectra of 1 and 6. As expected, $1^a$-π* species formed in the decomposition reaction are effectively quenched under the experimental conditions used.
Collecting the emission at 430 nm, we observe\(^1\) for 8a–d a
dissymmetry factor of chemiluminescence \(g_e = -(1.5 \pm 0.3) \times 10^{-3}\). The effect cannot be due to a CD artifact, because in the
original sample (i.e., before thermolysis) we observe a zero CD
signal at 430 nm.

Thermolysis of the optically active dioxetanes 8a–d furnishes
initially the excited diketone in its locally excited \(1^*\) state. The optical activity of this molecule is evidenced by the nonvanishing
circular polarization in the chemiluminescence. In the absence of racemization, the circular anisotropy in emission of the hydroxy
diketone \(1^*\) is similar to that of the chemiluminescent
hydroxy diketone \(1^*\). The fact that the dissymmetry factor in the
excited state in high enantiomeric excess, equally to the
optical activity of this molecule is evidenced by the nonvanishing
value of \(g_e\) at the same wavelength) implies that racemization due to energy transfer is
relatively small: \(k_{ET} \leq 10^8\) s\(^{-1}\), calculated with \(\tau_f = 2\) ns.\(^2\) This result for the 1,6-diketone 1 is in line with the available data on
the energy transfer for ketones 2–4. The distance between both carbonyl carbons in 1, \(R_{ab}\) as found from X-ray analysis,\(^3\)
amounts to 5.25 \(\AA\) (Figure 5).\(^4\) For the 1,7-diketone 2, energy transfer is relatively slow \((k_{ET} \leq 10^7\) s\(^{-1}\)) for an estimated \(R_{ab}\) of
6.95 \(\AA\) PM3 calculation\(^5\)), while for the 1,5-diketone 3 and the
1,3-diketone 4, having estimated \(R_{ab}\) values of 4.47 and 2.50 \(\AA\), respectively, the energy transfer is fast \((k_{ET} \approx 10^{10}\) s\(^{-1}\)).

The chiroptical results indicate that the value of \(g_{01m}\) for \(1^*\)
is determined only by optical activity due to the presence of a locally
excited state in a high enantiomeric excess, equally to the >98% ee and de of the hydroxy diketone 6.

### Concluding Remarks

In conclusion, the results presented in this paper show the
successful synthesis and detection of CPL of enantiomerically

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\(^{1}(11)\) For a description of the instrument, see: Rexwinkel, R. B.; Schakel, P.; Maskers, S. C. J.; Dekkers, H. P. J. M. Appl. Spectrosc. 1993, 47, 731.

\(^{2}\) Turro, N. J. Modern Molecular Photochemistry; Benjamin/Cummings: California, 1978.

\(^{3}\) Crystals were obtained from a solution of 1 in tetrahydrofuran by slow evaporation. Details of crystal structure analysis are available on request and are to be published. X-ray analysis was performed by A. Schouten and J. Kroon, Bijvoet Center for Biomolecular Research, Padualaan 8, 3584 CH Utrecht, The Netherlands.

\(^{4}\) The preliminary refinement \(R_{ab} = 5.248\) \(\AA\) in the X-ray analysis of
1, which crystallizes in the monoclinic space group \(P2_1/n\) (No. 14), confirms the structure. Crystal data: \(a = 5.2490(1)\, \text{Å}, b = 10.6801(3)\, \text{Å}, \text{and} c = 7.9484(2)\, \text{Å}, \beta = 96.30(2)\, \text{°}, Z = 2.

polarized fundamental beam. Following these lines, we have observed already SHG in centrosymmetric crystals of a racemic mixture,\(^{19}\) design of other systems with localized distortion of centrosymmetry by excitation is in progress.

