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Chiral Chromenes: Synthesis, Separation of Enantiomers and Barriers to Racemization#

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2*H*–Chromenes **3** and **4** have been synthesized by reduction of the appropriate lactone with diisobutylaluminium hydride and subsequent *O*–alkylation of the resulting lactols. Separations or enrichments of enantiomers were achieved by liquid chromatography on triacetylcellulose and tribenzoylcellulose, (+)–**3** and (–)–**3** being separated almost completely, while an enrichment of the enantiomers of **4** was achieved by using the recycling procedure. The barriers for the interconversion of enantiomers of **3** and **4** were determined by thermal racemization of enantiomers.

INTRODUCTION

2*H*–Chromenes or 2*H*–1–benzopyranes have been the subject of extensive studies largely because of their photochromic behaviour which consists of a reversible photoisomerization involving a rupture of the C(sp^3) – O bond.[1] In connection with our previous studies on 2,2′–spirobichromenes,[2] we have prepared chiral chromenes **3** and **4** in order to separate their enantiomers and determine the unknown barriers for the interconversion of enantiomers.

Chiral 2*H*–Pyrans, Part 3; Part 2: Ref. 2.

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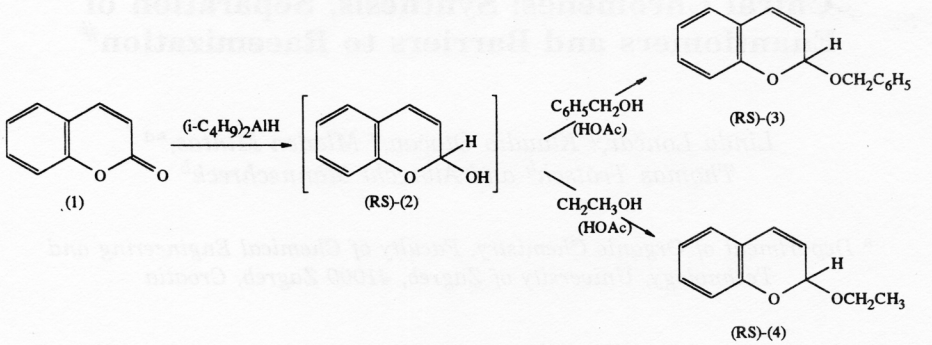
RESULTS

Synthetic Work

The desired novel chiral 2*H*–1–benzopyranes **3** and **4** were prepared by the following reaction sequence (Scheme 1).



Scheme 1

The reduction of the lactone carbonyl group which is conjugated with a carbon-carbon double bond in the coumarin (**1**) to the corresponding lactol-hemiacetal was performed by the highly specific reagent diisobutylaluminium hydride[3] at approximately –40 °C under nitrogen. That process was followed by monitoring gradual decrease in the infrared carbonyl absorption at 1730 cm^{-1} of **1** and eventually its complete disappearance. Compounds **3** and **4** were then obtained by treatment of the resulting hemiacetal which was not isolated either with benzyl or ethyl alcohol in the presence of catalytic amounts of acetic acid.

Separation of Enantiomers

The enantiomers of **3** and **4** were separated by liquid chromatography on triacetylcellulose (TAC) and tribenzoylcellulose (TBC). Capacity factors,[4,5] which correspond to the stabilities of diastereoisomeric sorbates, and polarimetric data of both enantiomers of (±)–**3** are given in Table I and the circular dichroism spectrum of (+)–**3** in Figure 1.

A complete preparative separation of enantiomers has been achieved for (±)–**3** as it can be seen from the analytical chromatogram showing no overlap of the peaks of the enantiomers (Figure 2). However, for chromene (±)–**4**, an enrichment of enantiomers was obtained by liquid chromatography on TAC using the recycling procedure. This pronounced difference in the chromatographic behaviour of both compounds may be explained by the presence of an additional phenyl group near the centre of chirality in **3** that markedly increases the retention differences of enantiomers. This is consistent with the earlier observation that separation of enantiomers in atropisomeric *N*–aryl–pyrroles[8,9] is improved by the presence of an additional phenyl group.

TABLE I.

