The Synthesis of Some Novel Polycyclic Chromans

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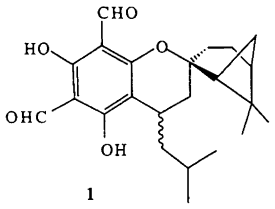
Some polycyclic compounds containing the chroman skeleton have been prepared by a two-step reaction sequence, starting from 5,7-dihydroxy-4-chromanone derivatives. Reactions of the chromanones with methallylzinc bromide followed by acid treatment proceeded with ring formation to polycyclic chromenes. With one exception these were not isolated, but hydrogenated catalytically to the corresponding chromans, which were formed in 71–87% overall yields. Some further derivatization has been carried out. The compounds have been tested *in vitro* for antimalarial acitivity.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

In connection with the synthesis of robustadial A and B (**1**),[1] two diastereomeric chroman derivatives isolated from the leaves of *Eucalyptus robusta*,[2] we encountered the transformation in high yield of the chromanone **2a** to the tricyclic chromene derivative **3a**, which was subsequently transformed into the corresponding chroman **4a** by catalytic hydrogenation. Although each of the reactions involved have some analogy in the literature,[3] the combination seemed novel, and we have encountered only a few examples of this particular heterocyclic ring assembly in the literature.[4,5] Furthermore, we were interested in analogues of robustadial for evaluation of antimalarial activity. The present paper describes the preparation of several compounds related to **4a**, including derivatives with a ring system spiro-bonded at the 2-position of one of the chroman rings, and thus closely resembling the structure of robustadial.



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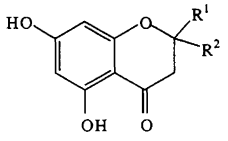
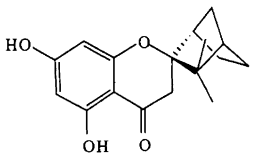
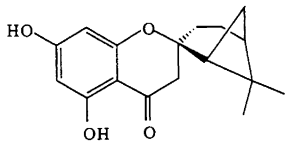


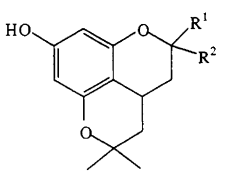
2 a: $R^1 = R^2 =$ Me
b: $R^1 = R^2 =$ -$(CH_2)_4$-
c: $R^1 = R^2 =$ -$(CH_2)_5$-



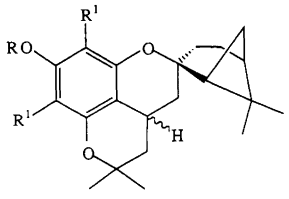
2 d



2 e



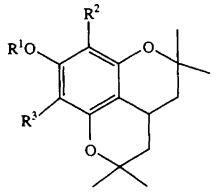
4 a: $R^1 = R^2 =$ Me
b: $R^1 = R^2 =$ -$(CH_2)_4$-
c: $R^1 = R^2 =$ -$(CH_2)_5$-

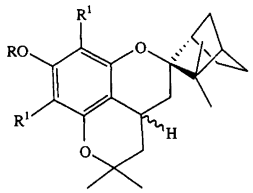


4 e: $R = R^1 =$ H

Results and discussion

The dihydroxychromanones **2** were prepared by a Friedel-Crafts type condensation of phloroglucinol with the respective α,β-unsaturated acid using aluminium trichloride in phosphoryl chloride, as previously reported.[1] The chromanones were converted into the corresponding homoallylic alcohols with methallylzinc bromide in THF. The organozinc derivative was formed in a few minutes from the metal and methallyl bromide under ultrasound conditions.[6] Because of the two hydroxy groups present in the chromanones the use of three equivalents of the organometallic compound was required, and the best results were actually obtained using an excess of this amount. The initially formed homoallylic alcohols were not isolated, but treated with aqueous 5% hydrochloric acid for a few minutes, to give the tricyclic chromenes **3**. We subsequently discovered that additional acid was not required; cyclisation took place when a THF solution of the alcohol was heated for some time. The crude chromenes were subsequently hydrogenated catalytically in ethanol solution to the chromans **4**, which were obtained in overall yields varying from 71 to 87%, based on the respective chromanone. The first two reactions were conveniently conducted as one-pot procedures. The structures were assigned on the basis of the spectroscopic data. The chromene **3a** was isolated and purified in order to determine its structure; otherwise the intermediate chromenes were not isolated and characterized. In the case of **4a** the presence of one hydroxy group was

