X = Cl : (+)-**2**
X = Br : (+)-**3**

(+)-**4**
(+)-**5**

Synthesis and Circular Dichroism of 5- and 6-Halogenobicyclo[2.2.1]hept-5-en-2-ones; Tests for the Dekkers' Quantitative Chirality Rule

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*In memoriam Professor Pierre Crabbé***

Abstract: Stereoselective syntheses of (+)-(1*R*,4*R*)-5-chloro-, -5-bromo-, -6-chloro-, and -6-bromobicyclo[2.2.1]hept-5-en-2-ones ((+)-**2**–(+)-**5**) are presented. The chiroptical properties (CD spectra) of these halogenated derivatives are compared with those of the non-substituted (+)-(1*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-one ((+)-**1**) and analyzed in the light of the General Octant Rule and the Dekkers' Quantitative Chirality Rule for the highest wavelength Cotton Effects of β,γ-enones.

Moscowitz et al.[1] proposed for rigid β,γ-enones that the sign of the highest wavelength Cotton effects (CE) in their circular dichroism (CD) spectra is given by the generalized octant rule (GOR). Due to n(CO)-π(C=C) overlap[2] contribution of the C=C chromophore to the $n\rightarrow\pi_{CO}$ CE is consignate with the ketone octant rule[3]. *Kuritani* et al.[4] found for (5*R*)-spiro[4.4]non-6-en-1-one and (1*R*,5*S*)-8-methylidenebicyclo[3.3.0]octan-2-one[5] a dissignate behaviour in their CD spectra. They also showed that the sign of the CE($n\rightarrow\pi_{CO}$) = (sign of octant of the double bond) × (sign of cosΘ), where Θ is the angle between $C\rightarrow O$ and $C_\gamma\rightarrow C_\beta$ vectors. More recently, *Schippers* and *Dekkers*[6] put that rule on a more quantitative basis:

$$R = D^{1/2}|\vec{\mu}|\cos\Theta \qquad (1)$$

where R is the electronic rotational strength, D the electric dipole strength given by $D = |\vec{r}|^2$ ($\vec{r}$ being the electric dipole moment), and $\vec{\mu}$ the magnetic dipole moment of the $n\rightarrow\pi_{CO}$ transition of β,γ-enones with C_β situated in a positive octant as shown for (1*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-one[7] in Fig. 1.

In order to test this useful analytical tool, we prepared (1*R*,4*R*)-5- and (1*R*,4*R*)-6-halogenobicyclo[2.2.1]hept-5-en-2-ones ((+)-**2**–(+)-**5**) and recorded their CD spectra.

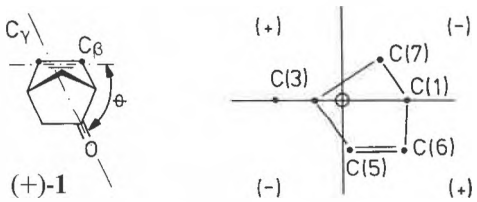

*Fig. 1. Octant rule representation of (1R,4R)-bicyclo[2.2.1]hept-5-en-2-one ((+)-**1**).*

Since the halogen substituents in (+)-**2** and (+)-**3** are situated in an octant with opposite sign than that in derivatives (+)-**4** and (+)-**5** (see Fig. 2), and since the Cl and Br atoms are expected to perturb significantly the electronic properties of the olefinic chromophores, we were intrigued to establish whether they would, or not, affect the rotational strength of the $n\rightarrow\pi_{CO}$ transitions in these rigid β,γ-enones. We report results that demonstrate validity of rule (1) for the longest wavelength CE's in (+)-**2**–(+)-**5**.

