# Three-Component Tandem Knoevenagel/Hetero Diels−Alder Reactions − Total Synthesis of (±)-Preethulia Coumarin

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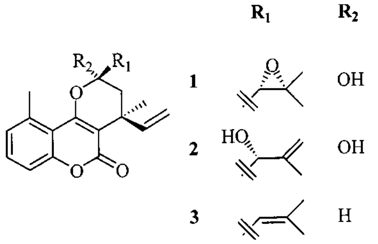
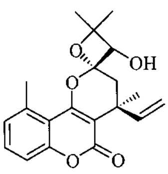
Starting from 4-hydroxy-5-methylcoumarin (**7**), (±)-preethulia coumarin (**3**) was synthesized in six steps and in 4% overall yield. The key synthetic procedure was a new type of Lewis acid catalysed, three-component Knoevenagel/hetero Diels–Alder reaction, which employs α-dicarbonyl compounds to generate chromandiones, and vinyl ethers to trap them. Some unexpected rearrangements were observed during the manipulation of various acetalic Diels–Alder adducts, resulting in the serendipitous assembly of bridgehead and fused tetracyclic coumarin assemblies.

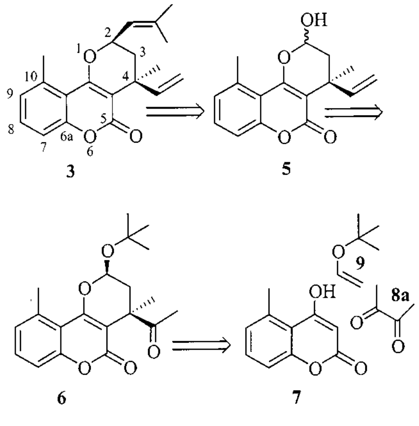
Over the past few decades, an impressive variety of prenylated 5-methylcoumarins have been characterised, mainly from plants belonging to the Mutisieae tribus of the Compositae family.[1] These prenylated polyketides represent a significant addition to the shikimate-derived coumarins from umbelliferous and rutaceous plants, a class of compounds extensively investigated for their anticoagulant and phototoxic properties.[2] Interest in polyketide coumarins was sparked by the discovery of the powerful anthelmintic[3] and molluscicidal[4] properties of ethuliacoumarin A (**1**), a constituent of the Egyptian medicinal plant *Ethulia conyzoides L.*[5] The related analogues **2**−**4** were also isolated,[6] and some of them showed biological activity comparable to **1**.[4]





**4**

All these compounds share a 4,10-dimethyl-4-vinylpyrano[3,2-*c*]coumarin core, and only differ in the oxygenation of C-2 and the norprenyl residue. The powerful biological activity of these compounds suggests interaction with a host-specific target. This, however, remains unidentified, and the pharmacological potential of these compounds, though recognised, is still untapped. Ethuliacoumarins are available in sizeable amounts by isolation,[5b] but their plant source is not readily available, nor is the number of natural analogues sufficient to sustain a significant medicinal chemistry effort. These considerations prompted us to develop a straightforward route to the acetal **6**. This compound features the 4,4,10-trisubstituted pyrano[3,2-*c*]coumarin core of ethuliacoumarins, and offers the potential to afford a library of analogues by modification of the oxygen function at C-2 and of the acetyl substituent at C-4, as outlined retrosynthetically in Scheme 1. We report here an expeditious route to the acetal **6**, its remodelling to the vinyl-substituted lactol **5** and the eventual straightforward conversion of the latter into (±)-preethulia coumarin (**3**),[6b] the least oxygenated member of ethulia coumarins.



Scheme 1. Retrosynthetic analysis of preethulia coumarin (**3**)

Our plan to assemble the acetal **6** entailed the development of a three-component tandem Knoevenagel/hetero Diels−Alder reaction[7] between 4-hydroxy-5-methylcoumarin (**7**), diacetyl (= 2,3-butandione, **8a**) and a vinyl ether, with diacetyl serving the dual purpose of generating the chromandione intermediate and providing a double bond equivalent in the form of an acetyl group. The assembly of a pyran ring by tandem Knoevenagel/hetero Diels−Alder

