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APPLICATIONS OF ASYMMETRIC BROMINATION TO THE ASSIGNMENT OF CONFIGURATIONS IN 3- AND 4-SUBSTITUTED CYCLOHEXENES AND THE CORRESPONDING DIBROMIDES

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Abstract—Previous work on the asymmetric bromination of cyclohexene derivatives in the presence of dihydrocinchonine has been extended to 4-t-butylcyclohexene, and the hypothesis that asymmetric selection in these reactions is determined by the preferential reaction of the cycloalkene in its 3,4M conformation with the alkaloid-bromine complex has been confirmed. The absolute configurations of 4-t-butylcyclohexene and of the *trans*-dibromides derived from it and from 3-methylcyclohexene have been independently determined, thus confirming the usefulness of the asymmetric bromination in configurational assignments.

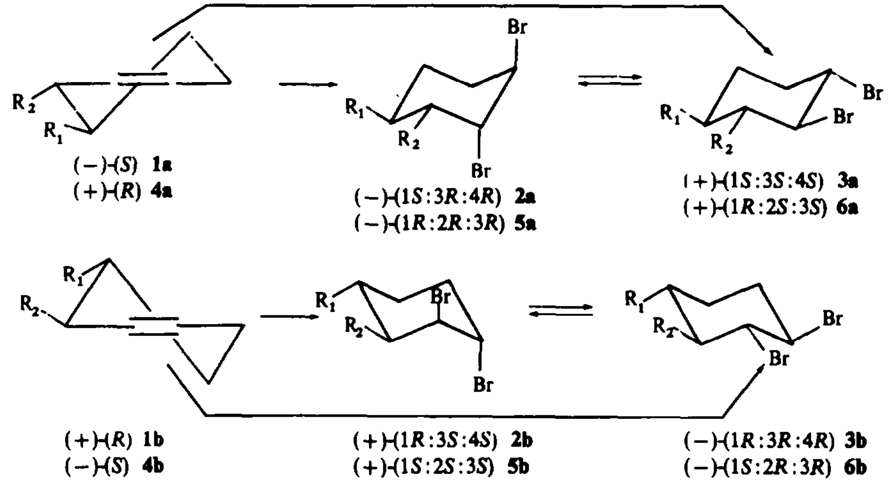
PREVIOUS investigations[1–3] on the asymmetric bromination of alkenes in the presence of cinchonine or dihydrocinchonine have shown that in all cases that have been so far examined there is a preferential formation of the enantiomers having the (*R*) configuration. Moreover, optically active (*R*)-4-methylcyclohexene was recovered from the partial asymmetric bromination of the racemic olefin.[2] A comparison of the steric course of the asymmetric bromination of cyclohexene and 4-methylcyclohexene strongly pointed to a reaction mechanism involving an alkaloid-bromine complex which reacts with different rates with the two dissymmetric monoplanar conformations of cyclohexene, and that this asymmetric selection is independent of the presence of a ring substituent.

The present work was undertaken in order to bring forward further examples in support of this hypothesis, and to establish that the partial asymmetric bromination is suitable for the determination of absolute configurations in substituted chiral cyclohexenes and the corresponding dibromides. 4-t-Butylcyclohexene (**1**) and 3-methylcyclohexene (**4**) were chosen as substrates. The absolute configuration of **4** is known:[4] that of **1** was determined in the course of this work.

RESULTS AND DISCUSSION

Racemic 4-t-butylcyclohexene (**1**) was brominated in chloroform solution, in the presence of dihydrocinchonine, to obtain a levorotatory mixture containing the four diastereoisomeric *trans*-dibromides **2a**, **2b**, **3a** and **3b**. The ratio of the diaxial (**2**) to the diequatorial (**3**) dibromides was 95:5, as determined by GLC and NMR analysis. Moreover, column chromatography on silica gel gave diastereoisomerically pure **2**, which was levorotatory. The rotation of **3** in the mixture was easily calculated: it was negative and its absolute value was much higher than that of **2**. When the bromination of **1** was stopped after the addition of one half of the equimolar amount of bromine, dextrorotatory olefin was recovered and the mixture of dibromides, containing **2** and **3** in the ratio 95·5:4·5, was again levorotatory. Also in this case both **2** and **3** had negative rotations, but the optical yield of **2** was much higher, and that of **3** lower than in the complete bromination.