Chromatographic and polarimetric properties of the enantiomers[a] of (±) — 3

	k		*P* / %	$[\alpha]_{365}$	$[\alpha]_{436}$	$[\alpha]_{546}$	$[\alpha]_{578}$
	TAC	TBC					
(+)–**3**	2.9	6.3	100	719 ± 67	236 ± 23	78 ± 9	61 ± 7
(–)–**3**	4.3	13.7	97	–721 ± 48	–238 ± 16	–80 ± 6	–63 ± 5

k: Capacity factors of enantiomers upon liquid chromatography on triacetylcellulose[5] (TAC) at 20 °C and 2.7 bar in EtOH/H_2O (96:4) and tribenzoylcellulose[6,7] (TBC) at 22 °C and 90 bar in MeOH.

P: Enantiomeric purity, determined by analytical low pressure liquid chromatography.

[α]: Specific rotation in MeOH at 22 °C

[a] [*P*] and [α] of the enriched samples of (+)– and (–)–**4** could not be determined because of a strong peak

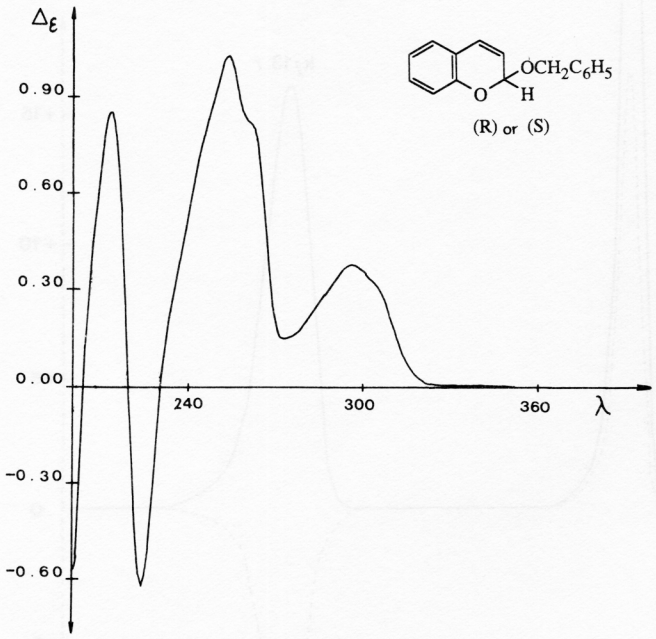


Figure 1. Circular dichroism spectrum of (+)–**3** in MeOH.

Barriers to Racemization

The barriers to the interconversion of enantiomers of **3** and **4** were determined by thermal racemization of preparatively enriched enantiomers. The first-order kinetics for this reaction was followed by polarimetry (Table II). The mechanism of interconversion of enantiomers requires a ring open *dienone* intermediate **5** with the most probable *Z*–stereostructure (Scheme 2). Though the postulation of such an intermediate is persuasive enough, there is no direct evidence for it. An alternative mechanism in-

