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The Synthesis of (−)-Robustadial A and Some Analogues

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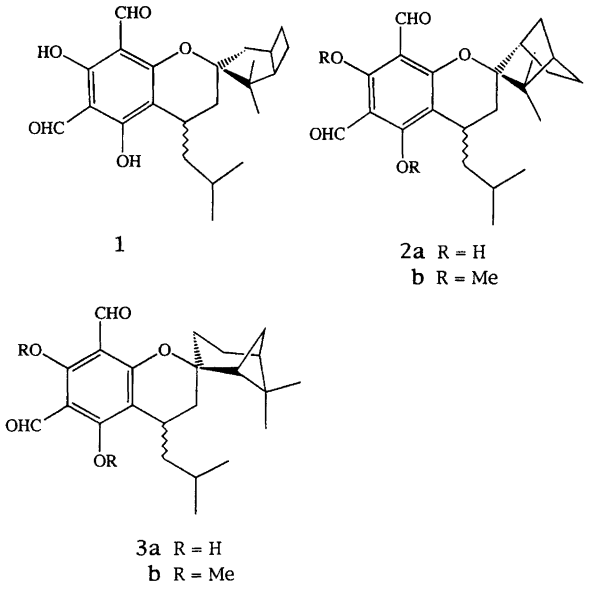
The naturally occurring chroman derivative, robustadial A, and several analogues have been prepared by a four-step synthesis starting from phloroglucinol. The synthetic scheme involves as the first step a Friedel–Crafts condensation of an α,β-unsaturated acid derivative with phloroglucinol to the corresponding chromanone. The isobutyl group at the 4-position was introduced with methallylzinc bromide followed by hydrogenation, carried out as a one-pot reaction. Finally, both aldehyde functions were attached using dichloromethyl methyl ether and titanium tetrachloride. Optically pure 6,6-dimethylbicyclo[3.1.1]heptan-2-ylideneacetic acid, needed for the synthesis of robustadial, was prepared from (−)-nopol by two consecutive oxidations in 77% overall yield.

The incidence of drug resistance is a serious problem in the treatment of malaria, and there is great need for new therapeutic agents for combating the disease. In 1986 Xu *et al.*[1] isolated two diastereomeric compounds robustadial A and B, from an extract of *Eucalyptus robusta* leaves, an old Chinese remedy for malaria. The compounds exhibited strong activity against *Plasmodium berghei in vivo*. The authors assigned the general structure **1** to the diastereomers, differing in the configuration at the carbon bearing the isobutyl group. However, the assignment of the terpene substructure was subsequently proved by synthesis to be incorrect, and the structures **2a** containing the camphane skeleton were proposed.[2] The methylated derivatives **2b** were synthesized and shown to be structurally different from those of the natural products.[3] The structures of the robustadials were finally established independently by Salomon *et al.*[4] and by Snyder[5] as the diastereomers **3a**, containing a spiro-annulated pinane framework. The former group synthesized stereoselectively the methylated robustadials **3b**, starting from (+)-nopinone, and determined the absolute configuration of the naturally occurring compounds based on an X-ray diffraction analysis of a bromine-containing intermediate.[4] Recently, Hoffmann *et al.*[6] and Majewski *et al.*[7] have reported stereoselective syntheses of the methyl ethers of robustadials A and B, starting from (−)-β-pinene.

The original assignment of structures **1** to the robustadials triggered our interest in synthesizing the compounds mainly because the terpene moiety was available to us from some previous research.[8] Although it was this terpene part that was subsequently changed as a result of new structural proposals, our interest in the total synthesis of the robustadials continued, and in this paper we describe our effort that led to the synthesis of robustadial A, the camphane isomers, as well as several other analogues.

Results and discussion

Retrosynthetic analysis suggested a chromanone of the general structure **4** as an intermediate in our synthesis;



Scheme 1.

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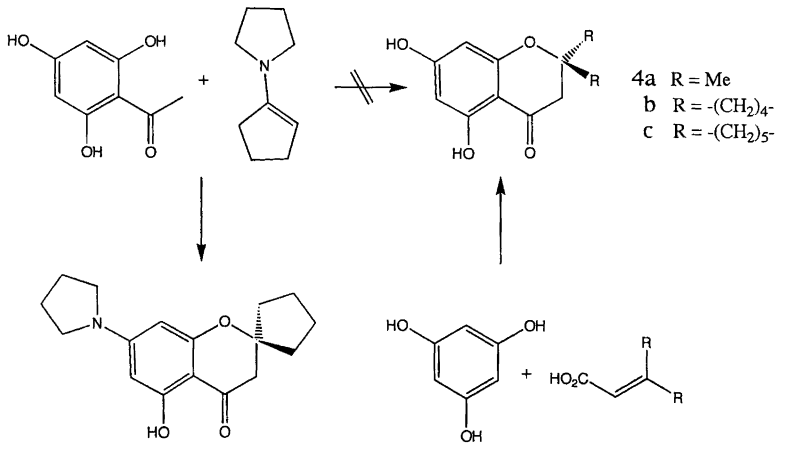
introduction of the isobutyl group followed by formylation should lead to the target molecules. We wanted to use as a model the dihydroxychromanone **4b** with a spiroannulated five-membered ring. Among the methods for chromanone synthesis the reaction of 2-hydroxyacetophenone derivatives with 1-pyrrolidinocyclopentene was known to give good yields,[9] but attempts to prepare **4b** from 2,4,6-trihydroxyacetophenone by this procedure resulted in formation of a crystalline compound, $C_{17}H_{21}NO_3$, as sole product in 85% yield. Chemical and spectral evidence was not conclusive, and the structure **5** for this compound was eventually secured by X-ray crystallography.[10] To our initial surprise a nucleophilic aromatic substitution had formally occurred, the displacement of a hydroxy group by an amine being reminiscent of the classical Bucherer reaction.[11] Our result could have been anticipated since a literature search revealed that ApSimon *et al.*[12] obtained a similar result from the reaction of 2,4,6-trihydroxyacetophenone with acetone and pyrrolidine. The reaction may very well proceed by addition of pyrrolidine to the tautomeric quinoid form of the acetophenone, a reaction promoted by the additional hydroxy group. Hence, we had either to look for a different route to **4b** or choose another chromanone derivative as the model compound. We opted for the latter alternative since the dimethylchromanone **4a** was readily available by condensing phloroglucinol with 3-methyl-2-butenoic acid under the influence of aluminium chloride in phosphorus oxychloride as solvent.[13] Subsequently we found that reactions of phloroglucinol with cyclopentylideneacetic acid and cyclohexylideneacetic acid under the same conditions afforded the crystalline chromanones **4b** and **4c** as sole products in 81% and 82% yields, respectively. Not unexpectedly the isomeric acid 1-cyclopentenylacetic acid undergoes the condensation equally well under the same conditions.