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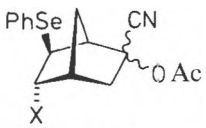
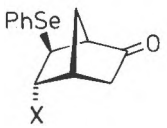
The optically active enones (+)-**2**–(+)-**5** were derived from the racemic Diels-Alder adducts **6** of cyclopentadiene and 1-cyanovinyl acetate[8] in the following way. Saponification (MeONa/MeOH, 20°C, 4 h) of **6** gave a mixture of cyanohydrins **7**. When dissolved in methanol with one equivalent of brucine[9], a 24% yield of a crystalline 1:1 complex of brucine and **7** was obtained, which, on treatment with MeONa/MeOH and 40% aq. H_2CO, afforded (+)-**1** with 50% *ee*. Recrystallization of the above complex from MeOH led to (+)-**1** with 64% *ee* in 10% yield. On treating the latter complex with Ac_2O/pyridine (3 equiv., $CHCl_3$, 20°C, 24 h), (+)-**6** ($\alpha_D^{20} = 87.6°$, $c = 1.5$, $CHCl_3$) was isolated in 55–60% yield and 64% optical purity (after saponification to (+)-**1**). (+)-**6** added one equivalent of PhSeCl ($CHCl_3$, 60°C, 2 d) yielding **8** (81%) stereo- and regioselectively[10,11]. Saponification (MeONa/MeOH), followed by treatment with 40% aq. H_2CO gave ketone **9** (63%). Oxidative elimination of the PhSe moiety (*m*-chloroperbenzoic acid, CH_2Cl_2, −70°C) afforded (+)-**2** in 52% yield with 64% *ee*. The same sequence of reactions using PhSeBr and (+)-**6** gave successively **10** (48%), **11** (60%), and (+)-**3** (58%) with 64% *ee*.

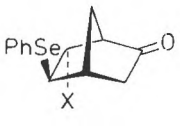
R = Ac : **6**
R = H : **7**



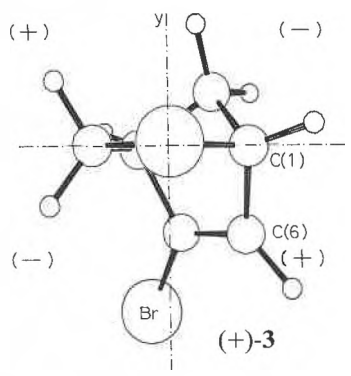
X = Cl : **8**
X = Br : **10**



9
11



(−)-**12**
(−)-**13**



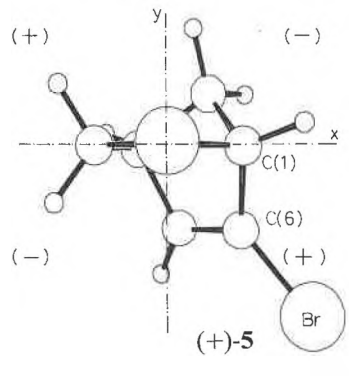


*Fig. 2. Representation of (+)-**3** and (+)-**5** as calculated by the MMPII method[13]. The geometries are projected in a plane perpendicular to the C=O direction.*

Table 1. Optical rotations, UV and CD characteristics of enones (+)-**1**–(+)-**5**[a].

	α_D^{20} [b]	UV (isooctane)[c] ε (at λ_{max}, nm)	CD (isooctane)[b,c] $\Delta\varepsilon$ (at λ, nm)	$\Delta\varepsilon/\varepsilon^{1/2}$ [d] for λ_{max}
(+)-**1**	+1150.0 (c = 2, $CHCl_3$)	277 (308)	+18.8 (306)[e]	1.13
(+)-**2**	+1225.0 (c = 2, $CHCl_3$)	242 (320)	+20.4 (318)	
		368 (306)	+30.8 (306)	1.61
		340 (296)	+25.8 (295)	
		231 (287)	+17.2 (286)	
		3520 (222)	−5.6 (220)	
(+)-**3**	+998.0 (c = 1.3, $CHCl_3$)	272 (320)	+23.3 (320)	
		423 (307)	+34.4 (308)	1.67
		382 (296)	+28.3 (297)	
		281 (286)	+17.2 (288)	
		3710 (220)	−7.2 (220)	
(+)-**4**	+1576.0 (c = 1.8, $CHCl_3$)	144 (322)	+18.6 (320)	
		227 (309)	+28.8 (308)	1.91
		205 (298)	+23.2 (297)	
		151 (288)	+15.0 (288)	
		2930 (220)	−6.6 (232)[f]	
(+)-**5**	+1212.0 (c = 1.3, $CHCl_3$)	174 (324)	+23.4 (320)	
		267 (310)	+34.0 (308)	2.08
		234 (300)	+28.4 (297)	
		158 (288)	+18.8 (286)	
		3375 (222)	−6.6 (232)[f]	

[a] Other spectral data of (+)-**2**–(+)-**5**, see Ref.[10b].
[b] Corrected to 100% *ee*.
[c] Similar spectra were observed in 95% EtOH and in the gas phase for the $n\rightarrow\pi_{CO}$ transitions.
[d] The Franck-Condon contour of the UV and CD spectra being all very similar, they allow one to consider $\Delta\varepsilon/\varepsilon^{1/2}$ proportional with $R/D^{1/2}$ of Equation (1).
[e] In heptane, see Ref.[6].
[f] Visible only in 95% EtOH or gas phase.