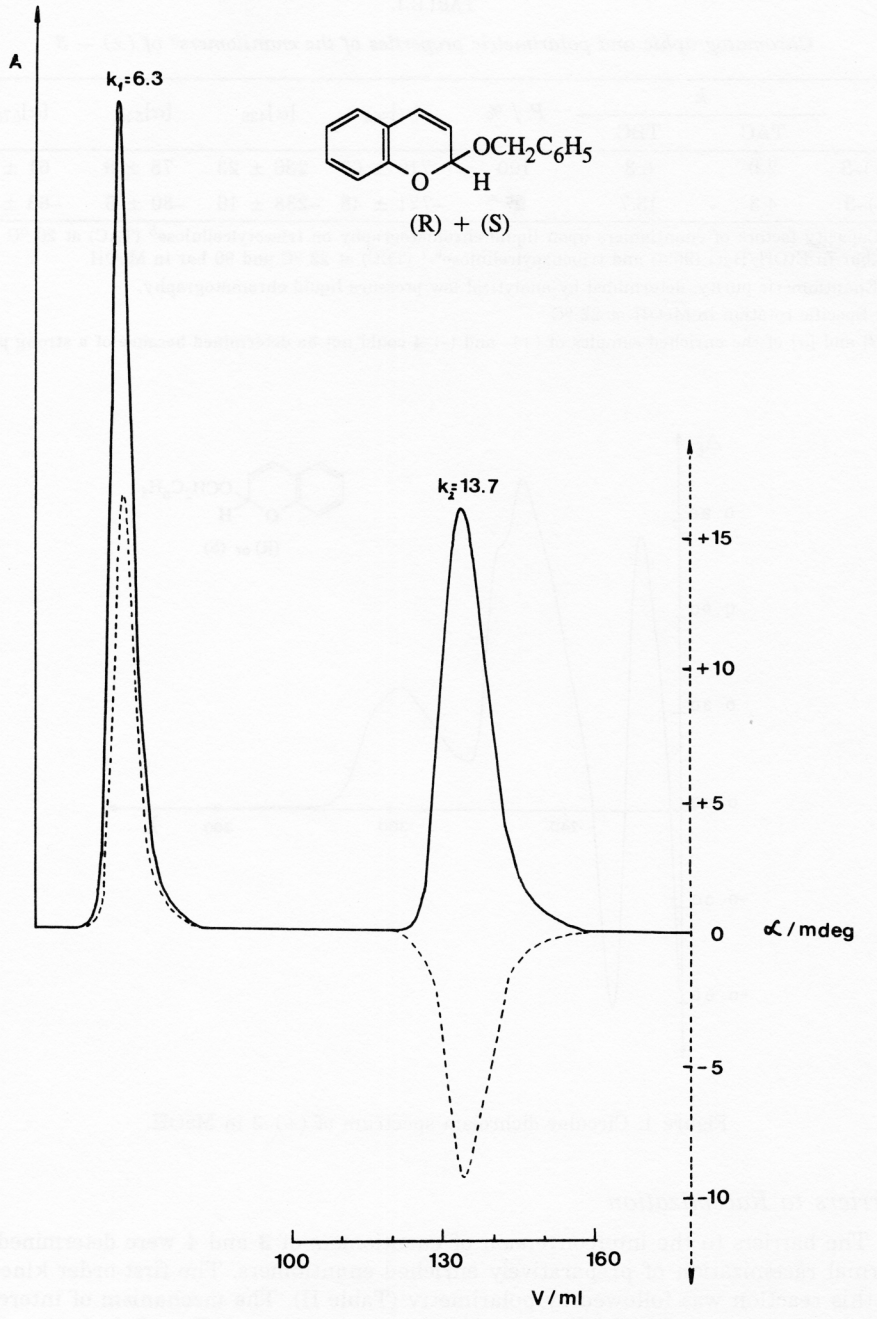


Figure 2. Liquid chromatogram of (±)–**3** in MeOH on tribenzoylcellulose. (-----) Rotational angle (α) at 405 nm; (———) Absorbance (A) at 278 nm; V, volume of eluate; k, capacity factor.

TABLE II

Barriers to the interconversion of enantiomers of ***3*** *and* ***4***

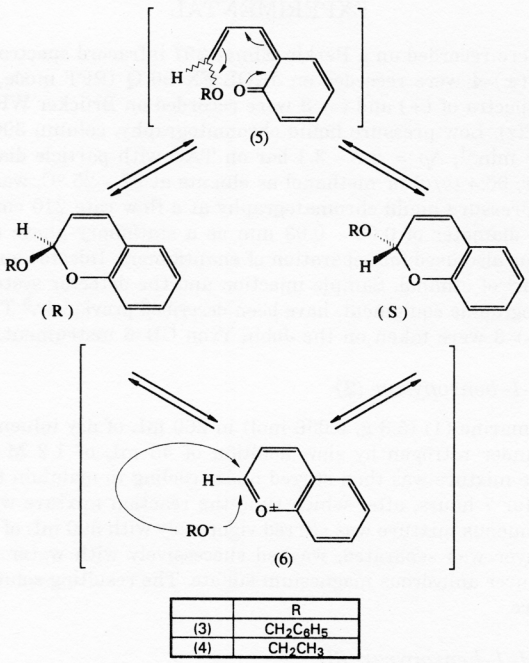
	R	Solvent	λ / nm	T / °C	$k \times 10^6$ / s^{-1}	$\Delta G^{\neq} / \pm 0.3$ / kJ mol^{-1}
3	$CH_2C_6H_5$	Diglyme	436	84.5	11.7	121.9
		Dioxane	365	80.0	4.8	122.9
		Dioxane	365	84.0	7.5	123.1
		CH_3CN	365	71.6	2.4	121.9
		CH_3CN	365	72.6	2.6	122.1
		C_4Cl_6	436	72.0	56.7	113.0
		C_4Cl_6	436	78.0	24.1	117.5
		C_4Cl_6	436	84.0	26.2	119.4[a]
4	C_2H_5	Diglyme	436	83.6	44.2	117.1
		Dioxane	365	83.6	19.9	120.0