Using the chromanone **4a** as model, an efficient way of introducing the isobutyl group at C-4 was sought. Alkylation with methallylzinc bromide proved convenient. The reagent was formed from zinc and methallyl bromide in THF in a few minutes under ultrasonic conditions. The reaction with **4a** afforded the alcohol **6**, which without isolation was treated with dilute hydrochloric acid, and subsequently subjected to catalytic hydrogenation. The product was formed in 87% overall yield from the chromanone and was shown to be the tricyclic derivative **7**. Its formation is readily explained by an acid-catalysed intramolecular addition of the phenolic hydroxy group to the isobutylene double bond followed by hydrogenation of the remaining double bond. Several tricyclic chroman derivatives have been prepared by this procedure,[14] of which the cyclisation step also constitutes a convenient route to chromenes.[15] Clearly, acids must be avoided as long as the terminal double bond of compound **6** is still intact. The desired isobutyl-substituted chromans **8** were finally obtained in excellent yields by first hydrogenating catalytically an ethanol solution of **6** until the terminal double bond was saturated, followed by further hydrogenation in the presence of a trace of sulfuric acid. The conversion was conveniently carried out as a one-pot procedure.

Introduction of the aldehyde functions caused the most serious problem. Several experiments were carried out with the chroman **8a** in order to find a suitable method. The reaction with triethyl orthoformate and aluminium chloride afforded the monoaldehyde **9** in 71% yield as light yellow crystals, and the Vilsmeier, Gattermann, Reimer–Tiemann and Duff reactions, respectively, also gave the same aldehyde in poorer yields. None of these methods produced a detectable amount of the dialdehyde **10a** under a variety of experimental conditions. The position of the formyl group in the monoaldehyde **9** could not be secured from the NMR data and is based mainly on analogy; Robertson and Subramaniam[16] have shown unequivocally by chemical means that formylation of 5,7-dihydroxy-2,2-dimethylchroman by the Gattermann



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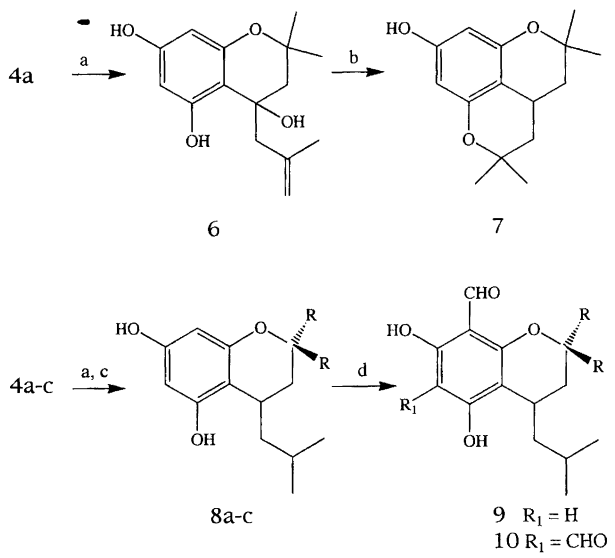
Scheme 2.

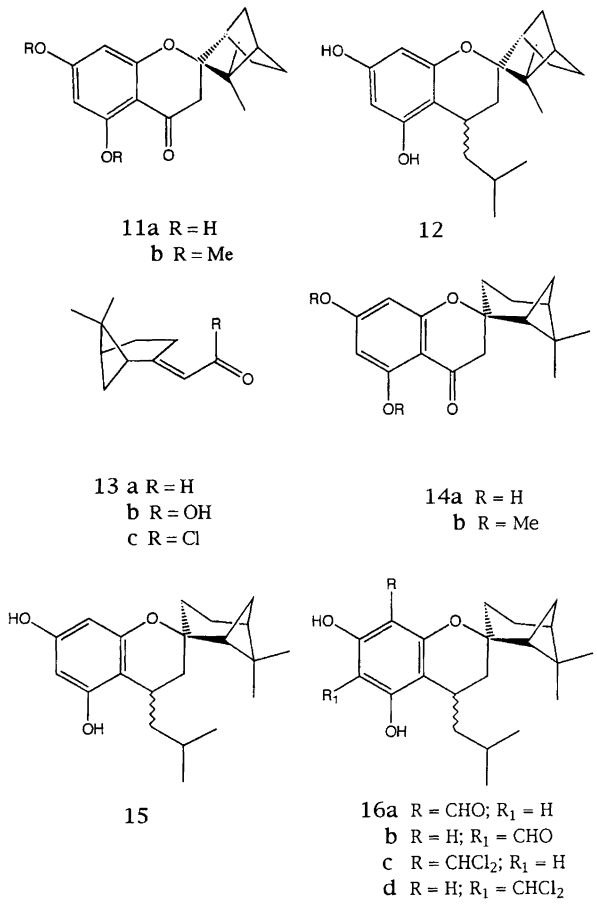


Scheme 3. Reagents: a, Methallylzinc bromide–THF; b, HCl, (ii) H_2–Pd; c, (i) H_2–Pd, (ii) H_2SO_4, H_2–Pd; d, Cl_2CHOMe–$TiCl_3$–$CHCl_3$.

method occurred exclusively at the 8-position. Finally, the dialdehyde was obtained in 45% yield from a reaction of **8a** with a large excess of dichloromethyl methyl ether and titanium tetrachloride in chloroform at room temperature (Rieche reaction).[17] Similar treatment of the chromans **8b** and **8c** provided the corresponding dialdehydes **10b** and **10c** in moderate yields. We have so far been unable to improve on the rather unsatisfactory yields of this formylation reaction.