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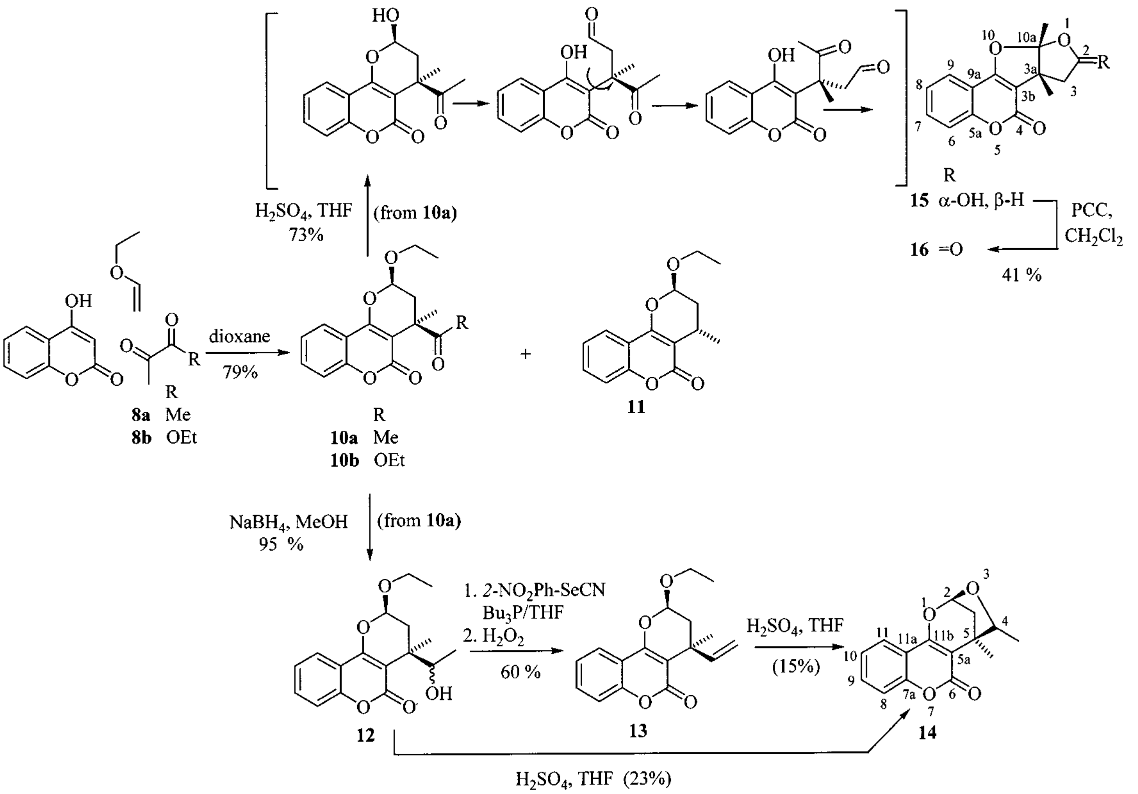
reaction of enals and enones with β-dicarbonyl derivatives has been thoroughly investigated, both in the two-component and three-component versions, by Tietze[7] and has been extensively employed in the synthesis of natural products and analogues.[8] To the best of our knowledge, however, the reaction with α-diketones as the electrophilic carbonyl component is totally unprecedented.

Preliminary experiments were carried out by treating diacetyl with 4-hydroxycoumarin and ethyl vinyl ether, both commercial and cheap chemicals. The reaction was carried out according to established methodology (refluxing in dioxane in the presence of a catalytic base and an excess vinyl ether).[9] The results showed that the critical reaction was taking place, but the yield of the desired Diels−Alder adduct **10a** was low and erratic (Scheme 2). The major reaction product (ca. 60% yield) was the 3-deacetyl derivative **11**, the result of Diels−Alder trapping of the chromandione formed by the condensation of 4-hydroxycoumarin and acetaldehyde.[9] This originated, presumably by means of acid catalysis by 4-hydroxycoumarin ($pK_a = 4.1$),[10] from reaction between ethyl vinyl ether and water liberated in the condensation step and/or present at trace levels in the solvent. Thus, when diacetyl was omitted from the reaction mixture and a substoichiometric amount of water was added, the adduct **11** was obtained as the only reaction product, in 75% yield. After considerable optimisation of solvent, temperature, catalyst and water trap, a reproducible technique limiting the formation of the acetaldehyde adduct was eventually developed. This involved the addition of activated molecular sieves to trap water formed in the condensation step, and a switch to Lewis acid catalysis ($YbOTf_3$)[11] to allow the reaction to be carried out at ambient temperature and with only a slight excess of vinyl ether. In this way, the desired adduct **10a** was obtained in satisfactory and reproducible yield (70−80%), while formation of the acetaldehyde adduct **11** was substantially reduced (< 10% yield). Remarkably, provided that water is efficiently removed from the reaction medium, acid catalysis appears to accelerate the condensation step more than it does the degradation of the enol ether.