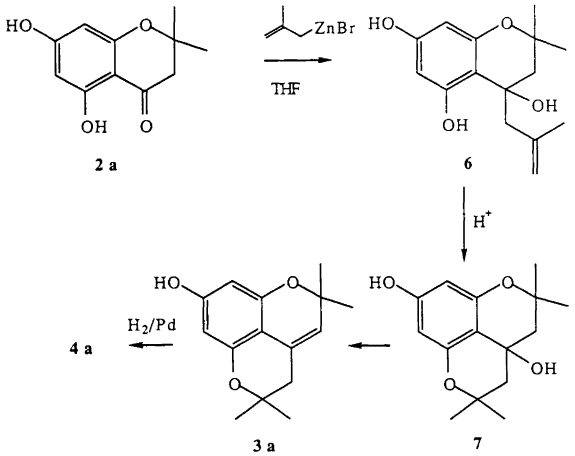




5 a: R^1 = Me; R^2 = R^3 = H
b: R^1 = H; R^2 = CHO; R^3 = H
c: R^1 = H; R^2 = R^3 = CHO
d: R^1 = Me; R^2 = R^3 = CHO
9: R^1 = R^2 = H; R^3 = Br

4 d: R = R^1 = H
8 a: R = H; R^1 = CHO
8 b: R = Me; R^1 = CHO

ascertained by preparing the methylated derivative **5a**, using methyl iodide and sodium carbonate in acetone.[7] The chroman **4d** was obtained as a 55:45 mixture of diastereomers, and in the case of **4e** a 9:1 mixture was obtained, as shown by the NMR spectra. We were unable to separate these mixtures. A rationalization of the results is given in Scheme 1, using the conversion of the chromanone **2a** as an example. The phenolic hydroxy group at the 5-position of the initially formed chromanol **6** undergoes acid-catalyzed addition to the double bond of the isobutenyl group, forming a new six-membered ring. The tricyclic alcohol **7** thus formed eliminates water to yield the chromene derivative **3a**. Apparently the phenolic hydrogens are sufficiently acidic to exert a catalytic effect on both these reactions. Subsequent hydrogenation of the chromene afforded the corresponding chroman **4a**. From unsymmetrically substituted analogs of **7**, mixtures of regioisomeric chromenes were obtained as indicated by the spectral data. In chromenes containing a chiral carbon the double bond is diastereotopic, and hydrogenation may give rise to mixtures of stereoisomeric chromans. This was observed in the cases of **4d** and **4e**, which were formed as inseparable mixtures of diasteromers.



Scheme 1.

Since we were engaged in the synthesis of robustadial analogs for biological evalutation as potential antimalarial compounds, the incorporation of aldehyde functions into the chroman derivatives was of particular interest. The chroman **4a** was used as a model substance in order to find a convenient formylation method. To our surprise, the introduction of two aldehyde groups was not an easy task. The monoaldehyde **5b** was readily available by all the methods employed, but the dialdehyde **5c** was formed only from the reaction of **4a** with dichloromethyl methyl ether and titanium tetrachloride in dichloromethane.[8] Subsequently, the dialdehyde **8** was also prepared by this procedure, but in both cases the yields were less than 50%. The hydroxy group of both aldehyde derivatives was methylated with methyl iodide in the usual way. Reaction of **4a** with bromine at room temperature afforded the monobromide **9** as a crystalline compound in practically quantitative yield.

Compounds **4-6**, **8** and **9** were tested *in vitro* for antimalarial activity against a resistant strain of *Plasmodium falciparum*.[9] Several of the compounds exhibited activity, but not at a concentration that would be regarded as interesting.