Having attained a synthetic strategy that appeared reasonable, we turned to the camphenyl analogues **2**, which at the time were actually the structures suggested for the robustadials by Salomon *et al.*[2] For the chromanone step camphene-8-carboxylic acid was required. It was prepared from commercially available 90% optically pure (−)-camphene by a Prins reaction followed by chromium trioxide oxidation of the intermediate alcohol.[18] The reaction of the acid with phloroglucinol, by the same method as that used for the synthesis of compounds **4**, furnished at 9:1 mixture of stereoisomeric chromanones **11**, from which the pure *exo*-isomer **11a** was obtained in 73% yield after one recrystallization from chloroform. Methylation with methyl iodide and potassium carbonate in acetone provided the dimethoxy derivative **11b**, the spectral properties of which agree well with those published.[3] Reaction of the chromanone **11a** with methallylzinc bromide in THF provided the chroman **12** in 72% yield as a 55:45 mixture of diastereomers. The major isomer was separated by recrystallization from methylene chloride and subsequent formylation with the Rieche reaction furnished the dialdehyde *cis*-**2a** as a yellow crystalline compound in 46% yield. In contrast with the other methods we tried, the isomeric monoaldehydes were formed initially as a practically 1:1 mixture. This was clearly seen from the ^1H NMR spectrum of a sample taken after a few minutes reaction time; signals due to aldehyde protons appeared at δ 10.02 and 10.21, while the aromatic protons gave rise to resonances at 5.84 and 5.91. Further conversion into the dialdehyde required several hours for completion. The diastereomer *trans*-**2a** was obtained by formylation of an enriched sample of the minor chroman isomer **12**. Methylation afforded the corresponding dimethoxy derivatives **2b**, with spectral data in good agreement with those published.[3]

At this time Salomon and co-workers had shown by synthesis of the methylated derivatives that the assignment of structures **2a** to the natural products was erroneous;[3] they suggested instead the diastereomers **3a** with the pinane skeleton spiro-annulated to the chroman ring system, and this was subsequently shown to be correct by synthesis of the dimethoxy derivatives **3b**.[4] We set out to synthesize **3a** by the same sequence of reactions as used for the synthesis of the camphane-containing isomers. The acid **13b**, required for the condensation reaction with phloroglucinol, was prepared in two steps from commercial (−)-nopol of better than 98% optical purity. Swern oxidation proceeded to the aldehyde with double-bond migration, furnishing a 4:1 mixture of (*E*)- and (*Z*)-**13a** in high yield. Further oxidation of the aldehydes with oxygen in the presence of benzoyl peroxide gave a corre-



Scheme 4.

sponding stereoisomeric mixture of the acid **13b** as a viscous liquid, that could not be separated by chromatography. However, oxidation with ethanolic silver nitrate gave the desired *E*-isomer as the only product in 77% overall yield from (−)-nopol. No detectable amount of the isomer with an endocyclic double bond was formed by either procedure, but several other oxidation methods gave complex mixtures of products resulting from rearrangements. The configurations of the acids were determined essentially on evidence from the NMR spectra. In the ^{1}H spectrum, the allylic bridgehead proton appears as triplets at δ 2.45 and 3.45 for the major and minor components, respectively; hence, the latter was assigned the *Z* -configuration due to the deshielding effect of the carbonyl group. For the same reason, the allylic bridgehead proton of *E*-camphene-8-carboxylic acid appears at δ 4.04 in the ^{1}H NMR spectrum.[18] A similar low-field shift was observed for the *Z*-aldehyde. Reaction of the acid (*E*)-**13b** with phloroglucinol, under the same conditions that successfully led to the camphenyl chromanones **11**, gave rise to a mixture of products. Rearrangement of the terpene framework had occurred, which was avoided by changing both reagents and reaction conditions. The acid chloride (*E*)-**13c** reacted with phloroglucinol in the presence of aluminium chloride at room temperature to a 55:45 mixture of diastereomeric chromanones of which **14a** was the major isomer. On replacement of aluminium chloride with zinc chloride, the condensation proceeded in better yield and the isomer ratio improved to 9:1. The best result, both stereochemically and with respect to yield, was achieved by reacting the acid chloride with phloroglucinol in the presence of zinc chloride with ether as the solvent. Heating an ethanol solution of the crude intermediate with potassium carbonate for several hours furnished the chromanone **14a** as sole product in 75% yield. The presence of a singlet at δ 6.85 in the intermediate showed that the double bond remained exocyclic during this process. A similar stereoselective ring closure has been reported by Majewski and Bantle.[19] Methylation furnished the dimethoxychromanone **14b** with spectral data in good agreement with those published.[4] Hence, the isomer **14a** has the same configuration of the terpene substructure as that of the natural products. Introduction of the isobutyl group, using methallylzinc bromide as described above, proceeded to give the chroman **15** in 72% yield as a 9:1 mixture of diastereomers. The major component, having the isobutyl group in an *R*-configuration (*vide infra*), was isolated by recrystallization, while an enriched sample of the *S*-isomer was obtained by flash chromatography of the mother liquor. We encountered difficulties in formylating **15** using the Rieche reaction. After a few minutes at 0 °C the chroman was consumed and quenching the reaction at this stage furnished a mixture of the monoaldehydes **16a** and **b** in 65% yield, without any detectable rearrangement. However, the prolonged reaction time required for introduction of the second formyl group caused partial rearrangement of the pinene skeleton. However, robustadial A (**3a**) was obtained reasonably pure as a liquid in 15% yield; the dimethylated derivative **3b** exhibited spectral data in agreement with those published.[4,5] As expected the formyl group deactivates the benzene ring for further electrophilic substitution, and in order to circumvent this reactivity problem it was converted into a less electron-attracting group that would easily reform the aldehyde. Such a protocol for the preparation of aromatic dialdehydes, using the Rieche reaction, has recently been reported by Belen'kii and co-workers.[20] Hence, treatment of the monoaldehydes with PCl_5 in CH_2Cl_2 for a few minutes at room temperature furnished the corresponding dichloromethyl derivatives **16c** and **16d**, as shown by the absence of aldehyde protons in the NMR spectrum. The crude mixture of chlorides was treated with the Vilsmeier reagent at room temperature furnishing robustadial A (**3a**) as a yellow liquid in 12% overall yield from the monoaldehydes. The ^{1}H NMR spectrum of the crude product showed that it contained essentially the dialdehyde. We were unable to induce crystallisation, and attempted purification by flash chromatography on silica gel was not successful due to rearrangement. From the mixture containing more of the other diastereomer an enriched sample of robustadial B was obtained, using the same formylation procedure. The robustadials are not stable towards acids generally, and even prolonged contact with silica gel gives rise to rearrangement products; however, the compound seems surprisingly stable towards oxygen.

In conclusion we have described the first synthesis of the naturally occurring antimalarial (−)-robustadial A in essentially four steps from phloroglucinol. Some of the compounds reported in the present paper have undergone biological evaluation of activity against resistant strains of the malaria causing parasite, *Plasmodium falciparum*.[21]

Experimental

General. GLC analyses were performed on a 30 m capillary column of SP2100, and for analyses of optical purity a 25 m Chirasil-L-Val column was used. IR spectra were recorded on a Perkin Elmer 1310 instrument. NMR spectra were obtained on Varian XL-300 and 200 instruments. MS data were recorded on a Fisons Instruments ProSpec-Q mass spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Capillary melting points were taken on a Büchi SMP-20 apparatus and are uncorrected.