The rotation of the olefin **1** was correlated with those of the corresponding dibromides by brominating in the presence of triethylamine the optically active **1** ($[\alpha]_D$ + 1·5°) recovered from the asymmetric half-bromination. From the mixture of **2** and **3** so formed, pure **2** (α_D + 1·87°) was isolated by chromatography. In order to increase the amount of **3**, the product was heated at 150°; under these conditions the dibromides **2** and **3** equilibrate cleanly, without racemization at C-1.[2, 5] The rotation of **3** (α_D − 2·95°) in the mixtures thus obtained was deduced on the basis of their composition and of the known rotation of **2**.



(−)-(S) **1a**
(+)-(R) **4a**

(−)-(1S:3R:4R) **2a**
(−)-(1R:2R:3R) **5a**

(+)-(1S:3S:4S) **3a**
(+)-(1R:2S:3S) **6a**

(+)-(R) **1b**
(−)-(S) **4b**

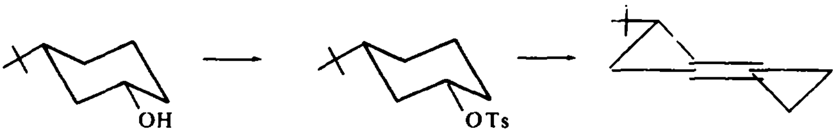
(+)-(1R:3S:4S) **2b**
(+)-(1S:2S:3S) **5b**

(−)-(1R:3R:4R) **3b**
(−)-(1S:2R:3R) **6b**

1, 2, 3; R_1 = t-Bu; R_2 = H
4, 5, 6; R_1 = H; R_2 = CH_3

If the previously presented hypothesis on the steric course of the asymmetric bromination is correct, one can assume that the configuration of (+)−**1** is (*R*), that of (−)−**2** (1*S*:3*R*:4*R*) and that of (−)−**3** (1*R*:3*R*:4*R*). This is in accordance with Brewster's theory,[6] which states that all 4-alkylcyclohexenes having configuration (*R*) should be dextrorotatory, irrespective of the nature of the achiral alkyl substituent. However, conformational effects such as ring deformations may be responsible for substantial differences between calculated and experimental optical rotations. In the case of 4-t-butylcyclohexene, a ring deformation may be produced by the interaction of the bulky substituent with the H atom at C-4.[7] Thus, it was believed necessary to determine the absolute configuration of **1b** by a rigorous method.

Partially resolved (+)-*cis*-3-t-butylcyclohexanol (**7**)[8] was converted into the tosylate (**8**), which, on heating in quinoline, afforded a 3:7 mixture of 3- and 4-t-butylcyclohexene. The latter compound was separated by preparative GLC and found to be dextrorotatory. Since it was shown that (+)-3-t-butylcyclohexanone, obtained by oxidation of (+)-7 has the (*R*) configuration,[8] the absolute configuration of (+)-1



7 **8** **1b**

must also be (R), in agreement with Brewster's theory.[6] From the results reported above, it also follows that (+)-**2** has the ($1R$:$3S$:$4S$) (**2b**) and (−)-**3** the ($1R$:$3R$:$4R$) configuration (**3b**). A rough estimate of the maximum optical rotations of (+)-**1**, (+)-**2** and (−)-**3**, made on the basis of the reported maximum rotation of (+)-**7** ($[\alpha]_D$ + 7·9°),[8] gave $[\alpha]_D$ + 70°, α_D + 86·6° and α_D − 136·6°, respectively. Brewster's theory[9] predicts negative rotation for **3b** and zero rotation for **2b**. The present values may be somewhat in error because it is assumed that optical purities correspond to enantiomeric purities, while it is known that there may be some difference between them.[10]

The bromination of (±)-3-methylcyclohexene (**4**) in the presence of dihydrocinchonine also gave a levorotatory mixture containing the four dibromides **5a**, **5b**, **6a** and **6b**, in which the ratio of **5** to **6** was 88 : 12, as determined by GLC and NMR analysis. It was possible to deduce that both **5** and **6** contained an excess of the levorotatory enantiomers. The olefin recovered from the asymmetric half-bromination of (±)-**4** was levorotatory [α_D − 0·58°, (S)-configuration[4]]. (S)-(−)-**4** was correlated with **5** and **6** by the method described for **1**; it was thus possible to deduce that (+)-**5** and (−)-**6** have the ($1S$:$2S$:$3S$) and ($1S$:$2R$:$3R$) configuration, and (−)-**5**, as obtained in the asymmetric bromination, has the ($1R$:$2R$:$3R$) configuration. Maximum rotations of (+)-**5** (34°) and (−)-**6** (201°), and their optical purities were calculated on the basis of the reported rotation of (+)-**4** ($[\alpha]_{579}$ 80·4°).[4]