Experimental

General. GLC analyses were performed on a 30 m capillary column of SP2100. IR spectra were recorded on a Perkin Elmer 1310 instrument. NMR spectra were obtained on Varian XL-300 and 200 and mass spectra on Micromass 7070 F instruments. Capillary melting points were taken on a Büchi SMP-20 apparatus and are uncorrected.

*2,2,5,5-Tetramethyl-3,3a,4,5-tetrahydro-2*H*-pyrano[4,3,2-de]-1-benzopyran-8-ol* (**4a**). A solution of methallyl bromide (31.5 g, 0.23 mol) in THF (100 ml) was added over 20 min to a suspension of activated zinc (47.5 g, 0.88 mol) in THF (200 ml) using ultrasound for stirring. After 1 h at room temperature the chromanone **2a**[1] (10.4 g, 50 mmol) in THF (150 ml) was added dropwise over 30 min. After 1 h at room temperature, aq. HCl (5%, 100 ml) was added and the mixture was stirred for 20 min. The organic phase was separated and the aq. phase extracted with ether. The combined organic phase was dried ($MgSO_4$) and the solvents evaporated off. The crude chromene **3a**, m.p. 109–110°C (from CH_2Cl_2), was dissolved in ethanol (300 ml) and hydrogenated in a Parr apparatus using Pd/C (10%, 1.0 g) as the catalyst. Evaporation of solvents and purification by flash chromatography on silica gel (pet. ether–EtOAc 85:15) afforded the chroman **4a** (10.9 g, 87%) as colorless crystals, m.p. 147–149°C, from EtOAc. **3a**: IR ($CHCl_3$): 3560, 3400–3200, 1620, 1590, 1450, 1140 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 6 H), 1.41 (s, 6 H), 2.31 (d, *J* 1.6 Hz, 2 H), 5.09 (t, 1 H), 5.89 (d, 1 H), 5.94 (d, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.68, 29.34 (CH_3), 39.50 (CH_2), 77.30, 78.08 (C), 96.54, 96.61 (CH), 101.32 (C), 120.50 (CH=), 124.08 (C=), 152.91, 153.84, 157.91 (C). **4a**: IR (KBr): 3600, 3450–3200, 1650, 1600, 1455, 1140 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.3–1.4 (m, 14 H),

1.80 (dd, *J* 13.5 Hz, 2 H), 2.80 (m, 1 H), 5.76 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.29 (CH), 25.87, 30.35 (CH_3), 39.98 (CH_2), 74.87 (C), 94.73 (CH), 98.43, 154.06, 157.30 (C–O). Methylation[7] afforded **5a** (65%), m.p. 140–142°C. IR (CCl_4): 2960, 2920, 1250, 1145 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.3–1.4 (m, 14 H), 1.82 (dd, *J* 13.5 Hz, 2 H), 2.80 (m, 1 H), 3.76 (s, 3 H), 5.76 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.18 (CH), 26.10, 29.08, 30.26 (CH_3), 38.84, 39.10 (CH_2), 64.78 (CH_3O), 76.54 (C), 96.88 (CH), 98.13 (C), 101.20 (CH), 154.12, 157.15, 157.65 (C–O).

5',5'-Dimethyl-3',3a',4',5'-tetrahydrospiro{cyclopentane-1,2'-[2H]pyrano[4,3,2-de][1]benzopyran}-8'-ol (**4b**). The chromanone **2b**[1] (2.5 g, 10.7 mmol) in THF (75 ml) was treated with methallyl bromide (7.5 g, 54.8 mmol) and activated zinc (13.4 g, 0.2 mol) in THF (170 ml) and the crude product was subsequently treated with acid, hydrogenated and purified as described for **4a**. The chroman **4b** (2.30 g, 78%) was obtained as colorless crystals, m.p. 153–154°C, from CH_2Cl_2. IR ($CHCl_3$): 3600, 3500–3200, 1600, 1440, 1140 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 3 H), 1.42 (s, 3 H), 1.60–2.05 (m, 12 H), 2.85 (m, 1 H), 5.89 (s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.20, 25.40 (CH_2), 27.80 (CH_3), 31.90 (CH), 38.50, 38.70, 40.08, 41.20 (CH_2), 76.40, 87.90 (C), 95.70, 95.80 (CH), 101.20, 154.50, 156.00 (C–O).

