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was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were dried and concentrated in vacuo. The crude product was distilled at 10 mmHg to give 65.2 g (92%) of iminodiacetic acid diethyl ester as a colorless liquid: ^1H NMR (250 MHz, $CDCl_3$) δ 4.18 (q, J = 7.1 Hz, 4 H), 3.45 (s, 4 H), 1.92 (s, 1 H), 1.27 (t, J = 7.1 Hz, 6 H); IR ($CHCl_3$, cm^{-1}) 3320, 3010, 2990, 1740, 1230, 1190, 1090; HRMS, $C_8H_{15}NO_4$ requires 189.1002, observed 189.1001.

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Registry No. 1, 113430-84-5; 1 (dibromide), 113430-93-6; **2**, 113430-85-6; **3**, 65907-71-3; **4**, 113430-86-7; **5**, 113430-87-8; **6**, 113430-88-9; 6 (diol), 113430-92-5; **7**, 113430-89-0; **8**, 113430-90-3; **9**, 113430-91-4; Ca^{2+}, 14127-61-8; Mg^{2+}, 22537-22-0; $Br(CH_2)_2OH$, 540-51-2; $HN(CH_2CO_2Et)_2$, 6290-05-7; $HN(CH_2CO_2H)_2$, 142-73-4; o-nitroveratraldehyde, 20357-25-9.

Synthesis and Chiroptical Properties of (1*S*)-[2,5-$^2H_2$]Bicyclo[2.2.2]octa-2,5,7-triene (2,5-Dideuteriobarrelene)

David A. Lightner,*[1a] Leo A. Paquette,*[1b] Paochai Chayangkoon,[1a] Ho-Shen Lin,[1b] and
John R. Peterson[1b,c]

Department of Chemistry, University of Nevada—Reno, Reno, Nevada 89557, and Department of Chemistry,
The Ohio State University, Columbus, Ohio 43210

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(1*S*)-[2,5-$^2H_2$]Bicyclo[2.2.2]octa-2,5,7-triene (1) (2,5-dideuteriobarrelene) was prepared from (1*R*)-bicyclo-[2.2.2]oct-7-ene-2,5-dione by $LiAlD_4$ reduction followed by pyrolysis of the bis[*O*-*p*-tolyl thionocarbonate] ester of the resulting dideuterio diol. The circular dichroism of 1 ($\Delta\epsilon_{max}^{246} = +0.008$, $\Delta\epsilon_{max}^{215} \simeq -0.07$) is the first example obtained from a deuteriated longicyclically conjugated triene, whose chirality is due only to isotopic substitution.

Introduction

Barrelene[2] (**2**, bicyclo[2.2.2]octa-2,5,7-triene), with its D_{3h} symmetry and longicyclically homoconjugated system of three carbon–carbon double bonds, has long interested chemists, especially from the standpoint of its chemical reactivity and its molecular and electronic structure. Strong nonbonded repulsions of the π centers lead to stretching of the C–C single bonds[3], and hence considerable intramolecular strain, as detected (i) by the largest (−37.57 kcal/mol) heat of hydrogenation[4] ever observed for saturation of a C=C bond, (ii) by a low barrier for thermal decomposition into acetylene and benzene, and (iii) by facile photochemical rearrangement to semibullvalene.[6] Dominant *through-space* interaction among the π orbitals leads to splitting of the three π levels into a totally antibonding π HOMO (a_2') and two lower energy, more bonding e′ (π) combinations, as detected by photoelectron spectroscopy: IP = 8.23, 9.65, and 10.02 eV.[7] Here again, intramolecular strain is evident by the comparatively low IP value (8.23 eV) vs that of, e.g., bicyclo[2.2.2]octa-2,5-diene (8.87 eV). Further evidence for unusual π-orbital interaction may be found in the near-UV spectrum of barrelene, for which two transitions have been detected [ϵ_{max}^{239} 320, ϵ_{max}^{208} 1120 (ethanol[2])]; cf. norbornadiene [ϵ_{sh}^{230} 200, ϵ_{sh}^{220} 870, $\epsilon_{sh}^{213}\epsilon cp$ 1550, ϵ_{sh}^{202} 2400].[8] Attempts to explain the electronic structure and spectrum from theory include the initial π-electron PPP study in 1960[9] to more recent[10] SCF–CI MO treatments.

In view of our previously reported success in detecting hidden electronic transitions in norbornadiene by circular dichroism (CD) spectroscopy[8], we initiated a similar study of transannular orbital interactions in barrelene. Our chiral, target molecule was dideuteriobarrelene (1), whose synthesis and CD spectrum we describe in this work.

Synthesis and Stereochemistry

Previous synthetic work on the synthesis of barrelene (**2**) provided two short, independent methods for the preparation of dideuteriobarrelene (**1**).[11,12] For both methods, the key chiral intermediate was bicyclo[2.2.2]-oct-7-ene-2,5-dione (**3a** + **3b**), which was available in three steps from hydroquinone and maleic anhydride: (1) Diels–Alder cycloaddition to afford (±)-5,7-dioxobicyclol[2,2,2]octane-2,3-dicarboxylic anhydride in low yield (15%), (2) hydrolysis to the corresponding dicarboxylic acid, and (3) lead tetraacetate or electrolytic double decarboxylation. The low yield in step 1 is not a major disadvantage because the starting materials are relatively

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[1] (a) University of Nevada—Reno. (b) The Ohio State University. (c) National Institutes of Health Postdoctoral Fellow.

[2] (a) Zimmerman, H. E.; Paufler, R. M. *J. Am. Chem. Soc.* **1960**, *82*, 1514–1515. (b) Zimmerman, H. E.; Grunewald, G. L.; Paufler, R. M.; Sherwin, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 2330–2338.

