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OPTICAL ROTATORY DISPERSION STUDIES CXX.[1] SYNTHESIS AND CIRCULAR DICHROISM OF CHIRAL 3-DEUTERIOCYCLOPENTANONE

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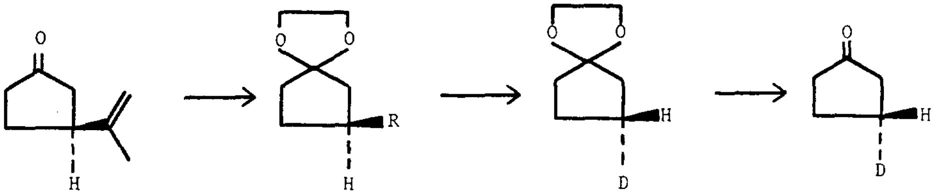
Although numerous examples of asymmetric molecules which owe their chirality to isotopic substitution are known,[3] few are reported[3] to display Cotton effects in either optical rotatory dispersion(ord) or circular dichroism(cd). We wish to report the successful synthesis and chiroptical properties of the first saturated cyclic ketone whose asymmetry is due only to deuterium substitution, (R)-3-deuteriocyclopentanone(VIII).[4]

(S)-(-)-3-Isopropenylcyclopentanone(I), obtained by pyrolysis[5] of the calcium salt of (+)-cis-pinonic acid derived[6] from (+)-α-pinene,[7] was ketalized under standard conditions[8] affording a 95% yield of II, bp 88-89°/8.5 torr; n_D^{20} 1.4694; $[\alpha]_D^{20}$ +5.07° ± 0.14° (c = 2.21% in $CHCl_3$); M^+ 168; ir(film): 3105 cm^{-1} (=C-H), 1650 (C=C), 890 ($-C(CH_3)=CH_2$); nmr (60 MHz, $CDCl_3$): δ1.72 (s, 3H, $=C-CH_3$), 2.3-2.9 (m, 1H, allylic methine), 3.90 (s, 4H, $-OCH_2CH_2O-$); calcd. for $C_{10}H_{16}O_2$: C, 71.39 H, 9.59%; found: C, 71.38%; H, 9.55%. Ozonolysis of II in ethyl acetate in the presence of tetracyanoethylene[9] at -78° gave III, $[\alpha]_D^{20}$ +3.95° ± 0.12° (c = 2.51% in $CHCl_3$); M^+ 170; ir(film): 1710 cm^{-1} (C=O); nmr: δ2.15 (s, 3H, $-COCH_3$); 3.00 (m, 1H, -COC-H), 3.90 (s, 4H, $-OCH_2CH_2O-$); uv: λ_{max} = 277 nm, ε = 27 (c = 0.16% in 95% ethanol); circular dichroism: λ_{max} = 287 nm, $[\theta]_{max}$ = -1198° (c = 0.16% in 95% ethanol); within 5 minutes after addition of two drops of 5% NaOH to III in ethanol, its cd had decreased to virtual baseline (<20°); calc. for $C_9H_{14}O_3$: C, 63.51%; H, 8.29%; found: C, 63.04%, H, 8.33%. Baeyer-Villiger oxidation[10] of III with m-chloroperbenzoic acid[6b] in $CHCl_3$ for 3 days in the dark gave IV: M^+ 186; ir(film): 1740 cm^{-1} (ester C=O), 1250 (=C-O); nmr: δ2.03 (s, 3H, $-OCOCH_3$), 3.90 (s, 4H, $-OCH_2CH_2O-$), 5.15 (m, 1H, AcO-C-H). Refluxing IV with 20% NaOH for one-half hour yielded V: M^+ 144; ir(film): 3400 cm^{-1} (OH); nmr: δ3.95 (s, 4H, $-OCH_2CH_2O-$), 4.30 (m, 1H, O-C-H); calcd. for $C_7H_{12}O_3$: C, 58.23%; H, 8.39%; found: C, 58.04%; H, 8.62%. The optical purity of V was determined via its α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)[11] by integration of the $Eu(fod)_3$-shifted diastereomeric fluorine signals in the nmr to be 65% enantiomeric excess. A second sample obtained through repetition of the synthesis gave a value of 98+% e.e. by its MTPA ester. These differences in optical purity are likely due to acid-catalyzed epimerization of III prior to peracid oxidation. Mesylation[12] of V with MsCl and Et_3N in ether for one-half hour at 0° gave VI (nmr: δ3.00, s, 3H, $-OSO_2CH_3$; 5.20, m, 1H, O-C-H) which was directly stirred for 16 hours at room temperature with a three-fold excess of $LiAlD_4$ in ether affording VII: M$^+$ 129; ir(film): 2200 cm^{-1} (C-D); nmr: δ1.72 (7H) and 3.88 (4H). A sample of VII in isopropanol gave no Cotton effect; in situ deketalization of VII with two drops of 5% HCl after 20 hours, gave a Cotton effect of [θ] = -80.2° at 293 nm (c = 0.49% in isopropanol).