5',5'-Dimethyl-3',3a',4',5'-tetrahydro{spirocyclohexane-1,2'-[2H]pyrano[4,3,2-de][1]benzopyran}-8'-ol (**4c**). The chromanone **2c**[1] (2.0 g, 8.0 mmol) in THF (50 ml) was treated with methallyl bromide (5.2 g, 38.0 mmol) and activated zinc (10.0 g, 0.15 mol) in THF (120 ml) and the crude product subsequently treated with acid, hydrogenated and purified as described for **4a**. The chroman **4c** (1.85 g, 80%) was obtained as colorless crystals, m.p. 92–93°C (from CH_2Cl_2). IR ($CHCl_3$): 3580, 3500–3200, 1590, 1440, 1120 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (m, 2 H), 1.39 (s, 3 H), 1.48 (s, 3 H), 1.50–1.70 (m, 7 H), 1.71–2.00 (m, 5 H), 2.88 (m, 1 H), 5.91 (dd, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.56 (CH_3), 22.80, 22.78, 26.83 (CH_2), 26.96 (CH_3), 31.28 (CH), 35.24, 38.99, 40.06, 40.27 (CH_2), 76.22, 76.80 (C), 95.44, 95.69 (CH), 101.50, 154.20, 155.90 (C–O).

3,3,5',5'-Tetramethyl-3',3a',4',5'-tetrahydrospiro{bicyclo[2.2.1]heptane-2,2'-[2H]pyrano[4,3,2-de][1]benzopyran}-8'-ol (**4d**). The chromanone **2d**[1] (9.0 g, 31.6 mmol) was treated with an excess of methallyl bromide (21.4 g, 0.15 mol) and zinc (37.9 g, 0.55 mol) in THF (230 ml), and the crude product was subsequently treated with acid, hydrogenated and purified as described for **4a**. The chroman **4d** (8.63 g, 82%) consisted of a 55:45 mixture of diastereomers which could not be separated, and the spectral data were recorded on the mixture. IR (CCl_4): 3580, 3400–3300 (w), 1620, 1450, 1240, 1140 cm^{-1}. MS [CI, (% rel. int.)]: *m/z* 329 (100), 328 (21). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94–1.42 (m, 36 H), 1.53–1.82 (m, 6 H), 1.95–2.08 (m, 2 H), 2.12–2.40 (m, 4 H), 2.69 (m, 2 H), 4.44 (br s, 2 H), 5.85 (s, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): Major isomer: δ 21.95 (CH_2), 22.49 (CH), 22.65, 24.95, 25.85 (CH_3), 29.32 (CH_2), 30.26 (CH_3), 34.18, 39.46 (CH_2), 45.71 (C), 49.05 (CH), 50.45 (CH), 75.37, 86.67 (C), 94.10 (CH), 100.30, 154.12, 154.62, 155.93 (C–O). Minor isomer: δ 22.03 (CH_2), 23.48 (CH), 22.80 (CH_3), 24.03 (CH_2), 25.43, 26.35, 30.12 (CH_3), 31.81, 34.48, 39.64 (CH_2), 44.62 (CH), 45.44 (C), 51.87 (CH), 75.10, 87.29 (C), 94.31 (CH), 100.39, 153.63, 155.22, 155.93 (C–O).

5',5',6,6-Tetramethyl-3',3a',4',5'-tetrahydrospiro{bicyclo[3.1.1]heptane-2,2'-[2H]pyrano[4,3,2-de][1]benzopyran}-8'-ol (**4e**). The chromanone **2e**[1] (1.00 g, 3.5 mmol) in THF (25 ml) was treated with methallyl bromide (2.05 g, 15 mmol) and activated zinc (3.43 g, 52.5 mmol) in THF (35 ml) and the crude product was subsequently treated with acid, hydrogenated and purified as described for **4a**. The chroman **4e** (0.82 g, 71%) was obtained as a 9:1 mixture of diastereomers, which could not be separated, and the spectral data were recorded on the mixture. IR ($CHCl_3$): 3580, 3400–3300, 1610, 1440, 1140 cm^{-1}. Major isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (m, 1 H), 1.02 (s, 3 H), 1.26 (m, 2 H), 1.29 (s, 3 H), 1.36 (s, 3 H), 1.41 (s, 3 H), 1.70–2.90 (m, 9 H), 2.85 (m, 1 H), 5.85 (s, 2 H). Major isomer: ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.44 (CH), 23.51 (CH_3), 25.19 (CH_2), 26.01 (CH_3), 26.88 (CH_2), 27.64 (CH_3), 28.80 (CH_2), 30.39 (CH_3), 38.19 (C), 39.39 (CH_2), 39.96 (CH), 40.55 (CH_2), 53.66 (CH), 75.57, 81.67 (C), 94.55, 95.09 (CH), 100.88 (C), 154.22, 155.79 (C–O).