5,7-Dihydroxyspiro[chroman-2,1'-cyclopentan]-4-one (**4b**). A mixture of phloroglucinol (5.0 g, 4.0 mmol), cyclopentylideneacetic acid[22] (5.0 g, 4.0 mmol), phosphoryl chloride (100 ml) and $AlCl_3$ (16.0 g) was stirred at room temp. for 6 h. The reaction mixture was poured carefully onto crushed ice, the product extracted with ether, washed with water and dried ($MgSO_4$). Flash chromatography and recrystallization furnished the chromanone **4b** (7.60 g, 81%) as light-yellow crystals, m.p. 134–135 °C, from $CHCl_3$. IR (film): 3400–3100, 2940, 1700 w,

1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.67 (m, 6 H), 1.90 (m, 2 H), 2.85 (s, 2 H), 5.81 (d, 1 H, *J* 1.4 Hz), 5.83 (d, 1 H, *J* 1.4 Hz), 10.73 (s, 1 H), 12.09 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.30, 36.71, 44.79 (CH_2), 89.46 (C), 95.39, 95.61 (CH), 101.51, 161.50, 163.30, 166.57 (C), 196.13 (C = O).

Use of 1-cyclopenteneacetic acid[23] and the same procedure gave **4b** (78%).

5,7-Dihydroxyspiro[chroman-2,1'-cyclohexan]-4-one (**4c**). The reaction of phloroglucinol and cyclohexylideneacetic acid[18] by the same procedure as for **4c** (82%) as light-yellow crystals, m.p. 114–115°C, from $CHCl_3$. IR (film): 3400–3100, 1700, 1635, 1460 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.20–1.80 (m, 8 H), 2.00 (m, 2 H), 2.64 (s, 2 H), 5.90 (s, 2 H), 8.40 (br s, 1 H), 11.90 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.93, 26.61, 36.25, 47.96 (CH_2), 80.71 (C), 96.79 (CH), 103.12, 161.54, 163.80, 165.92 (C), 196.10 (C = O).

7-Hydroxy-5-pyrrolidinospiro[chroman-2,1'-cyclohexan]-4-one (**5**). A solution of 2,4,6-trihydroxyacetophenone (10.1 g, 60 mmol) and 1-pyrrolidinocyclopentene (28.8 g, 0.21 mol) in anh. EtOH (300 ml) was heated under reflux for 16 h. The excess of enamine and ethanol was distilled off and the crude product was purified by flash-chromatography (silica; hexane–ethyl acetate 3:1). Recrystallization furnished 14.70 g (85%) of **5** as colourless crystals, m.p. 135–137°C, from EtOAc. ^1H NMR (300 MHz, $CDCl_3$): δ 1.75 (m, 4 H), 1.85 (m, 2 H), 1.99 (m, 6 H), 2.72 (s, 2 H), 3.32 (t, 4 H), 5.58 (d, 1 H), 5.61 (d, 1 H), 12.23 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.83, 25.21, 37.56, 45.60, 89.20, 91.30 (CH), 91.55, 99.63 (C), 154.51, 161.09, 163.51 (C), 193.83 (C = O). GC–MS (CI): m/z 288.

The same product was obtained in 75% yield from heating a solution of 2,4,5-trihydroxyacetophenone, cyclopentanone and pyrrolidine in toluene under reflux for 12 h.

5,7-Dihydroxy-2,2-dimethyl-4-isobutylchroman (**8a**). A solution of methallyl bromide (18.5 g, 0.14 mol) in THF (80 ml) was added over 20 min to a suspension of activated zinc (11.8 g, 0.18 mol) in THF (160 ml) using ultrasound for stirring. After 1 h at room temperature a solution of the chromanone **4a**[13] (6.4 g, 31 mmol) in THF (80 ml) was added dropwise over 30 min, 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 product was dissolved in ethanol (50 ml) and hydrogenated on a Parr apparatus using Pd–C (0.20 g, 10%) as the catalyst. After 4 h, 5 drops of conc. H_2SO_4 and an additional amount of Pd–C (0.20 g, 10%) were added and the hydrogenation was continued for 10 h. Flash chromatography (silica gel; pet. ether–EtOAc 85:15) provided the chroman **8a** (5.60 g, 73%) as colourless crystals, m.p. 47–49°C, from $CHCl_3$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (d, 3 H, *J* 6.6 Hz), 0.87 (d, 3 H, *J* 6.6 Hz), 1.09 (m, 1 H), 1.11 (s, 3 H), 1.28 (s, 3 H), 1.49 (dd, *J* 8.0, 14.0 Hz, 1 H), 1.64 (m, 1 H), 1.89 (dd, *J* 8.0 Hz, 14.0 Hz, 1 H), 2.11 (m, 1 H), 2.80 (m, 1 H), 5.73 (d, *J* 2.6 Hz, 1 H), 5.90 (d, *J* 2.6 Hz, 1 H), 8.40 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.80, 24.80 (CH_3), 25.77 (CH), 26.08 (CH_3), 27.19 (CH), 29.77 (CH_3), 40.67, 44.21 (CH_2), 74.11 (C), 95.94, 96.06 (CH), 105.62, 154.84, 155.49, 156.04 (C).

5,7-Dihydroxy-4-isobutylspiro[chroman-2,1'-cyclopentane] (**8b**). The chromanone **4b** was treated with methallyl bromide and activated zinc, and the crude product subsequently hydrogenated and worked up as described for **8a**. Flash chromatography afforded the chroman **8b** (72%) as colourless crystals, m.p. 98–100°C, from CH_2Cl_2. IR ($CHCl_3$): 3580, 3450–3200, 2950, 1620, 1600, 1430, 1230, 1030 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, *J* 6.4 Hz, 3 H), 0.97 (d, *J* 6.4 Hz, 3 H), 1.26–2.06 (m, 14 H), 2.92 (m, 1 H), 5.65 (br s, 1 H), 5.87 (d, *J* 2.4 Hz, 1 H), 5.93 (d, *J* 2.4 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.73 (CH_3), 25.13 (CH_2), 25.61 (CH_3), 25.76 (CH_2), 27.15, 28.79 (CH), 38.37, 38.90, 40.23, 44.92 (CH_2), 87.05 (C), 96.77, 98.12 (CH), 108.30, 154.40, 154.60, 154.81 (C).