(I)

(II) R = $-C(CH_3)=CH_2$
(III) R = $-COCH_3$
(IV) R = $-OCOCH_3$
(V) R = OH
(VI) R = OMs

(VII)

(VIII)

Deketalization of VII in ether with 5% HCl (5 hours, 25°) gave VIII which was isolated by preparative gc (10% SE30, 100°); $[\alpha]_D^{20}$ -3.1° ± 0.6° (corrected to 100% e.e.; c = 0.89% in EPA (5:5:2 ether:isopentane:ethanol)); M$^+$ 85 (isotopic purity 99% d_1); ir(film): 3480 cm^{-1} (carbonyl overtone), 2193 and 2160 (C-D), 1740 (C=O); circular dichroism (corrected to 100% e.e.; c = 0.89% in EPA): 25°C: $[\theta]_{max}$ = -62° at 304 nm, reduced rotational strength[13] [R] = -0.0605; -100°C: $[\theta]_{max}$ = -66° at 303 nm, [R] = -0.0543; -196°C: $[\theta]_{max}$ = -70° at 302 nm, [R] = -0.0769. Figure 1 shows the actual experimental cd trace of the sample of VIII of 98+% e.e. (c = 0.112% in EPA) with a value of $[\theta]_{max}$ = -63°.

One possible explanation for the negative Cotton effect of VIII could be that the refractivit of D is less than that of H, an interpretation generally[14] but not always[3e] supported by the few similar systems available for study. The low temperature results cited above showed only slight changes in the position and amplitude of $[\theta]_{max}$ which indicates no significant shift in the equilibrium between the two half-chair conformers[15] VIIIa and b depicted in Figure 2.

CNDO calculations[16] on VIIIa and b, which take into consideration the slightly shorter C-D vs C-H bond and the latest concepts regarding the ketone octant rule,[17] gave values of [R], respectively: -5.07 and +4.61, corresponding to a weighted average of -0.23 (observed -0.06) and a calculated [θ] of -165° (observed -62°). We find these calculations to be in reasonable agreement with our experimental results.

Further studies with ketones owing their chirality to isotopic substitution are in progress.

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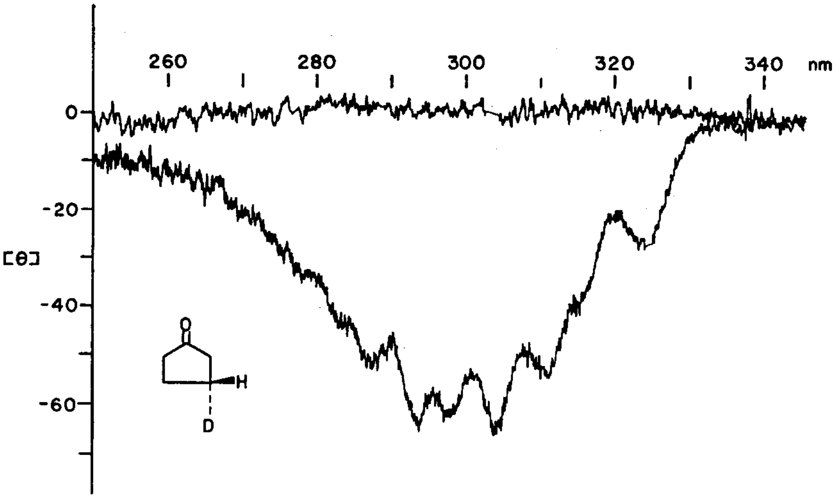
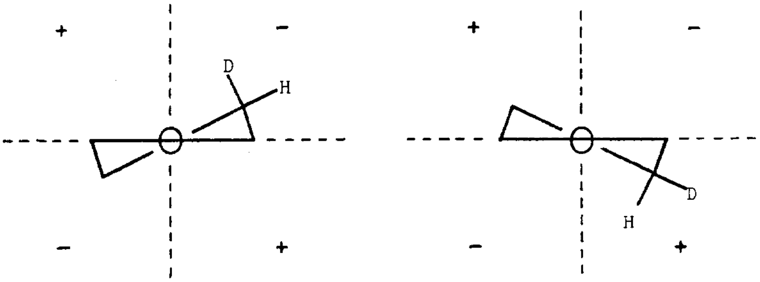


Figure 1. Circular Dichroism Spectrum of VIII in EPA at 25°C.



VIIIa

VIIIb

Figure 2. Two Half-Chair Conformers of VIII.

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