The results of the asymmetric brominations are summarized in Table 1. It can be seen that in the case of the complete brominations they are in fairly good agreement with the equations proposed by Guetté and Horeau,[11] which state that the optical purities of two diastereoisomeric products (P_a and P_e) formed in a quantitative kinetic asymmetric transformation should be inversely proportional to their molar fractions (C_a, C_e). Furthermore,[2] if exactly one half of the substrate undergoes the reaction, the recovered substrate should have an optical purity (P_0) corresponding to P_aC_a–P_eC_e. The latter assumption was verified in a less satisfactory way, since the recovered olefins **1** and **4** had optical purities which were somewhat lower than expected. These differences may depend, in our opinion, on the experimental difficulty of brominating exactly one half of the olefin, and on the uncertainty in the exact values of the optical purities.

The difficulties in analyzing the data reported above from a kinetic and mechanistic point of view have been discussed in our previous paper.[2] Information concerning the conformational and kinetic parameters of cyclohexene derivatives are still quite scarce. While in the case of **1** it can be assumed that a more or less distorted monoplanar (half-chair) form with an equatorial t-butyl group is strongly favoured over the axial conformer, and also over boat or twist conformations,[7] much less can be said about **4** in which the energy difference between the monoplanar forms with equatorial and axial 3-Me groups should be much lower than for **1**. The dibromides **2** and **5** are certainly formed by diaxial attack on the equatorial conformers of the cycloalkenes, those **3** and **6** could arise either by diequatorial attack on the same conformers, or by diaxial attack on the axial ones; the fact that the ratio of **2** to **3** is higher than that of **5** to **6** could be considered as evidence in favour of the latter hypothesis, even if the similarity in the ratios of **2** to **3** to those obtained in the bromination of 4-methylcyclohexene[2] would seem to indicate the contrary. Although much more experimental data will be necessary before attempting an interpretation, one interesting and useful point can be deduced from the available results: in the diaxial asymmetric addition of bromine in the presence of dihydrocinchonine to cyclohexene and to its 3-methyl-, 4-methyl-, 4-t-butyl-, 4-carboxy- and 4-carbomethoxy-[12] derivatives a preferential reaction takes place on the monoplanar conformation having a 3,4 M ring chirality (according to the helicity rule[13]) with the substituent (if present) in equatorial position. Therefore, the chirality of the ring has a predominant importance over that at the substituted carbon. This confirms our working hypothesis, and can provide a simple way for determining the absolute configuration of substituted cycloalkenes and of the dibromides derived from them.

EXPERIMENTAL

Optical rotations–Perkin–Elmer photoelectric polarimeter, mod. 141; unless stated otherwise, the values given are observed rotations at 25° for neat liquids in 1-dm tube, and are accurate within ±0·005°. Analytical GLC-Fractovap C. Erba, mod. G.V.; columns: 1% neopentyl glycol succinate (NPGS) on Chromosorb W 80–100 mesh for dibromides: 20% triethylene glycol saturated with $AgNO_3$ on Celite C 22, 45–60 mesh for olefins; carrier gas N_2. Preparative GLC–Perkin–Elmer, mod. F 21; column: 20% triethylene glycol saturated with $AgNO_3$ on Celite C 22, 45–60 mesh. IR spectra–Perkin–Elmer, mod. 257 grating spectrophotometer; spectra registered on liquid films, thickness 0·1 mm. NMR spectra–Varian DA-60-IL or JEOL C-60-HL spectrometers; spectra registered on pure liquids, TMS as internal standard.