The hetero Diels−Alder adducts **10a** and its analogues obtained by replacement of ethyl vinyl ether with other vinyl ethers (*tert*-butyl, *p*-methoxybenzyl and 3,5-dimethoxybenzyl, vide infra) were all isolated as single isomers, with the anomeric oxygen atoms axial ($J_{2,3a,b} = 4.4, 3.4$ Hz) and *trans* to the C-4 methyl groups (NOE effects between the hemiacetal protons and the 4-methyl groups). The stereoselective way in which the anomeric stereocentre was generated in the cycloaddition step is remarkable and difficult to explain. The related reaction producing **11** gave poorer stereoselectivity (5:1 mixture of *trans* and *cis* isomers), while, when diacetyl was replaced by ethyl pyruvate, the adduct **10b** was obtained as a 9:1 mixture of diastereomers, the major one again being that with the acetal oxygen atom *trans* to the 4-methyl group. Apparently, chromandiones from electron-poor ketones react more stereoselectively than those from aldehydes, a rather surprising observation, since *gem*-substitution would be expected to reduce face bias in cycloaddition reactions. Also remarkable is the exclusive formation of angular adducts, since chromandiones behave as ambident heterodienes in Diels−Alder cycloadditions, reacting with dienophiles both at the ketone and at the lactone carbonyl terminus.[9] We are currently pursuing the issues of regioselectivity and site-selectivity in a variety of other intermolecular hetero Diels−Alder reactions in which α-dicarbonyl compounds are employed as aldehyde surrogates to generate reactive heterodienes. Mechanistic details on these reactions will be published in due course.

With a good source of the model adduct **10a** to hand, we went on to investigate its modification by acetyl-to-vinyl remodelling and hydrolysis of the acetal group. Attempts to generate the vinyl group directly from the acetyl side chain of the Diels−Alder adduct **10a** by means of a Shapiro reaction[12] failed, as did the dehydration of the diastereomeric borohydride reduction products **12** with Burgess reagent[13] or Martin's sulfurane.[14] Thus, **10b** did not react with sulfonylhydrazines, and the monotosylhydrazide of diacetyl did not form a chromandione on treatment with 4-hydroxycoumarin, while complex mixtures were obtained on treatment of **12** with Burgess and Martin reagents. However, phenylselenylation/oxidative elimination (Grieco−Sharpless elimination[15]) of the side-chain alcohols **12** proceeded uneventfully, delivering the vinyl-substituted acetal **13** in an overall 60% yield. The vinyl group could also be generated by thermolysis of the diastereomeric xanthates of **12**, but the yield was lower. Hydrolysis of the ethyl acetal required harsh conditions ($H_2SO_4$/THF), which triggered further reactions involving the functionalities at C-4. Although failing to deliver the desired compound, these reactions revealed some interesting and unexpected reactivity of the C-4-disubstituted pyranocoumarin system. Thus, the C-4-vinyl-substituted coumarin **13** afforded a complex reaction mixture, containing as the major product the bridgehead acetal **14**, the result of an intramolecular Markovnikov addition of the hemiacetal hydroxy to the vinyl group. Compound **14** was obtained as a 6:1 mixture of diastereomers, but unambiguous stereochemical assignment by NMR spectroscopy was not possible. Attempts to effect the hydrolysis at the stage of the side-chain alcohol **12** gave a mixture, again containing the acetal **14** as the major component, while the Diels−Alder adduct **10a** afforded the crystalline tetracyclic lactol **15**. This compound lacked the side-chain oxo group, and afforded the γ-lactone **16** [$\tilde{\nu}_{C=O} = 1780$ cm$^{-1}$] on PDC oxidation. Spectroscopic analysis found a bis(furan) structure with a *cis* arrangement of the methyl groups at the ring junction. This is presumably responsible for the isolation of **15** as a single anomer, with the hemiacetal hydroxy group *trans* to the methyl groups at the ring junction.