[3] Yamamato, S.; Nakata, M.; Fukuyama, T.; Kuchitsu, K.; Hasselmann, D.; Ermer, O. *J. Phys. Chem.* **1982**, *86*, 529–533.

[4] Turner, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 3586–3587.

[5] Samson, E. Staatsarbeit, Rühr-Universität, Böchum, 1979. Reported in ref 3. See also ref 2b.

[6] Zimmerman, H. E.; Binkley, R. W.; Givens, R. S.; Grunewald, G. L.; Sherwin M. A. *J. Am. Chem. Soc.* **1969**, *91*, 3316–3323.

[7] Haselbach, E.; Heilbronner, E.; Schröder, G. *Helv. Chim. Acta* **1971**, *54*, 153–162.

[8] (a) Lightner, D. A.; Gawronski, J. K.; Bouman, T. D. *J. Am. Chem. Soc.* **1980**, *102*, 5749–5754. (b) Paquette, L. A.; Doecke, C. W.; Kearney, F. R.; Drake, A. F.; Mason, S. F. *Ibid.* **1980**, *102*, 7228–7233.

[9] Wilcox, C. F.; Winstein, S.; McMillan, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5450–5454.

[10] Meyer, A. Y.; Pasternak, R. *Tetrahedron* **1977**, *33*, 3239–3241.

[11] Jefford, C. W.; Wallace, T. W.; Acar, M. *J. Org. Chem.* **1977**, *42*, 1654–1655.

[12] Weitemeyer, C.; Preuss, T.; de Meijere, A. *Chem. Ber.* **1985**, *118*, 3993–4005.

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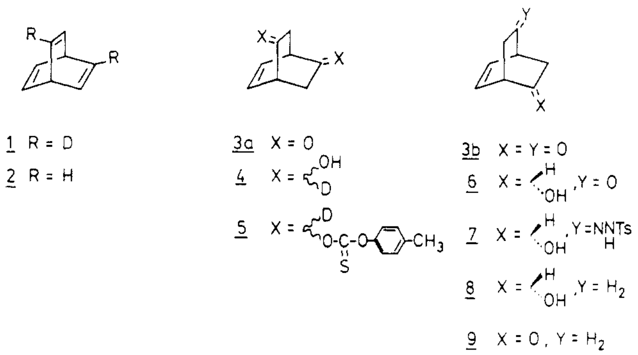

inexpensive, the reaction scale is large, and the desired product is easily isolated. The variable, low yields[5] (15–30%) in the lead tetraacetate oxidation step (step 3) were not improved by modification. On the other hand, electrolytic decarboxylation[3] was a cleaner reaction and gave a somewhat higher yield (40%) of (**3a** + **3b**).

Resolution of these compounds was realized in two ways. In the first, (±)-5,7-dioxobicyclo[2.2.2]octane-2,3-dicarboxylic acid was converted to its brucine salt.[13] Following selective crystallization of one diastereomer, a protocol found to be quite serviceable on a large scale, the purified amine salt was acidified and directly electrolyzed. The $[\alpha]^{22.5}_D$ of the enedione obtained in this manner, -1137° (*c* 0.52, CCl_4), showed it to be the 1*S* enantiomer **3b** of good optical quality (90.4% enantiomeric excess (ee)).

The second approach consisted in enantioselective reduction of the racemic enedione (**3a** + **3b**) using baker's yeast. The 1*S* enantiomer **3b** is reduced preferentially, affording hydroxy ketone **6**, which was easily separated from unreacted **3a** by column chromatography. In a short reaction period, the reduced product **6** is obtained nearly optically pure, and the unreacted enedione has a lesser ee. In a long reduction period, the unreacted enedione is optically pure **3a**, and the hydroxy ketone has a lesser ee.

Enedione **3** has been converted to **2** by several different procedures.[12] In one, the bis(*p*-toluenesulfonylhydrazone) undergoes a double Shapiro reaction through the action of CH_3Li.[11,12] This procedure was our initial choice, especially since we had successfully prepared both 2-deuterionorbornadiene and 2-deuteriobicyclo[2.2.2]octa-2,5-diene using the tosylhydrazone elimination reaction with D_2O quenching.[8] However, the reaction proved to disappointing and capricious, giving the desired product (in very low yield) once in six attempts. We abandoned this procedure, as others have done,[12] in favor of a modified Tschugaeff reaction on the diol of **3**. Thus, reduction of **3a** or **3b** with $LiAlD_4$ introduced two deuterium atoms and gave a diastereomeric mixture of diols (e.g., **4**), which was converted to the corresponding bis(*O*-*p*-tolyl thionocarbonate) esters (e.g., **5**).[12] Pyrolysis of **5** gave **1** in low, but reproducible yields. The desired dideuteriobarrelene (**1**), 99% d_2, was isolated by preparative gas chromatography (4% yield) in <99.9% purity. The enantiomer of **5** behaved identically, of course. Any d_0 or d_1 barrelene formed in the reaction sequence is achiral.

Assignment of absolute configuration to **3a** (and hence **3b**)[13,14] was achieved by using the (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA] Mosher ester[15] of its yeast reduction product **6** with $[\alpha]_D$ -328° (*c* 0.1, $CHCl_3$). In the ^{19}F NMR spectrum, the more intense upfield signal at 72.14 ppm (upfield from $CFCl_3$) moved faster downfield upon the addition of $Eu(fod)_3$ than the less intense signal at 71.88 ppm (upfield from $CFCl_3$), as predicted[15] for the absolute configuration assigned. The absolute configuration of **3a** could also be deduced by conversion of **6** to **3b** and, via tosylhydrazone **7**, to alcohol **8** of known absolute stereochemistry.[15,16] Hydroxy ketone **6** was easily converted to **3b** or to **7** in good yield by reaction with *p*-toluenesulfonylhydrazine in CH_2Cl_2 containing a catalytic amount of HCO_2H. Reduction of **7** with Dibal gave (-)-**8**, which could be converted to enone (-)-**9**. Since the absolute configuration of **8** and **9** had been reported previously,[15] the absolute configurations of **7** and **6** and hence **3b**, are as shown. These transformations also clarify the stereochemistry of the ketone enzymic reduction step afforded by yeast: the newly developed OH group is syn to the endocyclic C=C.