λ: Wavelength at which racemization was followed by polarimetry

k: Rate constant

$\Delta G^{\neq}$: Free enthalpy of activation obtained by thermal racemization of a preparatively enriched enantiomer, calculated from k and T, according to the Eyring equation

[a] The mean value of two measurements



	R
(3)	$CH_2C_6H_5$
(4)	CH_2CH_3

Scheme 2

volving a chromylium cation **6** as an intermediate (Scheme 2) might also be operative in this case. Therefore, these results call for further mechanistic studies, *e.g. via* a change of medium.

The comparison shows that the $\Delta G^{\neq}$ values for the *O*–benzyl–derivative **3** in both solvents, diglyme and dioxane, are by 4.8 kJ/mol and 3 kJ/mol higher than the corresponding values for the *O*–ethyl–derivative **4** obtained in the same solvents and at almost identical temperatures (Table II). These differences may be attributed to the more severe steric interaction in the open-chain intermediate for the enantiomeric interconversion of chromene **3** than in that for **4**. It is interesting to note that the $\Delta G^{\neq}$ values for both compounds **3** and **4** are higher in dioxane than in diglyme (Table II). Furthermore, the $\Delta G^{\neq}$ value for **3** is significantly higher, *i.e.* by 8.9 kJ/mol in CH_3CN than in hexachlorobutadiene (C_4Cl_6) at almost the same temperatures (Table II). This might be explained by a difference in the polarities of the solvents.

In conclusion, the reduction of the lactones with diisobutylaluminium hydride and subsequent *O*–alkylation of the resulting lactols was shown to be an elegant way for the preparation of the chiral 2*H*–1–benzopyranes **3** and **4**. Furthermore, liquid chromatography on triacetylcellulose and tribenzoylcellulose was successfully applied for the separation of the enantiomers of (±)–**3** and (±)–**4**. The barriers to the thermally induced interconversion of enantiomers were measured for the first time in that class of chiral chromenes by racemization.

EXPERIMENTAL

The IR spectra were recorded on a Perkin Elmer 297 infracord spectrometer. The ^{1}H NMR spectra of (±)–**3** and (±)–**4** were recorded on JEOL FX–90 Q (PFT mode, 8 K data points, 90 MHz). The ^{1}H NMR spectra of (+) and (–)–**3** were recorded on Brucker WH 250 (PFT mode, 32 K data points, 250 MHz). Low pressure liquid chromatography, column 300 x 25 mm, at a flow rate of 228 – 250 cm^3 min^{-1}, Δp = 2.7 – 3.1 bar on TAC with particle diameter of 0.02 – 0.03 mm and ethanol:water, 96:4 (*v*/*v*) or methanol as eluents at 22 – 25 °C, was used for separation of enantiomers. Low pressure liquid chromatography at a flow rate 210 cm^3 min^{-1}, Δp = 2 bar on TBC with particle diameter of 0.02 – 0.03 mm as a stationary phase and methanol as the eluent at 22 – 25 °C was also used for separation of enantiomers. Injected quantities of racemates were 2 – 6 mg in 1 cm^3 of ethanol. Sample injection and the detector system, along with other details of the chromatographic equipment, have been described previously.[5] The circular dichroism spectra of (+)– and (–)–**3** were taken on the Jobin Yvon CD–6 instrument.

*(±)–2–Hydroxy–2H–1–benzopyran (**2**)*

A solution of coumarine (**1**) (5.3 g, 0.036 mol) in 260 mL of dry toluene was reduced at approximately –40 °C under nitrogen by slow addition of 45 mL of 1.2 M diisobutylaluminium hydride in toluene. The mixture was then stirred under cooling to maintain the reaction temperature of about –40 °C for 7 hours, after which time the reaction mixture was poured into 125 g of ice. The resulting aqueous mixture was stirred vigorously with 500 mL of chloroform for about 5 min, the organic layer was separated, washed successively with water and aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. The resulting solution was concentrated under reduced pressure.