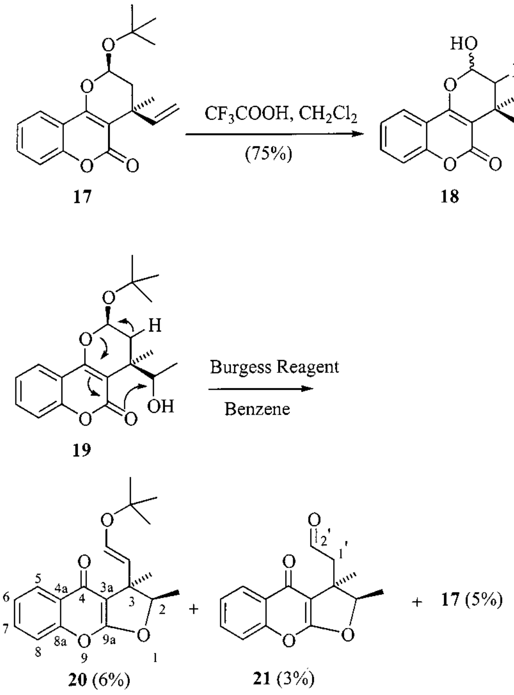
The pyranocoumarins **10a**, **12** and **13** contain electrophilic and nucleophilic groups prone to reaction under the strongly acidic conditions required to hydrolyse the ethyl acetal group. The harsh conditions required for this reaction are presumably due to the enolic character of the pyran oxygen atom, which makes it a poor electron donor to an adjacent cation centre. The disastrous consequences



Scheme 2. Model reactions en route to preethulia coumarin

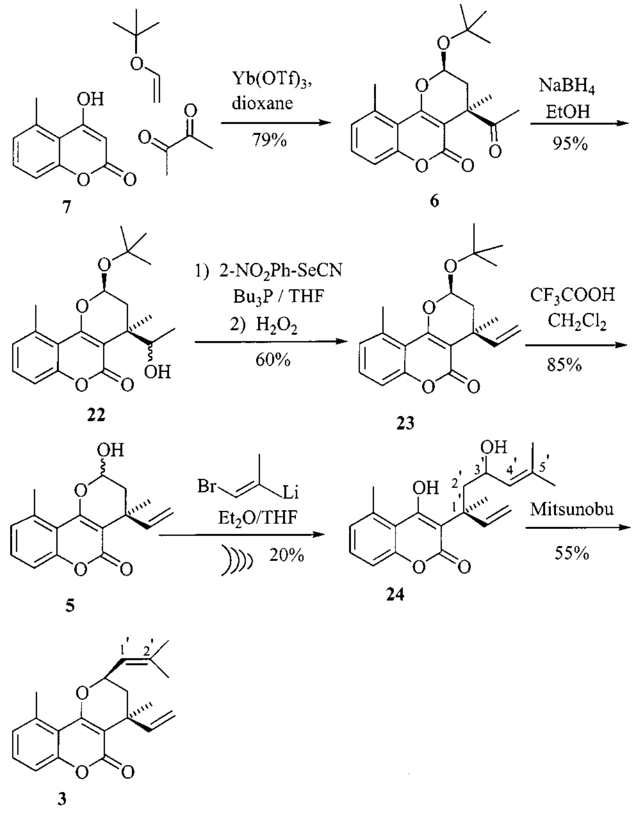
for our synthetic plan required replacement of ethyl vinyl ether in the cycloaddition step. After screening of various alkyl vinyl ethers (benzyl, 4-methoxybenzyl, 3,5-dimethoxybenzyl), the *tert*-butyl group emerged as the best balance between hydrolytic stability (as a vinyl ether) in the cycloaddition step and acidic sensitivity (as an acetal) in the cleavage step. Thus, provided that the reaction course was carefully monitored, 5% trifluoroacetic acid in dry dichloromethane cleanly removed the *tert*-butyl group from the vinyl-substituted adduct **17**, affording the lactol **18** in a reproducible 80−90% yield (Scheme 3).