The ee of **3a**, **3b**, and **6** may be determined from the data of Hill et al.,[13] who separated completely the diethyl (*R*,*R*)-(+)-tartrate ketals of *rac*-**3** using HPLC to afford **3a** of 100% ee with $[\alpha]^{29.5}_D$ +1252° (*c* 0.0012, cyclohexane) and $[\alpha]^{29.5}_D$ +1222° (*c* 0.0063, CCl_4) and **3b** of 100% ee with $[\alpha]^{29.5}_D$ -1257° (*c* 0.0015, cyclohexane) and $[\alpha]^{29.5}_D$ -1235° (*c* 0.0057, CCl_4). Our best yeast reduction experiment gave **3** with $[\alpha]^{25}_D$ +1070° (*c* 0.028, cyclohexane) and $[\alpha]^{25}_D$ +1161 (*c* 0.134, $CHCl_3$), hence 85% ee, along with **6**, $[\alpha]^{25}_D$ -575°, which could be oxidized to **3b** with $[\alpha]^{25}_D$ -1266° (*c* 0.193, $CHCl_3$). Thus, the yeast reduction afforded **6** of 100% ee and unreacted **3a** of 85% ee. The ee assigned to **6** was confirmed as ~100% in the ^{19}F NMR spectrum of the [(+)-MTPA] Mosher ester of **6**, which in this case showed only one signal at 72.14 ppm upfield from $CFCl_3$. In the conversion of **3a** to **1** and of **6** to **8** and then **9**, care was taken to guard against enantiomeric fractionation by avoiding crystallization. All purifications were accomplished by chromatography or sublimation.[17]

The specific rotation data for compounds of the sequence **6** → **8** → **9** raise some concern about previous determinations of ee (for **8** and **9**). Goering and Towns[19] reported a value of $[\alpha]^{25}_D$ +48.3° (*c* 1, $CHCl_3$) for the enantiomer of **8** with 66 ± 2% ee, the latter as determined from isotopic dilution studies. Assuming a linear relationship between $[\alpha]$ and ee, one extrapolates to a value $[\alpha]^{25}_D$ -74° ($CHCl_3$) for 100% ee **8** and $[\alpha]^{25}_D$ -497° ($CHCl_3$) for **9**.[18] However, the current work indicates that by interrelating **6** with **3b** and using the ee determination of **3b** by Hill et al.[15] or the Mosher ester ^{19}F NMR results, one calculates a value of $[\alpha]_D$ -134° for 100% ee **8** and $[\alpha]_D$ -851° for **9**. Since the samples of years ago are no longer available, the source of the discrepancy is unclear. The new ee data do point, however, to the likelihood that the CD data for the bicyclo[2.2.2]octadienes of our earlier work[8] may be low by a factor of ~2.

Results and Discussion

Interaction of Chromophores. Interatomic distances and bond angles, measured by electron diffraction[3], clearly

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(13) Hill, R. K.; Morton, G. H.; Peterson, J. R.; Walsh, J. A.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 5528–5533.

(14) Schippers, P. H.; Dekkers, H. P. J. M. *J. Chem. Soc., Perkin Trans 1* **1982**, 1429–1433.

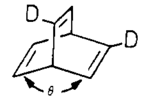
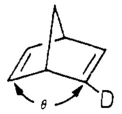
(15) The assignment of absolute configuration for **8** was also determined by LIS-NMR of its Mosher ester. Kalyanam, N.; Lightner, D. A. *Tetrahedron Lett.* **1978**, 415–418.

(16) Mislow, K.; Berger, J. G. *J. Am. Chem. Soc.* **1962**, *84*, 1956–1961. These authors reduced the enantiomer of **8** with $[\alpha]^{23}_D$ +68.2° (*c* 1.1, $CHCl_3$) to (-)-(2*R*)-bicyclo[2.2.2]octan-2-ol with $[\alpha]^{21}_D$ -28.0° (*c* 1.2, $CHCl_3$). The absolute configuration of the latter was determined by the synthesis of its enantiomer from (-)-(1*R*)-*exo*-2-(aminomethyl)norborane [Berson, J. A.; Willner, D. *J. Am. Chem. Soc.* **1962**, *84*, 675–676].

(17) The recent report of an example of spontaneous resolution by sublimation [Paquette, L. A.; Lau, C. J. *J. Org. Chem.* **1987**, *52*, 1634–1635] indicates, of course, that purification by sublimation need not adequately safeguard against enantiomeric fractionation.

(18) Goering, H. L.; Towns, D. J. *J. Am. Chem. Soc.* **1963**, *85*, 2295–2298.