5,7-Dihydroxy-4-isobutylspiro[chroman-2,1'-cyclohexane] (**8c**). The chromanone **4c** was treated with methallyl bromide and activated zinc, and the crude product subsequently hydrogenated and worked up as described for **8a**. Flash chromatography afforded the chroman **8c** (3.90 g, 84%) as colourless crystals, m.p. 52–54°C, from $CHCl_3$. IR ($CHCl_3$): 3560, 3450–3200, 1620, 1600, 1450, 1420, 1190, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, *J* 6.4 Hz, 3 H), 0.95 (d, *J* 6.4 Hz, 3 H), 1.28–1.85 (m, 14 H), 2.05 (m, 2 H), 2.88 (m, 1 H), 5.50 (br s, 1 H), 5.88 (d, *J* 2.4 Hz, 1 H), 5.99 (d, *J* 2.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.80 (CH_3), 23.47 (CH_2), 25.64 (CH_3), 27.22 (CH), 27.31 (CH_2), 27.63 (CH), 34.71, 38.98, 40.52, 45.57 (CH_2), 76.74 (C), 96.93, 98.25 (CH), 108.53, 154.44, 155.14, 155.16 (C).

8-Formyl-5,7-dihydroxy-2,2-dimethyl-4-isobutylchroman (**9**). To a stirred solution of chroman **8a** (250 mg, 1 mmol) and triethyl orthoformate (2.0 ml, 12 mmol) in ether (30 ml) was added $AlCl_3$ (400 mg, 3 mmol). The mixture was then stirred at room temp. for 1 h. Water (1 ml) was added and the solution extracted with ether. The extract was dried ($MgSO_4$) and the solvent evaporated off. Flash chromatography (silica; pet. ether–EtOAc 9:1) afforded the monoaldehyde **9** (200 mg, 72%) as a light yellow liquid. IR ($CDCl_3$): 3300–3100, 2900, 2840, 1790, 1610 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.91 (d, *J* 6.4 Hz, 3 H), 0.95 (d, *J* 6.4 Hz, 3 H), 1.26 (m, 1 H), 1.27 (s, 3 H), 1.43 (s, 3 H), 1.70 (m, 2 H), 2.02 (m, 2 H), 2.85 (m, 1 H), 5.90 (s, 1 H), 10.03 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.08, 24.07, 25.50 (CH_3), 25.61 (CH), 26.31 (CH_3), 28.88 (CH), 39.24 (CH_2), 43.47

(CH_2), 76.27 (C), 95.50 (CH), 105.79, 106.35, 158.68, 163.51 (C), 163.99 (C–O), 192.26 (CH = O).

6,8-Diformyl-5,7-dihydroxy-2,2-dimethyl-4-isobutylchroman (**10a**). A solution of the chroman **8a** (1.0 g, 4.0 mmol) and $TiCl_4$ (3.03 g, 16 mmol) in $CHCl_3$ (30 ml) was cooled in ice and dichloromethyl methyl ether (1.5 g, 13.0 mmol) was added with stirring. After 7 h, aq. H_2SO_4 (5%, 20 ml) was added, and the organic phase separated. The aq. phase was extracted with ether, and the combined organic phase dried ($MgSO_4$). Evaporation of solvents followed by flash chromatography of the crude product gave the dialdehyde **10a** (0.55 g, 45%) as a yellow liquid. IR (CCl_4): 3500–3250 w, 2940, 1640, 1480, 1300, 1155 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, *J* 6.4 Hz, 3 H), 0.98 (d, *J* 6.4 Hz, 3 H), 1.25 (m, 1 H), 1.31 (s, 3 H), 1.49 (s, 3 H), 1.72 (m, 2 H), 2.05 (m, 2 H), 2.90 (m, 1 H), 10.02 (s, 1 H), 10.14 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.38, 25.31, 26.96 (CH_3), 27.15 (CH), 30.02 (CH_3), 30.93 (CH), 39.84, 43.92 (CH_2), 79.03, 104.51, 105.10, 105.90, 163.40, 167.80, 169.80 (C), 191.45, 192.03 (CH = O).

6,8-Diformyl-5,7-dihydroxy-4-isobutylspiro[chroman-2,1'-cyclopentane] (**10b**). A solution of the chroman **8b** (1.0 g, 3.6 mmol) and $TiCl_4$ (2.72 g, 14.4 mmol) in $CHCl_3$ (30 ml), cooled in ice, was treated with dichloromethyl methyl ether (1.34 g, 11.7 mmol) as described for **10a**. The dialdehyde **10b** (0.51 g, 43%) was obtained as yellow crystals, m.p. 77–78°C, from methanol. IR (CCl_4): 2940, 1640–1540, 1435, 1300, 1170 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (d, *J* 6.4 Hz, 3 H), 0.97 (d, *J* 6.2 Hz, 3 H), 1.25 (m, 1 H), 1.70 (m, 10 H), 2.07 (m, 2 H), 2.92 (m, 1 H), 9.97 (s, 1 H), 10.13 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.08 (CH_3), 24.31 (CH_2), 24.99, 25.41 (CH_3), 26.63, 27.29 (CH), 35.75, 39.65, 39.78, 43.31 (CH_2), 90.06, 104.50, 105.10, 106.39, 163.80, 168.07, 169.68 (C), 191.58, 192.00 (CH = O).

6,8-Diformyl-5,7-dihydroxy-4-isobutylspiro[chroman-2,1'-cyclohexane] (**10c**). A solution of the chroman **8c** (1.0 g, 3.4 mmol) and $TiCl_4$ (2.72 g, 14.4 mmol) in $CHCl_3$ (30 ml) was treated with dichloromethyl methyl ether (1.34 g, 11.7 mmol) as described for **10a**. Flash chromatography (silica gel; methylene chloride) gave the dialdehyde **10c** (0.41 g, 35%) as a yellow liquid. IR (CCl_4): 2940, 1640–1540, 1435, 1300, 1170 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, *J* 6.4 Hz, 3 H), 0.95 (d, *J* 6.4 Hz, 3 H), 1.20–2.10 (m, 16 H), 2.90 (m, 1 H), 10.13 (s, 1 H), 10.18 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.80 (CH_3), 22.85 (CH_2), 24.96 (CH_3), 26.30 (CH_2), 26.47 (CH), 34.73, 37.99, 38.94, 43.96 (CH_2), 79.90, 105.10, 105.80, 106.42, 164.20, 168.31, 170.25 (C), 192.14, 192.29 (CH = O).