An intriguing rearrangement was observed in model compounds of the *tert*-butyl acetal series. Thus, treatment of the side-chain alcohol **19** with Burgess reagent triggered a rearrangement of the tricyclic angular pyranocoumarin system into a linearly fused furocoumarin, affording, besides the expected dehydration product **17**, the enol ether **20** and the aldehyde **21** as well. A possible mechanism for the rearrangement is shown in Scheme 3. Conversion of the side-chain hydroxy group into a leaving group triggers attack from the lactone carbonyl group, which in turn results in opening of the pyran ring and formation of a vinyl enol ether, which is next hydrolysed in part to the corresponding aldehyde. Chemical shift considerations showed a *trans* relationship between the vicinal methyl groups of **20** and **21**, which resonated at δ ≈ 15 (C-2 Me) and 24 (C-3 Me), respectively. In *cis*-2,3-dimethyl-3-alkyl linear furocoumarins, both methyl groups instead resonate at δ ≈ 15.[16]



Scheme 3. Deprotection of the *tert*-butyl acetal **17** and rearrangement of the pyranocoumarin **19** to the furocoumarins **20** and **21**

By capitalising on the information acquired in the model studies, it was finally possible to achieve an expeditious and uneventful synthesis of lactol **5**, with an overall yield of 38% from 4-hydroxy-5-methylcoumarin (Scheme 4).[17] Compound **5** was obtained as an unstable 2:1 mixture of anomers, the major one being that with the hemiacetal proton axial ($J_{2,3a,b}$ = 9.4, 2.0 Hz). As an example of the potential to access ethuliacoumarins from the hemiacetal **5**, its conversion into (±)-preethulia coumarin (**3**)[6b] was carried out. Thus, norprenylation of the hemiacetal by treatment with 2-methyl-1-propenyllithium under sonication gave a ca 2:1 pair of diastereomeric alcohols **24**, Mitsunobu intramolecular etherification[18] of which afforded a compound possessing spectroscopic properties identical (apart from the optical rotation) to those of natural preethulia coumarin (**3**).



Scheme 4. Synthesis of preethulia coumarin (**3**)

The low overall yield from **5** (ca. 10%) essentially reflects the poor efficiency, in terms both of yield and of stereocontrol, of the norprenylation step. Conversely, the Mitsunobu intramolecular etherification showed an unexpectedly high level of efficiency and stereoselectivity. Indeed, we were unable to isolate the C-2 epimer of **3** from the reaction mixture, showing that a strong bias towards the formation of the natural configuration exists. This might cause kinetic resolution of the mixture of diastereomeric alcohols, with the epimer producing the unnatural configuration at C-2 presumably undergoing extensive degradation during the reaction. The overall stereoselectivity observed during the cyclization parallels that observed in the hetero Diels–Alder reaction, since only the diastereomer with a *trans* relationship between the substituent at C-2 and the C-3 methyl group was formed. Remarkably, the substituents at C-2 have different orientations in **6** and **3** (pseudo-axial and pseudo-equatorial, respectively), making it difficult to propose a compelling unifying argument to interpret the selectivity of the reactions in which this stereocenter was generated.

## Conclusion

In conclusion, we have reported a straightforward synthesis of the acetal **6**, a versatile intermediate from which to access biologically active coumarins of the ethuliacoumarin type, and its conversion via **5** into (±)-preethulia coumarin (**3**), the "least oxidized" member of the class. A surprising selectivity was observed in the creation of the stereocenter adjacent to the pyran oxygen atom, both at the level of the cycloaddition reaction and that of the vinyllithium alkylation. This suggests the involvement of subtle and hitherto unappreciated factors, seemingly also implicated in the configurational stability of hemiacetal ethuliacoumarins, and worth pursuing in further mechanistic investigations.

## Experimental Section

**General:** Anhydrous conditions were achieved by flame-drying flasks and other equipment. Reactions were monitored by TLC on Merck 60 $F_{254}$ (0.25 mm) plates, which were viewed by UV inspection and/or staining with 5% $H_2SO_4$ in ethanol and heating. – Merck silica gel was used for column chromatography (CC). – Melting points: Büchi SMP-20 (uncorrected values). – IR: Shimadzu FT-IR 8001 spectrophotometer. – NMR: Bruker AM 300 (300 MHz and 75 MHz for $^1H$ and $^{13}C$, respectively). For $^1H$ NMR, $CDCl_3$ as solvent, $C\mathit{H}Cl_3$ at δ = 7.26 as reference. For $^{13}C$ NMR, $CDCl_3$ as solvent, $\mathit{C}DCl_3$ at δ = 77.0 as reference. The chemical shifts (δ) are given in ppm, and the coupling constants (*J*) in Hz. – Low-resolution mass spectra (LRMS): Finnigan-MAT TSQ70 in chemical ionization with isobutane as reactant gas. Commercially available reagents and solvents were used without further purification unless otherwise noted. $CH_2Cl_2$ was dried by distillation from $P_4O_{10}$, THF and dioxane by distillation from Na/benzophenone, and DMF by distillation from $CaH_2$. $MgSO_4$ was used for drying organic solutions in all workup procedures.