$CHCl_3$ was purified by washing with 2N NaOH, conc H_2SO_4, H_2O and distillation. Pet ether refers to the fraction of boiling range 30–50°. Brominations were made by slowly adding a 0·2 M soln of Br in $CHCl_3$ to the stirred soln of the olefin. The optical yields of the asymmetric brominations are temp-dependent. During the addition of Br_2 to the alkene-alkaloid soln a strong decrease of temp is observed. Thus, the reaction mixture was held in a thermostatic bath. However, the signs and the ratio between optical rotations of epimers do not change appreciably with temp. For more experimental details about brominations and isomerizations of dibromides, and about GLC and NMR analyses of the dibromides **2** and **3**, reference is made to previous papers.[1,2]

(R)-(+)-4-*t-Butylcyclohexene* (**1b**)

(±)-*cis*-3-t-Butylcyclohexanol (**7**), obtained by reduction of 3-t-butylcyclohexanone with LAH–$AlCl_3$[14] was partially resolved by fractional crystallization of the brucine salt of its acid phthalate.[8] A sample of the alcohol (3·15 g) having $[\alpha]_D^{25}$ + 2·7° (*c*, 5·1, $CHCl_3$) was dissolved in pyridine (30 ml) and tosyl chloride (4·9 g) was slowly added at 0° to the stirred soln. After 24 hr the precipitated pyridine hydrochloride was filtered off, the filtrate was taken up in Et_2O and the ethereal soln was thoroughly washed with dil HCl aq, $NaHCO_3$ aq, dried ($MgSO_4$) and evaporated. The crude residual tosylate (5·6 g) had m.p. 49–51°, $[\alpha]_D^{25}$ − 5·9° (*c*, 4·6, $CHCl_3$). (Reported:[15] rac tosylate, m.p. 58–59·5°). A soln of the product (5·0 g) in quinoline (80 ml) was heated at 180–200° for 4 hr. The mixture was then poured onto ice-cooled HCl aq and extracted with Et_2O. The residue obtained by evaporation of the ethereal soln was dissolved in light petroleum and filtered through neutral Al_2O_3. The eluted olefin mixture (1·8 g) was distilled; b.p. 70–72°/15 mm. It consisted of 4-t-butylcyclohexene and 3-t-butylcyclohexene in the ratio 69·5:30·5 (GLC). Pure 4-t-butylcyclohexene was obtained by preparative GLC; it had $[\alpha]_D^{25}$ + 23·9° (*c*, 4·1, $CHCl_3$), its optical purity being 34·2%, as calculated on the basis of the reported maximum rotation of (1*S*:3*R*)-(+)-*cis*-3-t-butylcyclohexanol ($[\alpha]_D^{25}$ + 7·9°).[8] Hence, the maximum rotation of (*R*)-(+)-4-t-butylcyclohexane should be $[\alpha]_D^{25}$ + 70°.

(1R:3S:4S)-(+)-trans-3-cis-4-*Dibromo-t-butylcyclohexane* (**2b**) *and* (1R:3R:4R)-(−)-cis-3-trans-4-*dibromo-t-butylcyclohexane* (**3b**)

TABLE 1. BROMINATIONS OF (±)-ALKYLCYCLOHEXENES IN THE PRESENCE OF DIHYDROCINCHONINE[a]

Compound	Type	t (°C)	C_a	C_e	α_a	α_e	α_o	P_a	P_e	P_o	P_aC_a	P_eC_e	$P_aC_a - P_eC_e$
1	*b*	25	0·95	0·05	−0·35°	−9·35°	—	0·40	6·84	—	0·380	0·342	—
	c	25	0·955	0·045	−2·65°	−4·66°	+1·51°[d]	3·06	3·41	2·16	2·920	0·153	2·76
4	*b*	0	0·88	0·12	−0·24°	−8·91°	—	0·70	4·43	—	0·616	0·532	—
	b	*e*	0·88	0·12	−0·10°	−3·78°	—	0·29	1·88	—	0·255	0·225	—
	c	0	0·885	0·115	−0·61°	−3·83°	−0·58°	1·79	1·90	0·90	1·584	0·218	1·36

[a] C_a = molar fractions of diaxial dibromides **2** or **5**; C_e = molar fractions of diequatorial dibromides **3** or **6**. α_a and α_e = optical rotations of dibromides (neat, 1 dm); α_o = optical rotations of olefins recovered from partial brominations; P_a, P_e, P_o = optical purities of diaxial and diequatorial dibromides, and of recovered olefins.

[b] Complete brominations.

[c] Partial brominations.

[d] $[\alpha]_D^{25}$ in $CHCl_3$.

[e] Bromination carried out without temperature control.