exo-5,7-Dihydroxy-6',6'-dimethyl-2',5'-methanospiro-[chroman-2,1'-cyclohexan]-4-one (**11a**). A mixture of phloroglucinol (12.6 g, 0.1 mol), camphene-8-carboxylic acid (18.0 g, 0.1 mol) and $AlCl_3$ (53.3 g, 0.4 mol) in $POCl_3$ (150 ml) was stirred at room temperature for 20 h and worked up as described for **4b**. According to the NMR spectra the product consisted of a 9:1 mixture of stereoisomers. Recrystallization from $CHCl_3$ gave the pure *exo*-chromanone **11a** (21.0 g, 73%), m.p. 160–162°C. IR (CCl_4): 3580, 3450–3050, 2970, 1710, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 3 H), 1.06 (s, 3 H), 1.3–1.6 (m, 5 H), 1.80 (s, 1 H), 2.15 (d, *J* 10.2 Hz, 1 H), 2.38 (t, *J* 3.6 Hz, 1 H), 2.78 (dd, 2 H), 5.88 (d, *J* 1.2 Hz, 1 H), 5.92 (d, *J* 1.2 Hz, 1 H), 11.88 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.27 (CH_2), 23.32 (CH_3), 23.39 (CH_2), 25.46 (CH_3), 34.44, 39.46 (CH_2), 45.42 (C), 46.91, 49.50 (CH), 90.75 (C), 95.55 (CH), 95.64, 102.75, 163.04, 165.61 (C–O), 196.69 (C = O).

Methylated derivative **11b**. Methylation of **11a** with methyl iodide and K_2CO_3 in acetone followed by flash-chromatography (silica; pet. ether–EtOAc 7:3) gave *exo*-**11b** (86%), m.p. 149–150°C (lit.[3] 148–149°C). The spectral data are in good agreement with those published.[3]

5,7-Dihydroxy-4-isobutyl-6',6'-dimethyl-2',5'-methanospiro-[chroman-2,1'-cyclohexane] (**12**). The chromanone **11a** (2.8 g, 9.7 mmol) was treated with an excess methallyl bromide (6.0 g, 44 mmol) and zinc (10.5 g, 154 mmol) in THF (105 ml) and the crude product subsequently hydrogenated as described for **10a**. The product (2.3 g, 72%) consisted of a 55:45 mixture of stereoisomers **12**. The major component, *cis*-**12**, was separated by recrystallisation from CH_2Cl_2, m.p. 77–79°C. The spectral data on the minor component, *trans*-**12**, was obtained from the mixture.

cis-**12**. IR ($CDCl_3$): 3560, 3450–3200, 1620, 1600, 1450, 1140 cm^{-1}. $[\alpha]^{20}_D$ −3.0 (*c* 15.0, MeOH). ^1H NMR (200 MHz, $CDCl_3$: δ 0.90–1.02 (m, 9 H), 1.11 (s, 3 H), 1.18–2.35 (m, 13 H), 2.78 (m, 1 H), 5.12 (br s, 1 H), 5.84 (d, 1 H), 5.91 (d, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.92, 23.39 (CH_3), 23.50, 24.77 (CH_2), 24.94, 25.66 (CH_3), 26.25, 28.53 (CH), 32.60, 34.90 (CH_2), 42.95 (CH), 44.66 (C), 44.80 (CH_2), 50.04 (CH), 86.95 (C), 96.48, 98.27 (CH), 108.57, 154.85, 155.80, 157.59 (C); *trans*-**12**. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88–1.00 (m, 12 H), 1.17–2.30 (m, 13 H), 2.85 (m, 1 H), 5.83 (d, 1 H), 5.92 (d, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.92 (CH_3), 23.29 (CH_2), 23.95, 24.57 (CH_3), 24.69 (CH_2), 25.98 (CH_3), 26.38 (CH), 27.09 (CH_2), 27.46 (CH), 35.59, 43.13 (CH_2), 46.38 (C), 47.32, 49.77 (CH), 86.07 (C), 95.77, 97.43 (CH), 107.63, 155.04, 155.44, 156.65 (C).

6,8-Diformyl-5,7-dihydroxy-4-isobutyl-6',6'-dimethyl-2',5'-methanospiro[chroman-2,1'-cyclohexane] (**2a**). A solution of the chroman **12a** (1.20 g, 3.6 mmol) and $TiCl_4$ (2.72 g, 14.4 mmol) in $CHCl_3$ (50 ml) was treated with dichloromethyl methyl ether (1.34 g, 11.5 mmol) as described for **10a**. The dialdehyde **2a** (0.64 g, 46%) was obtained as yellow crystals, m.p. 82–84°C, from MeOH. The dia-

stereomers were obtained from the mixture of chromans **12** by the same procedure. IR ($CHCl_3$): 3500–3100, 2950, 1640, 1530, 1440, 1300 cm^{-1}.

cis-**2a**. ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, *J* 6.4 Hz, 3 H), 0.95 (d, *J* 6.4 Hz, 3 H), 0.99 (s, 3 H), 1.14 (s, 3 H), 1.20–2.45 (m, 13 H), 2.92 (m, 1 H), 10.02 (s, 1 H), 10.21 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.55, 23.07, 24.67, 25.50 (CH_3), 23.30, 24.47, 31.51, 35.04, 44.61 (CH_2), 25.97, 27.58, 41.67, 49.56 (CH), 43.20, 90.94, 104.52, 105.76, 165.16, 168.41, 170.41 (C), 192.25, 192.50 (CH = O); *trans*-**2a**. ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, *J* 6.4 Hz, 3 H), 0.96 (d, *J* 6.4 Hz, 3 H), 0.99 (s, 3 H), 1.14 (s, 3 H), 1.25–2.42 (m, 13 H), 2.78 (m, 1 H), 10.04 (s, 1 H), 10.21 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.55, 23.07 (CH_3), 23.61 (CH_2), 24.18, 24.43, 25.18, 26.19, 26.24, 35.71, 43.19 (C), 45.51, 46.86, 47.93, 49.10 (CH), 90.20, 104.20, 104.96, 105.75, 164.00, 168.65, 170.05 (C), 192.12, 192.45 (CH = O).