**Reactions of 4-Hydroxycoumarin, α-Dicarbonyl Compounds and Vinyl Ethers:** The synthesis of **6** is given as representative. Dry dioxane (50 mL), activated molecular sieves (1.0 g), 4-hydroxy-5-methylcoumarin (2.0 g, 11.4 mmol) and a catalytic amount of ytterbium trifluoromethanesulfonate (ca. 50 mg) were placed in a 150-mL two-necked, round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet. After stirring at room temperature for 5 min, diacetyl (5.15 mL, 3.9 g, 45.6 mmol, 4.0 mol. equiv.) and *tert*-butyl vinyl ether (5.8 mL, 5.7 g, 57.0 mmol, 5.0 mol. equiv.) were added dropwise to the suspension. The reaction mixture was stirred for 30 h at room temperature under nitrogen, and then worked up by concentration. The residue was taken up in $CHCl_3$ and washed with 5% aqueous $Na_2CO_3$ and brine. The organic phase was dried ($MgSO_4$) and the solvents evaporated, and the residue was purified by CC [petroleum ether (PE)/EtOAc, 95:5] to give **6** (3.10 g, 79.0%) as off-white powder.

**(2*R**,4*R**)-4-Acetyl-2-*tert*-butoxy-4,10-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (6):** M.p. 136 °C. – IR (KBr disk): ṽ = 1718, 1689, 1638, 1103, 981, 797 $cm^{-1}$. – $^1H$ NMR ($CDCl_3$): δ = 1.29 (s, *t*Bu), 1.44 (m, 3b-H), 1.73 (s, 4-H), 2.10 (m, 3a-H), 2.29 (s, MeCO), 2.74 (s, 10-H), 5.70 (dd, *J* = 3.0, 5.5 Hz, 2-

H), 7.04 (d, $J$ = 7.4 Hz, 7-H), 7.17 (d, $J$ = 7.5 Hz, 9-H), 7.35 (t, $J$ = 7.5 Hz, 8-H),. − $^{13}$C NMR (CDCl$_3$): $\delta$ = 23.6 (q, C-10 Me), 22.4 (q, C-4 Me). 25.7 (q, C-4 acetyl), 28.4 (q, *tert*-butoxy), 38.3 (t, C-3), 46.0 (s, C-4), 76.6 (s, *tert*-butoxy), 96.5 (d, C-2), 115.1 (d, C-7), 105.9 (s, C-4a), 127.6 (d, C-9), 114.6 (s, 10a), 130.9 (d, C-8), 136.7 (s, C-10), 161.4 (s, C-10b), 153.9 (s, C-6a), 161.3 (s, C-5), 210.7 (s, C-4 acetyl). −$R_f$ = 0.38 (hexane/EtOAc, 7:3). − CIMS: 345 [M + H]$^+$. − C$_{20}$H$_{24}$O$_5$: calcd. C 69.75, H 7.02; found C 69.85, H 7.00.