Table I. Circular Dichroism and Ultraviolet Spectral Data[a,b] in *n*-Heptane

compd[e]	UV λ_{max} (ϵ)	CD λ_{max} ($\Delta\epsilon$)
	238 (125) 215[c] (185)	246 (+0.0083) 212 (−0.071)
	220 sh[d] (250)	222 (−0.05)
	230 sh[d] (200)	237 (−0.032)
	220 sh (870)	
	213 sh (1550)	216 (+0.14)
	202 sh (2400)	205 (−0.37)

[a] λ in nm, ε and Δε in cm^{-1} M^{-1}. [b] Data for norbornadiene and bicyclo[2.2.2]octa-2,5-diene from ref 8a. [c] Not maximum. [d] sh = shoulder. [e] θ is 120° in the upper and middle structures and 115° in the lower.

show the close proximity of double bonds of barrelene (**2**). The torsion angle (θ) between C=C chromophores has a value of 120°, and the C_2–C_6 distance is 2.676 Å. These data may be compared with those of norbornadiene ($\theta \simeq 115°$, C_2–C_6 = 2.42 Å) and bicyclo[2.2.2]octa-2,5-diene ($\theta \simeq 120°$, C_2–$C_6 \simeq 2.5$ Å) and provide a basis for expecting interaction between the three olefinic chromophores of **2** to lead to UV transitions more complex than those of the diene analogue or norbornadiene. Indeed, many studies have been directed toward the detection and theoretical explanation of the electronic interaction of the C=C chromophores of **2**, as summarized by Meyer and Pasternak.[10] These authors used a semiempirical SCF-CI MO treatment of compute 15 singlet–singlet transitions, including three allowed [247 nm, very weak, HOMO (a_2') → LUMO (e'') ($\pi \rightarrow$ CC* and $\pi \rightarrow$ CH*); 209 nm, f = 0.11 HOMO (a_2') e' (p → CC* and $\pi \rightarrow$ CH*); 181 nm, f = 0.86, mixed e'–e'' and a_2'–a_1'' (75%, π–π*)]. The two lower energy computed transitions match up well with the experimentally observed transitions at 239 (ε 320) and 208 nm (ε 1120). In addition, the computations provide evidence for a *through-bond* π–π interaction, in addition to *through-space* π–π interaction, with a raising of bonding π and a filling in of the π,π* gap with σ* orbitals.

Our UV data for **1** are shown in Table I and compare well with those of Zimmerman et al.,[2] with two well-defined λ_{max}. We could not detect the previously reported λ_{max} near 295 nm with an $\epsilon \simeq 2$. The UV data are distinct from those of the structurally analogous bicyclo[2.2.2]octa-2,5-diene and norbornadiene (Table I).

Symmetric and Dissymmetric Chromophores. In examining the optical activity of **1** (or the dienes of Table I), it is helpful to recall the classification of chromophores into two limiting types: (1) inherently symmetric but dissymmetrically perturbed and (2) inherently dissymmetric.[19,20] This classification has proved to be useful in isolating and predicting the principal structural components contributing to the CD of chiral molecules.[21] For example, the n–π* (+) Cotton effect (CE) of camphor is determined by the extrachromophoric perturbers, but the sign and much larger magnitude of the (−)-CE of dehydrocamphor,[22] **9**,[16,23] and **2**[13] are dominated by the dissymmetric interactions of the carbonyl and olefin groups.[20]

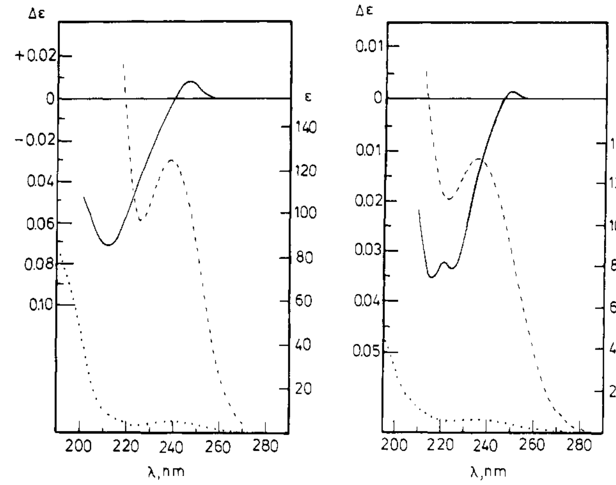


Figure 1. (Left) Circular dichroism (—) and ultraviolet (- - -) spectra of 9.2 × 10^{-3} M 1 in n-heptane at 21 °C. The UV spectrum (···) is a factor of 40 less sensitive than (- - -). (right) Circular dichroism (—) and ultraviolet (- - -) spectra of 7.3 × 10^{-3} M 1 in 2,2,2-trifluoroethanol (TFE) at 21 °C. The UV spectrum (···) is a factor of 40 less sensitive than (- - -).

The symmetrically disposed olefinic groups of **2** are sufficiently close to allow for interchromophoric interaction in a symmetric way. The resulting triene chromophore is symmetric, and the derived chiral structure **1** falls into classification 1. Thus, chiral electronic transitions (CE's) associated with those structures necessarily arise only for extrachromophoric dissymmetric perturbation by the two deuterium atoms—unless the perturbers induce molecular distortion resulting in an inherently dissymmetric diene chromophore. We believe the contributions of the latter type are relatively unimportant. The CD spectra of **1** therefore offer an additional way to detect new electronic transitions due to interaction of the olefin groups in **2**. This approach was used successfully to clarify the electronic transitions of norbornadiene[8] and 7-norbornenone,[24] both suitably substituted by deuterium. And it presents yet another interesting example of optical activity due to isotopic substitution.[25]

Circular Dichroism Data. The CD and UV spectra of **1** (Figure 1) clearly show the advantage of obtaining both sets of data whenever possible. The electronic transitions can be more clearly recognized in the CD spectra, and they provide evidence for two distinct near-UV electronic excitations in **1**. The data correlate particularly well with the UV data (Table I). The 1:1 correlations of the observed UV and CD spectral transitions parallel the case of (1S)-2-deuteriobicyclo[2.2.2]octa-2,5-diene, where only one near-UV transition is observed and is less like that of norbornadiene, where at least three and probably four transitions are seen.