The dimethylated derivatives, obtained in the usual way, exhibited spectral data in good agreement with those published.[3]

6,6-Dimethylbicyclo[3.1.1]heptan-2-ylideneacetaldehyde (**13a**). To a stirred solution of oxalyl chloride (21.0 g, 0.16 mol) in CH_2Cl_2 (375 ml), kept at −60 °C was added a solution of DMSO (28.5 g, 0.36 mol) in CH_2Cl_2 (75 ml) over 10 min. Stirring was continued for 20 min followed by addition of (−)-nopol (24.5 g, 0.15 mol) in CH_2Cl_2 (150 ml) over 10 min. After an additional 30 min with stirring, triethylamine (75 g, 0.74 mol) was added over 10 min. The cooling bath was removed and water (400 ml) was added at room temperature. The organic layer was separated and the aq. phase was extracted with CH_2Cl_2 (150 ml). The combined organic phase was dried ($MgSO_4$) and the solvent evaporated off. Flash chromatography gave the aldehyde **13a** (22.1 g, 90%) as a 4:1 mixture of *E* and *Z* isomers, respectively. Since we were unable to separate them, the spectral data are recorded on the mixture. IR (film): 2760, 2730, 1670, 1620 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.61 (s, 3 H), 0.62 (s, 3 H), 1.17 (s, 3 H), 1.20 (s, 3 H), 1.35 (m, 2 H), 1.85 (m, 4 H), 1.96 (m, 2 H), 2.30 (m, 2 H), 2.45 (t, 1 H), 2.62 (m, 2 H), 3.45 (t, 1 H), 5.55 (d, 1 H), 5.72 (d, 1 H), 9.72 (d, 1 H), 9.84 (d, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.74 (CH), 22.11, 22.23, 23.56, 23.69, 26.03, 26.12, 26.25, 26.49, 26.65, 40.28, 40.41, 41.82, 46.14, 53.87, 124.88, 126.34 (=CH), 172.82, 173.60 (=C), 190.02, 190.82 (C = O).

(E)-6,6-Dimethylbicyclo[3.1.1]heptan-2-ylideneacetic acid (**E-13b**). To a rapidly stirred solution of the aldehyde **13a** (10.0 g, 61 mmol) and $AgNO_3$ (12.4 g, 73 mmol) in ethanol (100 ml) and water (18 ml) was added a solution of NaOH (8.6 g, 21.6 mmol) at a rate sufficient to maintain ambient temperature. After addition stirring was continued for 20 h. The mixture was filtered and the residue washed with ethanol and water. The filtrate was extracted with ether to remove any neutral material, the basic aq. solution acidified with H_2SO_4 (10%) until pH 5 and extracted with ether. Evaporation of the ether gave (*E*)-**13b** (9.3 g, 85%) as a viscous liquid. ^1H NMR (200 MHz, $CDCl_3$): δ 0.75 (s, 3 H), 1.28 (s, 3 H), 1.38 (d, 1 H), 1.80–2.20 (m, 2 H), 2.38 (m, 2 H), 2.52 (t, 1 H), 2.60–2.80 (m, 1 H), 3.25 (m, 1 H), 5.52 (s, 1 H), 9.40 (br s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.55, 23.19, 24.07, 26.49, 27.63, 40.77, 41.45, 54.45, 112.61, 172.38, 172.97.

(E)-6,6-Dimethylbicyclo[3.1.1]heptan-2-ylideneacetyl chloride (**13c**). Oxalyl chloride (7.2 g, 56.7 mmol) was added dropwise to the acid (*E*)-**13b** (4.0 g, 22.2 mmol) in benzene (5 ml). Stirring was continued at room temperature for 5 h. Excess oxalyl chloride and benzene was evaporated off and the residue was distilled under reduced pressure to give the acid chloride (*E*)-**13c** (3.90 g, 84%), b.p. 80–82 °C (0.2 mmHg); ^1H NMR (200 MHz, $CDCl_3$): δ 0.76 (s, 3 H), 1.28 (s, 3 H), 1.32 (m, 1 H), 1.82–2.18 (m, 3 H), 2.20–2.50 (m, 1 H), 2.55 (t, 1 H), 2.68 (m, 1 H), 3.50 (m, 1 H), 5.85 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.36, 23.53, 24.24, 26.10, 27.30, 40.29, 41.54, 54.08, 119.31, 162.32, 178.71.

5,7-Dihydroxy-3',3'-dimethyl-2',4'-methanospiro[chroman-2,1'-cyclohexan]-4-one (**14a**). A solution of phloroglucinol (2.36 g, 19.0 mmol), the acid chloride **13c** (4.0 g, 19.0 mmol) and $ZnCl_2$ in ether (70 ml) was stirred at room temperature for 2 h. The reaction mixture was poured carefully into ice-cooled 10% aq. $NaHCO_3$ (300 ml). The product was extracted with ether and washed with water. The solvent was evaporated off, the crude product dissolved in ethanol (80 ml), K_2CO_3 (5.0 g) was added and the mixture heated under reflux for 10 h. When cold, the salt was filtered, washed with ether and the solvents evaporated off. The residue was purified by flash chromatography (silica gel; pet. ether–EtOAc 8:2) to yield as the sole product the *exo*-chromanone **14a** (4.10 g, 75%), $[\alpha]^{20}_D$ −32.79 (*c* 5.7, MeOH). IR (film): 3580, 3440–3060, 2960, 1705, 1635 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (s, 3 H), 1.25 (s, 3 H), 1.48–1.71 (m, 1 H), 1.78–2.32 (m, 7 H), 2.75 (d, *J* 17.4 Hz, 1 H), 2.91 (d, *J* 17.4 Hz, 1 H), 5.88 (d, 1 H), 5.93 (d, 1 H), 8.42 (br s, 1 H), 11.82 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.90 (CH_3), 24.30, 26.39 (CH_2), 27.20 (CH_3), 28.62 (CH_2), 37.87 (C), 40.13 (CH), 48.11 (CH), 48.84 (CH_2), 85.81 (C), 95.94, 96.26 (CH), 102.60, 161.86, 163.47, 166.04 (C), 196.73 (C = O).