**Experimental Section**

**General Techniques.** Melting points were determined on a Unicam THMS heating apparatus. Infrared (FT-IR) spectra were recorded on a Perkin-Elmer 1605 FT-IR spectrophotometer. CD spectra were recorded on a Jasco spectropolarimeter J600. UV spectra were recorded on a Perkin-Elmer UV/vis spectrophotometer Lambda 3B. Elemental analyses were performed on a Perkin-Elmer 240 apparatus. Optical rotations were measured on an Optical Activity Ltd. AAI0 polarimeter. Proton, deuterium, and carbon-13 NMR spectra were recorded on a Bruker AM400 spectrometer using tetramethylsilane (TMS, 0 ppm) as internal standard. GC analyses were performed on a Kipp Analytica 8200 instrument with FID detection (25 m × 0.25 mm i.d., column type WCOT fused silica, stationary phase CP SIL-5 CB, film thickness 0.25 μm). Chemiluminescence spectra were recorded on a Spex Fluorolog II emission spectrometer.

**Circular Polarization of Luminescence.** Measurements of the circular polarization of the luminescence (CPL) and chemiluminescence were performed at Leiden University on a custom-built spectrometer operating in the photon counting mode. A detailed description of the instrument has been published.\(^{11}\) The measurements were performed on ~0.05 M solutions in spectrometric grade CD3CN for 6 and bis-(2-methoxyethyl) ether for 1.\(^{1}\) The bandwidth of the emission channel was chosen to be 30 nm.

**Materials.** Column chromatography was performed using Merck silica gel 60, 230–400 mesh as the stationary phase. Analytical thin-layer chromatography was conducted on precoated TLC plates, silica gel 60, F-254 layer thickness 0.25 mm, using UV (254 nm) and iodine detection. Preparations of dioanestes were carried out in a 700-mL reaction vessel. All solvents and commercial reagents were reagent grade. Diethyl ether was dried over CaH\(_2\) and stored over sodium wire. Dichloromethane was distilled from CaH\(_2\), pyridine from KOH pellets. Oxygen was dried over several traps, one containing concentrated sulfuric acid and two containing 30% H\(_2\)SO\(_4\). Preparations of dioxetanes were carried out in a 700-mL reaction vessel. Water (250 mL) was added to the mixture; 1.4 g (5.3 mmol) of 6 was added in small portions. To a solution of 6 (1.5 g, 9.52 mmol) in anhydrous THF, 3.8 mL of 2.5 M n-butyllithium (9.52 mmol), was added rapidly to the dark red solution. After the mixture was stirred for another 2 h at room temperature, 10 mL of a saturated ammonium chloride solution was added. The reaction was quenched with water (250 mL) and washed with water (3 × 20 mL). The product was purified by column chromatography on silica gel (hexane/ethyl acetate, 92:8 elution) to give 1.25 g of (1S,6R,8S)-3-((E,Z)-methoxymethylene)bicyclo[4.4.0]dec-8-yl acetate (8).\(^{4}\) The compound was recrystallized from ethyl acetate, mp (after crystallisation from ethyl acetate) 77–79 °C (lit.\(^{9b}\) mp 77–79 °C). A solution of 8 (2.0 g, 9.52 mmol) in anhydrous THF (250 mL) was added to 3.8 mL of 2.5 M n-butyllithium (9.52 mmol), and the mixture was stirred for 2 h at room temperature. After 8 days maximum reaction time, the mixture was poured into 100 mL of dry diethyl ether. The dark brownish mixture was decanted. The collected ether layers were filtered over MgSO\(_4\) and rotary evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 92:8 elution) to give 1.25 g of (1S,6R,8S)-3-((E,Z)-methoxymethylene)bicyclo[4.4.0]dec-8-yl acetate (8).