**(2*R**,4*R**)-4-Acetyl-2-ethoxy-4-methyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (10a):** M.p. 85 °C. − IR (KBr disk): $\tilde{\nu}$ = 1710, 1620, 1570, 1390, 1340, 1140, 1010, 755 cm$^{-1}$. − $^1$H NMR (CDCl$_3$): $\delta$ = 1.24 (t, 2-Et), 1.71 (s, 4-Me), 1.98 (m, 3b-H), 2.23 (m, 3a-H), 2.24 (s, MeCO), 3.73 (m, 2-Et), 3.97 (m, 2-Et), 5.48 (t, $J$ = 4.0, 5.5 Hz, 2-H), 7.30 (m, $J$ = 7.5 Hz, 9 and 7-H), 7.51 (br. t, $J$ = 8.0 Hz, 8-H), 7.81 (br. d, $J$ = 8.0 Hz, 10-H), − $R_f$ = 0.30 (hexane/EtOAc, 6:4).). − $^{13}$C NMR (CDCl$_3$): $\delta$ = 15.1 (q, OEt). 22.0 (q, C-4 Me), 25.6 (q, C-4 acetyl), 36.8 (t, C-3), 45.6 (s, C-4), 65.6 (t, OEt), 98.5 (d, C-2), 106.1 (s, C-4a), 115.5 (s, C-10a), 124.0 (d, C-10), 116.6 (d, C-7), 122.9 (d, C-9), 158.0 (s, C-10b), 152.7 (s, C-6a), 161.4 (s, C-5), 209.9 (s, C-4 acetyl). − CIMS: 303 [M + H]$^+$. − C$_{17}$H$_{18}$O$_5$: calcd. C 67.54, H 6.00; found C 67.45, H 6.01.

**Ethyl (2*R**,4*R**)-2-Ethoxy-4-methyl-5-oxo-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromen-4-carboxylate (10b):** M.p. 70 °C. − IR (KBr disk): $\tilde{\nu}$ = 1740, 1707, 1682, 1397, 1103, 1013, 909, 770 cm$^{-1}$. − $^1$H NMR (CDCl$_3$): $\delta$ = 1.23 (t, $J$ = 7.05 Hz, 2-Et), 1.26 (t, = 5.05 Hz, 4-Et), 1.72 (s, 4-Me), 2.13 (m, 3b-H), 2.38 (m, 3a-H), 3.73 (m, 4-Et), 4.01 (m, 4-EtO), 4.17 (q, $J$ = 7.05 Hz, 2-Et), 5.49 (t, $J$ = 4.5 Hz, 2-H), 7.29 (m, $J$ = 7.5 Hz, 9 and 7-H), 7.51 (br. t, $J$ = 8.0 Hz, 8-H), 7.82 (br. d, $J$ = 8.0 Hz, 10-H). − $^{13}$C NMR (CDCl$_3$): $\delta$ = 15.1 (q, OEt), 22.0 (q, C-4 Me), 14.8 (q, C-4 COOEt). 37.9 (t, C-3), 46.9 (s, C-4), 60.6 (t, C-4 COOEt), 66.1 (t, OEt), 98.2 (d, C-2), 117.0 (d, C-7), 115.5 (s, C-10a), 106.8 (s, C-4a), 124.3 (d, C-10), 123.6 (d, C-9), 152.1 (s, C-6a), 156.9 (s, C-10b), 161.7 (s, C-5), 168.9 (s, C-4 COOEt), − $R_f$ = 0.30 (hexane/EtOAc, 6:4). − CIMS: 333 [M + H]$^+$. − C$_{18}$H$_{20}$O$_6$: calcd. C 65.05, H 6.07; found C 65.09, H 6.10.

**(2*R**,4*S**)-2-Ethoxy-4-methyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]-chromen-5-one (11):** M.p. 102 °C. − IR (KBr disk): $\tilde{\nu}$ = 1710, 1630, 1410, 1170, 1100, 1010, 755 cm$^{-1}$. − $^1$H NMR (CDCl$_3$): $\delta$ = 1.33 (m, 2-Et), 2.02 (m, 3a and 3b-H), 3.80 (m, 2-Et), 3.06 (m, 4-H), 4.13 (m, 2-Et), 5.36 (dd, $J$ = 7.7, 2.9 Hz, 2-H), 7.27 (m, 9 and 7-H), 7.50 (br. t, $J$ = 7.3 Hz, 8-H), 7.75 (dd, $J$ = 7.7, 1.3 Hz, 10-H). − $^{13}$C NMR (CDCl$_3$): $\delta$ = 15.1 (q, OEt), 20.1 (d, C-4), 24.3 (q, C-4 Me), 34.3 (t, C-3), 65.4 (t, OEt), 98.9 (s, C-2), 105.7 (s, C-4a), 115.5 (s, C-10a), 116.3 (d, C-7), 122.4 (d, C-9), 123.5 (d, C-10), 131.3 (d, C-8), 152.5 (s, C-6a), 157.5 (s, C-10b), 162.2 (s, C-5), − $R_f$ = 0.49 (hexane/EtOAc, 6:4). − CIMS: 261 [M + H]$^+$. − C$_{15}$H$_{16}$O$_4$: calcd. C 69.22, H 6.20; found C 69.35, H 6.16.