(*R*)-(+)-4-t-Butylcyclohexene (**1b**) [α_D + 1·35°, $[\alpha]_D^{25}$ + 1·51° (*c*, 16, $CHCl_3$)] (4 g) was treated with Br_2 in $CHCl_3$ soln at 0–5° in the presence of an equimolar amount of Et_3N. After the usual work-up[2] 6·6 g of dibromides were obtained, b.p. 80°/0·6 mm, α_D + 1·74°. (Reported:[16] rac dibromide, b.p. 68°/0·3 mm, n_D^{25} 1·5247). The IR spectrum of the mixture showed strong bands at 646 and 672 cm^{-1} (diaxial dibromide),[17] and weak ones at 680 and 699 cm^{-1} (diequatorial dibromide).[17] Chromatography on neutral SiO_2 allowed to separate, from the first light petroleum eluate fractions, pure (GLC) diaxial dibromide (3·5 g), b.p. 74°/0·5 mm, n_D^{25} 1·5240, α_D + 1·87°, α_{546} + 2·14°, α_{436} + 3·82°, α_{365} + 6·36°. The product was partially isomerized by heating at 150° in a sealed tube under N_2; the mixture thus obtained (b.p. 88°/0·8 mm) consisted (GLC and NMR) of 79% diaxial and 21% diequatorial dibromide, α_D + 0·86°, α_{546} + 0·98°, α_{436} + 1·75°, α_{365} + 2·93°. The mixture was again heated at 150°; the mixture, b.p. 88°/0·8 mm, 67·8% diaxial and 32·2% diequatorial dibromide, had α_D + 0·32°, α_{546} + 0·36°, α_{436} + 0·64°, α_{365} + 1·09°. The calculated rotation of the diequatorial dibromide in the two mixtures is therefore α_D − 2·95°. By assuming for the starting **1b** an optical purity of 2·16%, the calculated maximum optical rotations of **2b** and **3b** at 25° are +86·6° and −136·6°, respectively.

Asymmetric brominations of (±)*-4-t-butylcyclohexene*

(a) *Total bromination.* The olefin (5·0 g), dissolved in $CHCl_3$ (850 ml) in the presence of dihydrocinchonine (6·6 g), was treated at 25° with a slight excess of the Br soln. After the usual work-up (solvent removed at reduced press, room temp) the crude mixture (9·0 g), decolourized with charcoal, had α_D − 0·82° and consisted of 95% diaxial and 5% diequatorial dibromide (GLC). After distillation (b.p. 76–78°/0·5 mm) the composition was unchanged; α_D − 0·80°, α_{546} − 0·92°, α_{436} − 1·65°, α_{365} − 2·70°. The pure diaxial dibromide was obtained by chromatography of the mixture on SiO_2; it had α_D − 0·35°. The calculated optical rotation of the diequatorial dibromide in the original mixture is therefore α_D − 9·35°.

(b) *Partial bromination.* The olefin (13·8 g, 0·1 mole) was dissolved in $CHCl_3$ (1800 ml) in the presence of dihydrocinchonine (17·0 g, 0·057 mole) and treated with 0·05 mole of Br_2. After the usual work-up (solvent removed at reduced press, room temp) the residue was fractionally distilled to give 4-t-butylcyclohexene (5·8 g), b.p. 65°/20 mm, α_D + 1·35°, α_{546} + 1·54°, α_{436} + 2·64°, α_{365} + 3·21°, $[\alpha]_D^{25}$ + 1·51° (*c*, 16, $CHCl_3$); mixed dibromides (10·8 g), b.p. 78–80°/0·6 mm. composition: 95·5% diaxial, 4·5% diequatorial dibromide: α_D − 2·74°, α_{546} − 3·15°, α_{436} − 5·64°. A sample of the dibromides (5·0 g) was chromatographed on SiO_2; the pure diaxial dibromide (2·8 g) so obtained had α_D − 2·65°, α_{546} − 3·04°, α_{436} − 5·42°, α_{365} − 9·01°. Calculated optical rotation of the diequatorial dibromide, α_D − 4·66°.