The syntheses of the 6-halogeno derivatives (+)-**4** and (+)-**5** exploited the electron-donating ability of the carbonyl function[12] which is believed to be responsible of the reversal of regioselectivity of the electrophilic additions of the olefinic moiety in **1** compared with those of precursor **6**[10,11]. (+)-**1** (50% *ee*) added to PhSeCl and PhSeBr ($CHCl_3$, 20°C)[10] giving adducts (−)-**12** (63%, *m.p.* 78–80°C, $\alpha_D^{20} = -12.1°$ (c = 2, $CHCl_3$)) and (−)-**13** (58%, *m.p.* 80–82°C, $\alpha_D^{20} = -9.8°$ (c = 2, $CHCl_3$)), respectively. Oxidation of (−)-**12** and (−)-**13** with *m*-chloroperbenzoic acid (CH_2Cl_2, −70°C) afforded (+)-**4** (42%, *b.p.* 100°C/14 Torr) and (+)-**5** (45%, *b.p.* 120°C/14 Torr), respectively. The chiroptical properties of the new enones (+)-**2**–(+)-**5** are reported in Table 1.

Comparison of the UV absorption spectra of **2–5** with that of **1** shows that substitution at C-5 or C-6 by an halogen atom does not affect significantly the $n\rightarrow\pi_{CO}$ transition of the β,γ-enone.Comparison of the CD spectra of (+)-**2**–(+)-**5** with that of (+)-**1** shows a sligth increase of the rotational strength (as given by $\Delta\varepsilon$ values, see Table 1) due to halogen substitution. However, the most striking observation is that there is no differential effect on $\Delta\varepsilon$ values between 5- and 6-halogenobicyclo[2.2.1]hept-5-en-2-ones although the halides are expected to have dissignate and consignate behaviours in the former and latter derivatives, respectively (Fig. 2), according to the GOR[1]. Our results, thus, confirm the interpretation that the chiroptical properties of the $n\rightarrow\pi_{CO}$ transition in β,γ-enones are to a large extent determined by admixture of olefinic transitions ($\pi\rightarrow\pi_{CC}$) polarized along the C_γ–C_β direction[5,6].

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[1] A. Moscowitz, K. Mislow, M.A.W. Glass, C. Djerassi, *J. Am. Chem. Soc. 84* (1962) 1945; A. Moscowitz, A.E. Hansen, L.S. Förster, K. Rosenbeck, *Biopolym. Symp. 1* (1964) 75; P. Crabbé: *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco (1965); P. Crabbé: *Optical Rotatory Dispersion and Circular Dichroism in Chemistry and Biochemistry*, Academic Press, New York (1977).
[2] H. Labhart, G. Wagnière, *Helv. Chim. Acta 42* (1959) 2219.
[3] K.N. Houk, *Chem. Rev. 76* (1976) 1; D.N. Kirk, *Tetrahedron 42* (1986) 777.
[4] H. Kuritani, F. Iwata, M. Sumiyashi, K. Shingu, *J. Chem. Soc. Chem. Commun* (1977) 542.
[5] H. Kuritani, K. Shingu, M. Nakagawa, *Tetrahedron Lett. 21* (1980) 529.
[6] P.H. Schippers, H.P.J.M. Dekkers, *J. Am. Chem. Soc. 105* (1983) 79.
[7] D.A. Lightner, W.A. Beavers, *J. Am. Chem. Soc. 93* (1971) 2677; P.-A. Carrupt, P. Vogel, *Tetrahedron Lett. 22* (1981) 4721.
[8] W.L. Dilling, R.D. Koening, J.C. Little, *J. Am. Chem. Soc. 92* (1970) 928.
[9] K.A. Black, P. Vogel, *Helv. Chim. Acta 67* (1984) 1612.
[10] a) P.-A. Carrupt, P. Vogel, *Tetrahedron Lett. 23* (1982) 2563; b) *ibid.*, submitted.
[11] K.A. Black, P. Vogel, *J. Org. Chem. 51* (1986) 5341.
[12] P.-A. Carrupt, P. Vogel, *Tetrahedron Lett. 25* (1984) 2879.
[13] We thank Molecular Design Ltd. for an Academic Grant with COMPDS programs.