*(±)–2–Benzyloxy–2H–1–benzopyran (**3**)*

The oily residue of **2** was heated under reflux with benzyl alcohol (7.5 mL 0.073 mol) and a few drops of acetic acid for 3 hours. Fractional distillation under reduced pressure with a 15x1.5 cm Vigreux column gave a colourless oil: in 17% yield, b.p. 110–114 °C / 0.0018 Torr; ^{1}H NMR ($CDCl_3$) δ: 4.70, 4.88 (AB, 2H, $^2J_{AB}$ = 12.0 Hz, CH_AH$_B$), 5.76 (d, 1H, ^3J = 3.8 Hz, 2–*H*), 5.87

(m, 1H, ^3J = 3.8 Hz, $^3J_{AB}$ = 9.6, 3-*H*), 6.75 (d, 1H, $^3J_{AB}$ = 9.6 Hz, 4-*H*), 6.93 – 7.43 (m, 9H, sp^2-*H*); UV (abs. MeOH) λ_{max} (log ε): 212 nm (4.49), 254 (3.93), 261 (3.86), 294 (3.45); IR (film) ν: 3060, 3030 (= C–H), 2920, 2860 (–C–H), 1635, 1600 (C = C), 1200 (C–O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}O_2$(238.3): C 80.65, H 5.92%; found: C 80.85, H 5.96%.

*(+)-and (–)-2-Benzoyloxy-2H-1-benzopyran (***3***)*

Preparative separation by low-pressure liquid chromatography on TBC using MeOH as an eluent (*c.f.* Figure 2). Colourless oils. The ^{1}H NMR spectra were in agreement with that of (±)-**3**. (+)-**3**: CD (MeOH, P = 0.97) : λ_{max} = 213 nm ($\Delta\varepsilon$ = +8.5 l cm^{-1} mol^{-1}), 224 (–6.1), 254 (10.2), 297 (3.7). (–)-**3**: CD (MeOH, P = 0.97): λ_{max} = 211 nm ($\Delta\varepsilon$ = –7.8 l cm^{-1} mol^{-1}), 224 (4.9), 254 (–9.7), 296 (–3.8). P-values were determined by low-pressure liquid chromatography.

*(±)-2-Ethoxy-2H-1-benzopyran (***4***)*

The oily residue of **2** prepared in the second charge was heated under reflux with ethyl alcohol (4.3 mL 0.073 mol) and a few drops of acetic acid for 3 hours. Fractional distillation under reduced pressure using a 15 x 1.5 cm Vigreux column gave a colourless oil in 14% yield, b.p.: 82–83 °C / 0.001 Torr. ^{1}H NMR ($CDCl_3$) δ: 1.2 (t, 3H, ^3J = 7.1 Hz, CH_3), 3.47–3.96 (m, 2H, ^2J = 17.6 Hz, ^3J = 7.1 Hz, CH_AH_B), 5.67 (d, 1H, ^3J = 3.8 Hz, 1H, 2-*H*), 5.74 (m, 1H, ^3J = 3.8 Hz and $^2J_{AB}$ = 9.6 Hz, 3-*H*), 6.70 (d, 1H, $^2J_{AB}$ = 9.6 Hz, 4-*H*), 6.8–7.3 (m, 4H, sp^2 *H*).

Anal. Calcd. for $C_{11}H_{12}O_2$176.2): C 74.98, H 6.86%; found: C 75.01, H 7.15%.

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SAŽETAK

Kiralni kromeni: sinteza, separacija enantiomera i barijere racemizacije

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Pripravljeni su novi 2*H*-kromeni **3** i **4** redukcijom odgovarajućeg laktona uz pomoć diizobutilaluminijeva hidrida i *O*-alkiliranjem nastalih laktola. Tekućinskom kromatografijom na triacetilcelulozi i tribenzoilcelulozi postignuta je gotovo potpuna separacija (+)-**3** i (–)-**3** enantiomera. Enantiomeri **4** obogaćeni su recikliranjem. Barijere za interkonverziju enantiomera **3** i **4** određene su termičkom racemizacijom enantiomera.