Brominations of (±)*-3-methylcyclohexene*

(a) *Total bromination.* The olefin (3·0 g), dissolved in $CHCl_3$ (500 ml) was treated with an equimolar amount of Br_2 in the presence of dihydrocinchonine (3·0 g) at 0–5°. After the usual work-up the residue (6·3 g) was distilled; b.p. 58–59°/0·8 mm, α_D − 1·28°. (Reported:[18] rac dibromide, b.p. 130°/35 mm). Bands at 658 and 670 cm^{-1} (axial C—Br) in the IR spectrum of the mixture were attributed to the *cis*-2-*trans*-3-dibromide **5**,[19] weaker ones at 687 and 700 cm^{-1} (equatorial C—Br), to the *trans*-2-*cis*-3-dibromide **6**.[19] Ratio **5** to **6** (GLC), 88:12; retention times (injection block temp 130°, column temp 100°, flow rate 48 ml/min), **5**, 4 min 15 sec; **6**, 11 min 30 sec. Column chromatography on SiO_2 allowed separation of pure (GLC) diaxial dibromide (3·1 g) b.p. 57°/0·6 mm, n_D^{25} 1·5415, α_D − 0·24°, α_{436} − 0·54°, α_{365} − 0·97°. The IR spectrum of the product showed no bands at 687 and 700 cm^{-1}. The protons α to Br in the NMR spectrum appear as two unresolved signals at δ 4·62 and 4·86 ppm (½ W 6·5 and 6 c/s), in accordance with the expectations for a conformation in which the Br atoms are axial and H_a equatorial. The calculated optical rotation of the diequatorial dibromide is therefore α_D − 8·91°.

(b) *Partial bromination.* The olefin (10·0 g, 0·104 mole), dissolved in $CHCl_3$ (1700 ml) was treated at 0–5° with 0·052 mole of Br in the presence of dihydrocinchonine (10·0 g, 0·034 mole). After removal of the alkaloid a part of the dried ($MgSO_4$) soln (400 ml) was evaporated at 40° under reduced press. The residue (3·6 g) containing only the dibromides (88·5% diaxial, 11·5% diequatorial) was distilled; b.p. 56–58°/0·6 mm, α_D − 0·98°. The pure diaxial dibromide (1·4 g), obtained by chromatography of the mixture on SiO_2, had α_D − 0·61°, α_{546} − 0·71°, α_{436} − 1·38°, α_{365} − 2·29°. From these data one can calculate α_D − 3·83° for the diequatorial dibromide. The remaining soln (1300 ml) was slowly distilled through a spinning band fractionating column. The fraction b.p. 101–102° (2·5 g) consisted of pure 3-methylcyclohexene, α_D − 0·58°, α_{546} − 0·66°, α_{436} − 1·18°, α_{365} − 1·93°.

(1S:2S:3S)-(+)-cis-2-trans-3-*Dibromomethylcyclohexane* (**5b**) *and* (1S:2R:3R)-(−)-trans-2-cis-3-*dibromomethylcyclohexane* (**6b**)

The olefin and the whole solvent obtained from the partial bromination of (±)-3-methylcyclohexene were combined; Et_3N (5·0 g) was added to the mixture and this was treated with an excess of the Br soln. The mixture of dibromides (7·8 g), obtained after the usual work-up, had b.p. 54–58°/0·4 mm, α_D + 0·12°, α_{546} + 0·14°, α_{436} + 0·27°. The pure diaxial dibromide (5·8 g) was obtained by chromatography on SiO_2; b.p. 60–62°/0·8 mm, n_D^{25} 1·5415, α_D + 0·31°, α_{546} + 0·36°, α_{436} + 0·69°, α_{365} + 1·24°. A sample of this dibromide was heated under N_2 at 150° for 2·5 hr. The mixture obtained, b.p. 58–62°/0·6 mm, α_D − 0·21°, α_{546} − 0·25°, α_{436} − 0·42°, α_{365} − 0·64°, contained the diaxial and the diequatorial dibromides in the ratio 75·3:24·7 (GLC). A similarly obtained mixture contained the two dibromides in the ratio 71·6:28·4, and had α_D − 0·30°, α_{546} − 0·34°, α_{436} − 0·59°, α_{365} − 0·94°. The NMR spectrum of the mixtures showed, beside the bands mentioned above for the diaxial compound, a complicated pattern of signals between δ 3·62 and 4·42 ppm, which can be attributed to the H_a of the diastereoisomer **6**, that must be essentially in the diequatorial conformation. Integration gave compositions which were very similar to those obtained by GLC. The optical rotation of the diequatorial dibromide in the mixtures is therefore α_D − 1·81°. By assuming for the olefin recovered in the half-bromination an optical purity of 0·9%,[4] the maximum rotations of **5b** and **6b** are, respectively, +34° and −201°.

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