7-Formyl-2,2,5,5-tetramethyl-3,3a,4,5-tetrahydro-2H-pyrano[4,3,2-de]-1-benzopyran-8-ol (**5b**). To a stirred solution of chroman **4a** (250 mg, 1 mmol) and triethyl orthoformate (2.0 ml, 12 mmol) in ether (30 ml) was added aluminium trichloride (400 mg, 3 mmol) at 0°C. The mixture was then stirred at room temperature for 1 h. Water (50 ml) was added and the solution was extracted with ether. The extract was dried ($MgSO_4$) and the solvent evaporated off. Flash chromatography (silica gel, pet. ether–EtOAc, 9:1) afforded **5b** (170 mg, 62%) as colorless crystals, m.p. 126–128°C. IR ($CHCl_3$): 2960, 2920, 1660, 1295, 1160 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35–1.55 (m, 14 H), 1.88 (dd, *J* 13 Hz, 2 H), 2.81 (m, 1 H), 5.82 (s, 1 H), 10.03 (s, 1 H), 12.11 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.11 (CH), 26.10, 30.08 (CH_3), 30.18 (CH), 38.68, 38.95 (CH_2), 76.88 (C), 95.20 (CH), 98.21, 105.08, 157.54, 162.05, 163.82 (C), 191.55 (C=O).

7,9-Diformyl-2,2,5,5-tetramethyl-3,3a,4,5-tetrahydro-2H-pyrano[4,3,2-de]-1-benzopyran-8-ol (**5c**). A solution of the chroman **4a** (1.0 g, 4.0 mmol) in CH_2Cl_2 (50 ml) and $TiCl_4$ (3.03 g, 16 mmol) was cooled in ice, and dichloromethyl methyl ether (1.5 g, 13.0 mmol) was added with

stirring. Stirring was continued for 7 h after which aq. H_2SO_4 (5%, 20 ml) was added, and the organic phase was separated. The aq. phase was extracted with ether, and the combined organic phases were dried ($MgSO_4$). Evaporation of solvents followed by flash chromatography of the crude product gave the yellow dialdehyde **5c** (580 mg, 48%). IR (CCl_4): 2960, 2930, 1735, 1675, 1200, 1125 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 6 H), 1.46 (dd, 2 H), 1.53 (s, 6 H), 1.95 (dd, *J* 13.2 Hz, 2 H), 2.85 (m, 1 H), 10.21 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.77 (CH), 26.12, 29.83 (CH_3), 38.38 (CH_2), 78.77, 97.68 (C), 104.88, 162.55, 166.68 (C–O), 189.19, 189.29 (CH=O). Methylation in the usual way[7] afforded **5d** (75%) as light yellow crystals, m.p. 138–140°C. IR ($CDCl_3$): 2980, 1820, 1790, 1670, 1450, 1130 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 6 H), 1.47 (dd, 2 H), 1.53 (s, 6 H), 1.97 (dd, 2 H), 2.90 (m, 1 H), 3.96 (s, 3 H), 10.29 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.11 (CH), 26.13, 29.78 (CH_3), 38.09 (CH_2), 63.89 (O–CH_3), 78.22, 102.95, 111.08, 161.13, 165.33 (C), 187.16 (CH=O).