Experimental Section

General. Circular dichroism (CD) spectra were recorded on a JASCO J-600A instrument. Ultraviolet (UV) spectra were

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[19] Moffitt, W.; Moscowitz, A. *J. Chem. Phys.* **1959**, *30*, 648–660.

[20] For a discussion of this classification, see: Deutsche, C. W.; Lightner, D. A.; Woody, R. W.; Moscowitz, A. *Annu. Rev. Phys. Chem.* **1969**, *20*, 407–448.

[21] See, for example: Lightner, D. A.; Jackman, D. E.; Christiansen, G. D. *Tetrahedron* Lett. **1978**, 4467–4470.

[22] Sandman, D. J.; Mislow, K. *J. Org. Chem.* **1968**, *33*, 2924–2926.

[23] Lightner, D. A.; Beavers, W. A. *J. Am. Chem. Soc.* **1971**, *93*, 2677–2684.

[24] Lightner, D. A.; Gawronski, T. D.; Hansen, Au. E.; Bouman, T. D. *J. Am. Chem. Soc.* **1981**, *103*, 4291–4296.

[25] For leading references and reviews, see: Barth, G.; Djerassi, C. *Tetrahedron* **1981**, *37*, 4123–4142. Lightner, D. A.; Gawronski, J. K.; Bouman, T. D. *J. Am. Chem. Soc.* **1980**, *102*, 1983–1990.

recorded on a Cary 219 spectrophotometer, and rotations were determined in chloroform, unless otherwise indicated, on a Perkin-Elmer 141 polarimeter. Infrared (IR) spectra were measured on a Perkin-Elmer Model 599 instrument. All melting points are uncorrected and were determined on a Thomas-Hoover capillary apparatus. Analytical gas chromatography (GC) was performed on a Varian-Aerograph Model 2400 F/I instrument with a 6 ft × $^1/_8$ in. diameter column packed with 30% QF-1 adsorbed on 80/100 Chromosorb W AW-DMCS. Preparative gas chromatography (GC) was performed on a Varian-Aerograph Model 1720 T/C instrument with a 6 ft × $^3/_8$ in. diameter column packed with 30% QF-1 adsorbed on 80/100 Chromosorb W AW-DMCS. Spectral data were obtained with the use of spectral grade solvents (MCB): *n*-heptane, 2,2,2-trifluoroethanol (TFE), and acetonitrile. Other solvents were distilled and dried before use: benzene, hexane, cyclohexane, chloroform, and dichloromethane from P_2O_5; tetrahydrofuran and diethyl ether from $LiAlH_4$ and N_2. The solvents were used freshly distilled or stored over 4-Å molecular sieves (Linde). Column chromatography was accomplished on 60–200 mesh silica gel (J. T. Baker or Woelm).

(±)-Bicyclo[2.2.2]oct-7-ene-2,5-dione (2).[11] As per the method of Jefford et al.,[11,12,15] a mixture of hydroquinone (330 g, 3 mol) and maleic anhydride (558 g, 6 mol) was heated in an atmosphere of nitrogen under strong reflux in a 2-L round-bottom three-necked flask for 2 h. The mixture was cooled to −70 °C, then carefully poured with stirring into ethyl ether (1.6 L) in a 5-L beaker, and left overnight. The product was collected by filtration and washed with ether. The beige crystals (93.5 g, 15%) of (±)-5,7-dioxobicyclo[2.2.2]octane-2,3-dicarboxylic anhydride were used in either of the next steps without further purification.

The crude anhydride (93.5 g) from above was dissolved in water (50 mL) and warmed to 80 °C with stirring for 2 h. The mixture was cooled to room temperature and allowed to stand in a refrigerator overnight. The pale yellow crystals of (±)-5,7-dioxobicyclo[2.2.2]octane-2,3-dicarboxylic acid, mp 267–269 °C (lit.[13] mp 264–266 °C) were collected in 2 crops, 41.6 g in the first and 20.2 g in the second. The material was taken directly on the next step.

A mixture of the diacid (22.6 g, 0.1 mol) from above and lead tetraacetate (88.0 g, 0.2 mol) in dioxane (200 mL) was purged with nitrogen for 15 min and then placed in a water bath. Pyridine (200 mL) was added over a period of 10 min, and the resulting mixture was warmed at 60 °C in a water bath for 30 min. The mixture then was cooled and poured into 3 N nitric acid (1.2 L). The acid solution was extracted with dichloromethane (8 × 100 mL), and the combined organic layers were separated, washed with water, 5% sodium bicarbonate solution, and brine, and then dried. Evaporation of the solvent gave a brown oil, which was chromatographed on silica gel, eluting with ethyl acetate–hexane (1:9), to give a white solid (2.0 g, 15%): mp 97–98 °C (lit.[11] mp 97–99 °C; IR (film, cm^{-1}) 2960, 2900, 1725, 1400, 1340, 1300, 1060, 940, 885; ^{1}H NMR (100 MHz) δ 2.37 (4 H, m), 3.3–3.5 (2 H, m), 6.4–6.6 (2 H, m); ^{13}C NMR (ppm) 34.8 (t, C_3, C_6), 49.7 (d, C_1, C_4), 132.0 (d, C_7, C_8), 207.5 (s, C_2, C_5).

(−)-(1*S*)-Bicyclo[2.2.2]oct-7-ene-2,5-dione (3b). Brucine dihydrate (221 g, 0.513 mol) was added to a mechanically stirred solution of the (±)-diacid (116 g, 0.513 mol) in 2800 mL of methanol, and the resulting mixture was heated at gentle reflux for 7 days. After being allowed to cool to room temperature and to stand for 1 day, the precipitated brucine salt was filtered off and washed with cold methanol. There was obtained after thorough air-drying 81.0 g (25%) of optically enriched salt: mp 190–200 °C; $[\alpha]^{25}_D$ −57.7° (*c* 1.12, DMSO).