**Analytical Data**

<table>
<thead>
<tr>
<th>Compound</th>
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<th>13C NMR (CDCl(_3))</th>
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<td>8</td>
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<td>138.86 (d, CI~), 138.76 (d, C~~), 117.24 (s, C3), 117.17 (s, C3), 69.99 (d, s, C3), 59.11 (s, C3), 2839 (-0-CH3, C-H stretch), 1687 (C=C stretch)</td>
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<td>8</td>
<td>6 4.20 (1H, br, Hs), 3.55 (6H, d, OCH3), 2.85–2.95 (1H, dd, Hz), 2.75–2.85 (1H, m, Hz)</td>
<td>139.01 (d, C1), 138.89 (d, C1), 117.24 (s, C3), 117.17 (s, C3), 69.99 (d, s, C3), 59.11 (s, C3), 2839 (-0-CH3, C-H stretch), 1687 (C=C stretch)</td>
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<td>6 1.0–2.4 (26H, m)</td>
<td>138.86 (d, CI~), 138.76 (d, C~~), 117.24 (s, C3), 117.17 (s, C3), 69.99 (d, s, C3), 59.11 (s, C3), 2839 (-0-CH3, C-H stretch), 1687 (C=C stretch)</td>
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**Compound 7** (700 mg, 3.5 mmol) and sensitizer methylene dioxetane (8) were added to the mixture; 1.4 g (5.3 mmol) of 6 was added in small portions. To a solution of 6 in anhydrous THF (250 mL), was added to 3.8 mL of 2.5 M n-butyllithium (9.52 mmol), and the mixture was stirred for another 2 h at room temperature. After 8 days maximum reaction time, the mixture was poured into 100 mL of dry diethyl ether. The dark brownish mixture was decanted. The collected ether layers were filtered over MgSO\(_4\) and rotary evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 92:8 elution) to give 1.25 g of (1S,6R,8S)-3-((E,Z)-methoxymethylene)bicyclo[4.4.0]dec-8-yl acetate (8).

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blue (10 mg) were dissolved in 600 mL of dichloromethane and photooxygenated for 1 h at -80 °C. The irradiations were carried out with a Hanau TQ78 500-W medium-pressure mercury lamp through quartz, using a sheet of brownish polyimide (Kapton 500H, du Pont de Nemours) wrapped around the lamp compartment as short wavelength filter (cutoff 550 nm). Cooling of the lamp and primary cooling of the reaction vessel were accomplished by means of a closed circuit filled with methanol from a cryostat. The temperature of -80 °C was reached by extra external cooling baths of ethanol and liquid nitrogen. Column chromatography at -30 °C using dichloromethane/ethyl acetate, 60:40 elution, resulted in removal of the sensitizer, yielding a mixture of dioxetanes and allylic hydroperoxides in a ratio of 60:40. Pure dioxetane was obtained by concentrating 700 mL of the crude dioxetane solution to ~250 mL and subsequent column chromatography at -30 °C using dichloromethane/acetone, 96:4 as eluent. The relatively low-boiling solvents, dichloromethane, acetone, and ethyl acetate, were removed in the presence of an appropriate high-boiling solvent, bis(2-methoxyethyl) ether (diglyme) or toluene-δ4. CPL measurements were carried out using a concentrated dioxetane solution (a solution of 550 mL of 1,2-dioxetane was concentrated into 20 mL of diglyme). For recording 1H and 13C NMR spectra, an aliquot of the dioxetane solution was concentrated at 0 °C. During evaporation, cold CDCl3 or toluene-δ4 was added in such a way that the 1,2-dioxetane was always present in solution. The 1,2-dioxetane was stored as a solution in dichloromethane below -20 °C. 1H NMR (toluene-δ4, T = 25 °C): δ 5.25, 5.22, 5.20, 5.18 (4 × 1H, s, H11), 3.28, 3.26 (2 × 3H, s, OCH3), 3.16 (6H, s, OCH2), 2.7−0.7 (envelope). 13C NMR (CDCl3, T = -20 °C): δ 211.28, 211.08 (s, 2 × C8), 109.60, 109.44 (d, 2 × C11), 89.54, 89.51, 89.43, 89.34 (s, 4 × C3), 56.04, 55.99, 55.69, 55.62 (q, 4 × OCH3), 47.98, 47.25, 46.91, 46.74 (t, 4 × C10), 41.16, 40.92, 40.67, 40.52, 40.16, 40.92, 40.67, 40.06, 39.37, 38.02, 37.11, 35.70, 35.38, 34.94, 33.79, 33.52, 32.64, 32.44, 32.28, 30.23, 29.2, 28.04, 27.7, 26.27.