7,9-Diformyl-3,3,5',5'-tetramethyl-3',3a',4',5'-tetrahydrospiro{bicyclo[2.2.1]heptane-2,2'-[2H]pyrano[4,3,2-de]-[1]benzopyran}-8'-ol (**8a**). A solution of the chroman **4d** (1.0 g, 3.0 mmol) and $TiCl_4$ (2.27 g, 12 mmol) in CH_2Cl_2 (50 ml), cooled in ice, was treated with dichloromethyl methyl ether (1.10 g, 9.6 mmol) as described for **5c**. Flash chromatography (silica gel, pet.ether–EtOAc 8:2) gave the dialdehyde **8a** (0.52 g, 45%) as a yellow liquid, consisting of a 55:45 mixture of stereoisomers. These could not be separated and the spectral data were recorded on the mixture. IR (CCl_4): 2975, 2930, 1730, 1680, 1200, 1130 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (m, 6 H), 0.99 (m, 6 H), 1.11–1.43 (m, 18 H), 1.52 (s, 6 H), 1.61 (m, 4 H), 1.86 (m, 4 H), 2.16 (m, 4 H), 2.34 (m, 2 H), 2.70 (m, 2 H), 10.13 (s, 1 H), 10.15 (s, 1 H), 10.20 (s, 1 H), 10.26 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.65 (CH), 21.74, 21.94 (CH_2), 22.60 (CH_3), 22.80 (CH), 23.53, 23.92 (CH_2), 25.14, 25.74, 26.08, 26.31 (CH_3), 28.62 (CH_2), 29.64, 29.80 (CH_3), 31.05, 34.31, 34.58, 38.55, 38.69 (CH_2), 45.27, 45.45 (C), 46.28, 48.82, 50.22, 51.74 (CH), 77.95, 78.30, 90.82, 91.56, 98.23, 98.26, 104.31, 104.53, 105.27 (C), 163.00, 166.66, 166.92, 189.40, 189.80 (CH). Methylation in the usual way[7] afforded **8b** (73%) as a mixture of stereoisomers. The spectral data were recorded on the mixture. IR (film): 2960, 1685, 1625, 1570, 1445, 1300, 1145 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88–1.58 (m, 36 H), 1.60–2.00 (m, 8 H), 2.10–2.60 (m, 4 H), 2.74 (m, 2 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 10.27 (s, 1 H), 10.28 (s, 1 H), 10.30 (s, 1 H), 10.33 (s, 1 H).

Isomer I: ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.73 (CH_2), 22.13 (CH), 22.45 (CH_3), 23.99 (CH_2), 25.76, 26.18, 29.63 (CH_3), 30.87, 34.57, 38.50 (CH_2), 45.32 (C), 50.25, 51.76 (CH), 63.97 (CH_3O), 77.93, 90.95, 103.46, 110.41, 110.61, 160.69, 161.14, 165.79 (C), 186.95 (CH).

Isomer II: ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.79 (CH_2), 22.45 (CH_3), 22.60 (CH), 23.62 (CH_2), 25.22, 26.18 (CH_3), 28.30 (CH_2), 29.80 (CH_3), 34.60, 38.41 (CH_2), 45.08 (C), 46.19, 48.88 (CH), 63.85 (CH_3O), 78.30, 90.21, 103.46, 110.84, 111.46, 160.86, 161.19, 165.50 (C), 186.70 (CH).

7-Bromo-2,2,5,5-tetramethyl-3,3a,4,5-tetrahydro-2H-pyrano[4,3,2-de]-1-benzopyran-8-ol (**9**). A solution of the chroman **4a** (1.25 g, 5.0 mmol) and bromine (1.20 g, 7.5 mmol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 24 h. The crystalline residue remaining after evaporation of solvent was recrystallized from cyclohexane to give the bromide **9** (1.53 g, 93%), m.p. 172–173°C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.37–1.55 (m, 14 H), 1.88 (dd, *J* 13.2 Hz, 2 H), 2.80 (m, 1 H), 5.80 (s, 1 H), 12.09 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.08, 26.16 (CH), 30.01, 30.22 (CH_3), 38.47, 39.00 (CH_2), 77.11 (C), 95.15 (CH), 98.16, 110.88, 154.10, 157.28, 158.91 (C).

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