Methylated derivative **14b**. Methylation of **14a** with methyl iodide and K_2CO_3 in acetone gave, after flash chromatography (silica gel; pet. ether–EtOAc 7:3) **14b** (0.25 g, 80%). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.29 (CH_3), 24.67, 26.68 (CH_2), 27.42 (CH_3), 28.72 (CH_2), 38.11 (C), 40.49, 48.88 (CH), 50.99 (CH_2), 55.45, 55.97 (CH_3), 85.54 (C), 92.08, 93.96 (CH), 105.63, 161.28, 163.03, 165.49 (C), 189.50 (C = O). The other spectral data are in good agreement with those published.[3]

5,7-Dihydroxy-4-isobutyl-3',3'-dimethyl-2',4'-methanospiro-[chroman-2,1'-cyclohexane] (**15**). The chromanone **14a** was treated with methallyl bromide and activated zinc, and the crude product subsequently hydrogenated and worked up as described for **8a**. Flash chromatography (silica gel; ether–EtOAc 85:15) provided the a 9:1 mixture of diastereomeric chromans, which by recrystallization from CH_2Cl_2 gave the major isomer **15** (72%) as colourless crystals, m.p. 68–70°C, $[\alpha]^{20}_D$ −48.29 (*c* 2.4, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, *J* 6.4 Hz, 3 H), 0.97 (d, *J* 6.4 Hz, 3 H), 1.00 (s, 3 H), 1.27 (s, 3 H), 1.80–2.05 (m, 9 H), 2.10–2.95 (m, 3 H), 2.87 (m, 1 H), 5.40 (br s, 1 H), 5.60 (br s, 1 H), 5.85 (d, *J* 2.2 Hz, 1 H), 5.92 (d, *J* 2.2 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.24, 23.51, 24.05 (CH_3), 24.92 (CH_2), 25.78, 26.47 (CH), 26.74 (CH_2), 27.21 (CH_3), 27.49 (CH_2), 38.99 (C), 40.53 (CH_2), 40.64 (CH), 43.90 (CH_2), 50.90 (CH), 81.41, 95.93 (C), 96.02, 98.75 (CH), 108.93, 154.60, 155.43, 155.83 (C).

Robustadial A (**3a**)*: Method I.* A solution of the chroman **15** (0.70 g, 2.1 mmol), $TiCl_4$ (0.48 g, 2.1 mmol) in CH_2Cl_2 (30 ml) and dichloromethyl methyl ether (0.36 g, 3.15 mmol) was stirred at 0°C for 10 min. Water was added, and the product extracted with ether and dried ($MgSO_4$). The solvent was evaporated off and the residue dissolved in CH_2Cl_2 (30 ml), $TiCl_4$ (0.48 g, 2.1 mmol) and dichloromethyl methyl ether (0.36 g, 3.15 mmol) were added, and the reaction mixture stirred at 0°C for 20 min. Water was added, the product extracted with ether and the extract dried ($MgSO_4$). Evaporation gave the dialdehyde **3a** (0.12 g, 15%) as a yellow liquid. The compound is unstable to acids. IR ($CDCl_3$): 2950, 2700, 1640, 1460, 1380, 1300 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87–1.02 (m, 9 H), 1.25 (s, 3 H), 1.29 (m, 1 H), 1.45–2.40 (m, 12 H), 2.95 (m, 1 H), 10.10 (s, 1 H), 10.15 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.50, 23.52, 24.02 (CH_3), 24.51 (CH_2), 25.61, 26.32 (CH), 26.84 (CH_2), 27.15 (CH_3), 27.65, 37.82 (CH_2), 38.52 (C), 40.02 (CH), 44.05, 52.15 (CH_2), 84.03, 104.45, 105.25, 164.82, 167.78, 169.64 (C), 191.25, 191.32 (CH = O).

Dimethylated derivative (**3b**). Methylation of **4a** with methyl iodide and K_2CO_3 in acetone followed by flash chromatography (silica gel; pet. ether–EtOAc 7:3) gave **3b** as a yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88–1.00 (m, 9 H), 1.25 (s, 3 H), 1.29 (m, 1 H), 1.50–2.35 (m, 12 H), 2.95 (m, 1 H), 3.85 (s, 3 H), 3.93 (s, 3 H), 10.28 (s, 1 H), 10.39 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.82, 23.32, 23.99 (CH_3), 24.79 (CH_2), 25.53, 26.37 (CH), 26.82 (CH_2), 27.70 (CH_3), 28.10 (CH_2), 37.85 (C), 38.97 (CH_2), 40.20 (CH), 44.84 (CH_2), 49.20 (CH), 62.50, 64.80 (CH_3), 84.75, 115.67, 116.00, 118.65, 163.47, 165.65, 165.71 (C), 187.69, 187.79 (CH = O).

Method II. To a stirred solution of the chroman **15** (0.92 g, 2.8 mmol) in DMF (20 ml) was added phosphorus oxychloride (0.46 g, 3.0 mmol) at room temperature. Stirring was continued for 5 h, the solution cooled and a solution of NaOAc (2 g) in water (9 ml) was added. The product was extracted with ether, the extract washed successively with aq. Na_2CO_3 and water, and dried ($MgSO_4$). Evaporation of the solvent gave the monoaldehydes **16a,b** (0.62 g, 62%) in a 3:1 ratio. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87–1.03 (m, 9 H), 1.23 (m, 1 H), 1.25 (s, 3 H), 1.52–2.30 (m, 12 H), 2.87 (m, 1 H), 5.90 (s, 1 H), 10.05 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.6, 24.0, 24.5, 25.5, 26.2, 26.9, 27.2, 27.8, 28.2, 39.0, 40.1, 44.0, 51.8, 83.9, 96.1, 107.8, 159.5, 164.4. 165.2, 192.8.

A solution of **16a,b** (0.50 g, 13.9 mmol) and phosphorus pentachloride (0.29 g, 13.9 mmol) in CH_2Cl_2 (15 ml) were stirred at room temperature for 2 h. Cold water was added, the organic phase was separated and dried ($MgSO_4$). Evaporation of the solvent gave the chlorides **16c,d** (0.40 g, 70%) in a 3:1 ratio. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87–1.03 (m, 9 H), 1.24 (m, 1 H), 1.25 (s, 3 H), 1.55–2.35 (m, 12 H), 3.05 (m, 1 H), 7.17 (s, 1 H), 7.23 (s, 1 H).

To a stirred solution of the chlorides **16c,d** (0.37 g, 0.9 mmol) in DMF (20 ml) was added phosphorus oxychloride (0.16 g, 1.0 mmol) at room temperature. Stirring was continued for 5 h, the solution was cooled and a solution of NaOAc (1 g) in water (4.5 ml) was added. The product was extracted with ether, the extract washed successively with aq. Na_2CO_3 and water, and dried ($MgSO_4$). The residue obtained by evaporation of the solvent was dissolved in EtOH, acidified with hydrochloric acid and stirred for 15 min at room temperature. Cold water was added and the product extracted with $CHCl_3$ and dried ($MgSO_4$). Evaporation of the solvents gave a residue that, according to the ^{1}H NMR spectrum, contained essentially the dialdehyde **3a**, but attempts at purification by flash chromatography on silica gel were unsuccessful.

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