Chloroform (150 mL) was placed in a 1-L separatory funnel containing the brucine salt (20.0 g, 32.2 mmol), followed by 300 mL of aqueous sodium hydroxide (3.87 g, 96.7 mmol) solution. The mixture was shaken vigorously until two clear phases were formed. The aqueous layer was extracted with additional chloroform (2 × 150 mL), and the combined organic layers were washed with water (80 mL), dried, and concentrated to return 17.8 g of brucine.

The combined aqueous layers were acidified to pH 1 with 32.2 mL of 6 N hydrochloric acid and concentrated in vacuo to leave a pale yellow solid. This material was washed with dry acetone, filtered, and concentrated to give 6.2 g of crude diacid contaminated with sodium chloride.

The above solid was dissolved in 300 mL of pyridine–water (1:1), treated with triethylamine (15.3 mL, 110 mmol), and electrolyzed at 45 V while being rapidly stirred at 18 °C. After 6 h, the reaction mixture was slowly acidified with concentrated hydrochloric acid (190 mL) while being cooled in an ice bath and extracted with chloroform (5 × 200 mL). The combined organic layers were washed with brine (200 mL), dried, filtered, and concentrated at room temperature. The residual solid was purified by MPLC on silica gel (elution with 40% ethyl acetate in petroleum ether) to give 1.47 g (40%) of **3b** as faintly yellow crystals: $[\alpha]^{22}_D$ −1137° (*c* 0.16, CCl_4); mp 98–100 °C (lit.[13] mp 95–99 °C for the racemic mixture).

Resolution of (±)-Bicyclo[2.2.2]oct-7-ene-2,5-dione (3a + 3b). In a typical experiment, dry baker's yeast (Fleischman's) (5.0 g) was suspended in a solution of sucrose (7.5 g) in water (50 mL) in a 1-L Erlenmeyer flask. After 30 min, enedione (**3a** + **3b**) (1.0 g) was added to the suspension, a cotton plug was placed at the top of the flask, and the mixture was shaken gently at room temperature on a reciprocating platform shaker. Additional sucrose (2.5 g) was added everry 24 h. After 5 days, the mixture was continuously extracted with dichloromethane and dried. The solvent was removed and the residue was chromatographed on silica gel, eluting with ethyl acetate–hexane (1:2) to give enedione **3a** (0.28 g) ($[\alpha]^{25}_{589}$ + 1005° (*c* 0.107); mp 98–100 °C) and keto alcohol **6** (0.12 g) ($[\alpha]^{25}_{589}$ −528° (*c* 0.123); mp 140–157 °C).

Enedione **3a** was further purified by sublimation at 80 °C (2 mm) to give a white solid: mp 98–100 °C; $[\alpha]^{25}_{589}$ +1161° (*c* 0.134) and $[\alpha]^{25}_D$ +1070° (*c* 0.028, cyclohexane) (lit.[13] $[\alpha]^{29.5}_D$ + 1222° (*c* 0.0063, CCl_4), $[\alpha]^{29.5}_D$ +1252° (*c* 0.0012, cyclohexane) for 100% ee).

Keto alcohol **6** was sublimed at 120 °C (2 mm) to yield a white solid: mp 162–164 °C; $[\alpha]^{25}_{589}$ −575° (*c* 0.156). A 40-mg sample of **6** was oxidized with pyridinium chlorochromate in dichloromethane to give 25 mg of diketone, $[\alpha]^{25}_{589}$ −1266° (*c* 0.193). Keto alcohol **6** exhibited the following UV spectrum (*n*-heptane): ϵ_{max}^{317} 58, ϵ_{max}^{306} 112, ϵ_{max}^{296} 124, ϵ_{max}^{287} 103, ϵ_{max}^{216} 1426; IR (film, cm^{-1}) 3410, 3050, 2940, 1720, 1610, 1510, 1400, 1340, 1310, 1270, 1210, 1160, 1100, 1060, 1020, 925; ^{1}H NMR (100 MHz) δ 1.25–1.47 (1 H, m), 1.87 (2 H, m), 2.05–2.33 (1 H, m), 2.52 (1 H, m), 3.00 (2 H, m), 4.18 (1 H, m), 6.32 (2 H, t, J = 4 Hz); ^{13}C NMR (ppm) 34.47 (t, C_3), 35.87 (t, C_6), 39.97 (d, C_4), 48.16 (d, C_1), 68.87 (d, C_5), 129.83 (d, C_8), 133.46 (d, C_7), 211.44 (s, C_2).

(1*S*)-2,5-Dideuteriobicyclo[2.2.2]octa-2,5,7-triene (1). A modification of the method of Weitemeyer et al.[12] was used. To a suspension of $LiAlD_4$ (785 mg, 18.7 mmol) in dry tetrahydrofuran (40 mL) under a N_2 atmosphere was added a solution of (+)-(1*R*)-bicyclo[2.2.2]oct-7-ene-2,5-dione (**3a**) ($[\alpha]^{25}_{589}$ +965° (*c* 0.135), 71% ee) (850 mg, 6.25 mmol) in dry tetrahydrofuran (10 mL). The mixture was heated under reflux for 2 h, cooled, and quenched with successive addition of water (0.785 mL), 15% aqueous sodium hydroxide (0.785 mL), and water (2.355 mL). The resulting mixture was allowed to stir at room temperature for 30 min. A white precipitate was collected by filtration and the filtrate was saved. The white precipitate was extracted with tetrahydrofuran using a Soxhlet extractor. The tetrahydrofuran extract was combined with the filtrate, and the solvent was evaporated, leaving a white solid. Sublimation of the white solid at 150 °C and 2 Torr gave a mixture of epimeric dideuterio diols (4) (830 mg, 94%) that had the following properties: mp 210–226 °C; $[\alpha]^{25}_D$ +80.4° (*c* 1.0); IR (KBr, cm^{-1}) 3298, 2920, 2100 (C–D), 1310, 1190, 1120, 1060, 950; ^{1}H NMR (100 MHz) δ 0.85–1.25 (2 H, m), 1.65–1.95 (2 H, m), 2.15–2.8 (4 H, m), 6.05–6.45 (2 H, m) (lit.[12] mp 218 °C; partial ^{1}H NMR (100 MHz) δ 3.90 (2 H, m) for crystallized racemic d_0 diol). The dideuterio diol was carried through to the next step without separation of diastereomers.

To a solution of (+)-(1*R*)-2ξ,5ξ-dideuteriobicyclo[2.2.2]oct-7-ene-2,5-diol (**4**) $[\alpha]^{25}_{589}$ +80.4° (*c* 1.0), 71% ee (710 mg, 5 mmol) in dry pyridine (15 mL) at 0 °C was added a solution of *p*-tolyl chlorothioformate (3 g, 16 mmol, Fluka) in dry dioxane (2 mL). The mixture was allowed to stir at room temperature for 2 days, poured into ice water (60 mL), and extracted with benzene. The benzene extract was washed with dilute aqueous sulfuric acid, brine, and sodium bicarbonate solution. After drying, the solvent was evaporated and the brown residue was chromatographed on silica gel (elution with benzene–hexane (1:3)) to give a white solid mixture of diastereomeric bis(*O*-*p*-tolyl thionocarbonate) esters

(**5**): 1.65 g (75% yield); $[\alpha]^{25}_{\mathrm{D}}$ +45° (*c* 1.2); IR (KBr, cm^{-1}) 2910, 1750, 1500, 1310, 1100, 1060, 1040, 820; ^{1}H NMR (100 MHz) δ 1.2–1.8 (4 H, m), 2.35 (6 H, s), 3.05–3.35 (2 H, m), 6.35–6.65 (2 H, m), 6.85–7.35 (8 H, m). This material was used directly in the modified Tschugaeff reaction that follows.

The (+)-bis(*O*-*p*-tolyl thionocarbonate) ester mixture (**5**) from above (1.65 g, 3.73 mmol) was pyrolyzed at 170 °C under vacuum (2 Torr).[12] The pyrolysate was collected at liquid nitrogen temperature and the barrelene product (**1**) was separated by preparative gas chromatography at 130 °C as a highly volatile oil (17 mg, 4%). It was >99.9% pure by analytical gas chromatography and had a retention time identical with that of an authentic sample of barrelene-d_0:[26] UV (*n*-heptane) $\epsilon^{238}_{\max}$ 125, ϵ^{215} 185, ϵ^{190} 2850; CD (*n*-heptane) $\Delta\epsilon^{246}_{\max}$ +0.0083, $\Delta\epsilon^{215}_{\max}$ –0.071; UV (TFE) $\epsilon^{235}_{\max}$ 132, ϵ^{225} 113, ϵ^{215} 260, ϵ^{190} 2650; CD (TFE) $\Delta\epsilon^{248}_{\max}$ +0.0018, $\Delta\epsilon^{225}_{\max}$ –0.036, $\Delta\epsilon^{215}_{\max}$ –0.003 (CD data corrected to 100% ee); IR (CCl_4, cm^{-1}) 3060, 2980, 1550, 1300, 1190; ^{1}H NMR (100 MHZ) δ 4.83 (2 H, m), 6.76 (4 H, m); 1^3C NMR (ppm) 48.07 (d, C_1, C_4), 140.36 (d, C_3, C_6, C_7, C_8), 141.29, 140.24, 139.19 (wt, C_2, C_5).

(1*R*)-2,5-Dideuteriobicyclo[2.2.2]octa-2,5,7-triene (*ent*-1). Reduction of **3b** (510 mg, 3.74 mmol) with $LiAlD_4$ (158 mg, 3.74 mmol) in dry tetrahydrofuran (40 mL) as described above gave 499 mg (94%) of *ent*-**4**. A cold (0 °C) solution of these diols in dry pyridine (10 mL) was treated dropwise under argon with *p*-tolyl chlorothioformate (1.73 mL, 11.2 mmol). This mixture was stirred in the dark for 7 days and processed in the predescribed manner. Flash column chromatography of the crude product on silica gel (elution with benzene–petroleum ether (1:3)) gave 1.37 g (88%) of a mixture of thionocarbonates.

Pyrolysis of the above solid at 180 °C and 20 Torr followed by preparative gas chromatographic purification of the condensate afforded 65 mg (20%) of *ent*-**1**. Hydrocarbon prepared in this manner exhibited ^{1}H and ^{13}C NMR spectra identical with those of **1**, but with CD effects of opposite sign.

(–)-(1*S*,5*S*)-2-Oxobicyclo[2.2.2]oct-7-en-5-ol *p*-Toluenesulfonylhydrazone (7). A mixture of (–)-(1*S*,5*S*)-2-oxobicyclo[2.2.2]oct-7-en-5-ol (**6**) ($[\alpha]^{25}_{\mathrm{D}}$ –328° (*c* 0.16)) (550 mg, 4 mmol), *p*-toluenesulfonylhydrazine (Aldrich) (745 mg, 4 mmol), and formic acid (3 drops) in dichloromethane (25 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (elution with ethyl acetate–hexane (2:1)) to give a white solid (930 mg, 76%): mp 152–155 °C; $[\alpha]^{25}_{589}$ –141° (*c* 0.65); UV (CH_3CN) $\epsilon^{229}_{\max}$ 1225, $\epsilon^{206}_{\max}$ 1198; IR (KBr, cm^{-1}) 3400, 3180, 3040, 2920, 1710, 1640, 1590, 1320, 1150, 1020, 910; ^{1}H NMR (100 MHz) δ 1.25 (2 H, t, *J* = 7 Hz), 1.99 (3 H, m), 2.42 (3 H, s), 3.01 (1 H, m), 3.18 (1 H, m), 4.15 (2 H, m), 6.29 (2 H, m), 7.3 (2 H, d, *J* = 8 Hz), 7.81 (2 H, d, *J* = 9 Hz).

(–)-(1*R*,2*S*)-*endo*-Bicyclo[2.2.2]oct-5-en-2-ol (8). To a suspension of tosylhydrazone **6** (615 mg, 2 mmol) in dry dichloromethane (10 mL) at 0 °C was added Dibal (1 M in hexane; 6 mL, 6 mmol). The mixture was allowed to stir at room temperature for 15 min. The excess hydride was then decomposed by adding 3 M sodium hydroxide (2 mL), and the solution was diluted with dichloromethane. The organic solution was washed with brine and dried. The solvent was removed by distillation through a Vigreux column (bath temperature 60 °C). The residue was sublimed at 120 °C (5 mm) to give alcohol **8** as a white solid (125 mg, 50%): mp 163–165 °C; $[\alpha]^{25}_{589}$ –76.5° (*c* 1.0) (lit.[18] mp 166.2–166.8 °C, $[\alpha]^{23}_{\mathrm{D}}$ +48.3° (*c* 1), 66 ± 2% ee); IR (KBr, cm^{-1}) 3440, 3030, 2920, 2850, 1440, 1370, 1320, 1270, 1220, 1080, 1050, 1020, 960, 920, 850; ^{1}H NMR (100 MHz) δ 0.95–1.35 (4 H, m), 1.7–2.05 (3 H, m), 2.4–2.75 (2 H, m), 3.86 (1 H, m), 6.05 (1 H, t, *J* = 7 Hz), 6.37 (1 H, t, *J* = 6.5 Hz); ^{13}C NMR (ppm) 21.77 (t, C_7), 23.88 (t, C_8), 29.96 (d, C_4), 37.57 (d, C_1), 38.97 (t, C_3), 70.27 (d, C_2), 129.65 (d, C_6), 136.44 (d, C_5). The present solid had the same GC retention time and same IR and NMR spectral properties as that of an authentic sample of *endo*-alcohol.[23]

(–)-(1*S*)-Bicyclo[2.2.2]oct-5-en-2-one (9). To a stirred solution of bicyclic *endo*-alcohol **8** ($[\alpha]^{25}_{\mathrm{D}}$ –76.5° (*c* 1.0)) (100 mg, 0.8 mmol) in dry dichloromethane (10 mL) was added pyridinium chlorochromate (170 mg, 0.8 mmol). The mixture was allowed to stir at room temperature for 30 min and passed through a short column of silica gel. The silica gel was then washed with dichloromethane. The dichloromethane was removed by distillation through a Vigreux column (bath temperature ~60 °C). The residue was sublimed at 40 °C (2 mm) to give **8** as a white solid (4.6 mg, 47%): mp 75–78 °C; $[\alpha]^{25}_{589}$ –485° (*c* 0.153) [(lit.[18] mp 90.5–93 °C, $[\alpha]^{28}_{\mathrm{D}}$ +267° (*c* 1.2) from *endo*-alcohol precursor having $[\alpha]^{26}_{\mathrm{D}}$ +39.6° ($CHCl_3$)]; UV (*n*-heptane) $\epsilon^{317}_{\max}$ 54, $\epsilon^{306}_{\max}$ 103, $\epsilon^{296}_{\max}$ 110, $\epsilon^{287}_{\max}$ 90, $\epsilon^{217}_{\max}$ 1069; IR (KBr, cm^{-1}) 3040, 2930, 2850, 1720, 1440, 1400, 1350, 1250, 1200, 1150, 1070, 850; GC retention time (analytical column) same as that of a sample of the authentic ketone.[23]

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Oxidative Cyclization of Arylhydrazones of Chalcones and Benzalacetones to Pyrazoles by Thianthrene Cation Radical

Albert C. Kovelesky and Henry J. Shine*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409

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Phenyl-, (*p*-nitrophenyl)-, and (2,4-dinitrophenyl)hydrazones of chalcone (benzalacetophenone), benzalacetone, and of some of their derivatives undergo oxidative cyclization in reactions with thianthrene cation radical perchlorate. The products are, respectively, 1,3,5-triaryl- (**3**) and 3-methyl-1,5-diarylpyrazoles (**4**) and are formed in excellent yields. Cyclization appears to occur by way of the arylhydrazone cation radical and not via the preliminary, acid-catalyzed formation of the corresponding pyrazoline.

Introduction

Recently, we have described the oxidative cycloaddition of arenealdehyde phenylhydrazones to nitriles, induced by the thianthrene cation radical ($Th^{\bullet+}$).[1,2] We have found now that reaction of $Th^{\bullet+}$ with arylhydrazones of chalcones (**1**) and benzalacetones (**2**) causes their oxidative, intramolecular cyclization into pyrazoles (**3** and **4**) in excellent yields.

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(1) Hoque, A. K. M. M.; Kovelesky, A. C.; Lee, W.-K.; Shine, H. J. *Tetrahedron Lett.* **1985**, *26*, 5655.

(2) Shine, H. J.; Bae, D. H.; Hoque, A. K. M. M.; Kajstura, A.; Lee, W.-K.; Shaw, R. W.; Engel, P. S.; Keys, D. *Phosph. Sulfur* **1985**, *23*, 111.