**Conversion of the 4-Acetyl Adducts to the 4-Vinyl Adducts:** The synthesis of **23** is given as representative. The adduct **6** (1.35 g, 3.9 mmol) was dissolved in EtOH (20 mL) in a 50-mL round-bottomed flask, and an excess of NaBH$_4$ (385 mg, 9.75 mmol, 2.5 mol. equiv.) was added portionwise. The mixture was stirred for 3 h at room temperature, quenched with a saturated solution of NH$_4$Cl (20 mL), extracted with EtOAc and washed with brine (30 mL). After drying (MgSO$_4$) and removal of the solvent, the white residue was purified by CC (PE/EtOAc, 20:1) to afford **22** (1.27 g, 94%) as a 3:2 mixture of epimers. A portion of this mixture was further purified by CC (same eluent) to give the major isomer as white crystals.

**(2*R**,4*R**)-2-*tert*-Butoxy-4-(1-hydroxyethyl)-4,10-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (22):** M.p. 157 °C. − IR (KBr disk): $\tilde{\nu}$ = 1705, 1599, 1560, 1024, 962, 785 cm$^{-1}$. − $^1$H NMR (CDCl$_3$): $\delta$ = 1.20 (d, 2′-H), 1.36 (s, *t*Bu), 1.45 (s, 4-Me), 1.47 (s, 10-Me), 2.26 (dd, 3a-H), 2.47 (br. s, OH), 4.40 (m, 1′-H), 5.93 (dd, $J$ = 3.0, 5.5 Hz, 2-H), 7.28−7.27 (m, 7 and 9-H), 7.49 (t, $J$ = 7.5 Hz, 8-H), H), − $R_f$ (hexane/EtOAc, 6:4) = 0.42, minor isomer = 0.33. − CIMS: 347 [M + H]$^+$. − C$_{20}$H$_{26}$O$_5$: calcd. C 69.34, H 7.56; found C 69.42, H 7.50. − Another portion of the mixture, (257 mg, 1.04 mmol) was dissolved in THF (15 mL) and treated with 2-nitrophenyl selenocyanate (590 mg, 2.6 mmol, 2.5 mol. equiv.) and tri-*n*-butylphosphane (648 µL, 2.6 mmol, 2.5 mol. equiv.). The reaction mixture was stirred at 60 °C for 12 h. After cooling to 0 °C, an excess of H$_2$O$_2$ (30%, 450 mL) was added dropwise, and stirring was continued for further 30 min. The solution was diluted with water and extracted with EtOAc; the organic phase was washed with brine and dried with MgSO$_4$. The residue was purified by CC (PE/EtOAc, 20:1) to give 204 mg of (**23**) (60%) as a colourless gum.

**(2*R**,4*R**)-2-*tert*-Butoxy-4-ethenyl-4,10-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (23):** IR (KBr disk): $\tilde{\nu}$ = 1715, 1615, 1390, 1325, 1150, 995 cm$^{-1}$. − $^1$H NMR (CDCl$_3$): $\delta$ = 1.30 (s, *t*Bu), 1.72 (s, 4-Me), 2.24 (m, 3a-H), 2.74 (s, 10-Me), 5.12 (m, 2′-H), 5.50 (dd, 2-H), 6.13 (dd, $J$ = 17.2, 10.4 Hz, 1′-H), 5.50 (dd, 2-H), 5.12 (m, 2′-H) 7.14 (d, $J$ = 8.0 Hz, 7-H), 7.34 (dd, $J$ = 8.1, 7.7 Hz, 8-H). − $R_f$ = 0.47 (hexane/EtOAc, 8:2).). − $^{13}$C NMR (CDCl$_3$): $\delta$ = 23.9 (q, C-4 Me), 28.6 (q, *tert*-butoxy), 38.1 (t, C-3), 45.8 (s, C-4), 77.3 (s, *tert*-butoxy), 106.1 (s, C-4a), 114.0 (s, C-10a), 98.9 (d, C-2), 115.6 (d, C-7), 112.8 (t, C-4 vinyl), 126.9 (d, C-9), 130.6 (d, C-8), 136.8 (d, C-10), 140.3 (d. C-4), 162.3 (s, C-10b), 153.9 (s, C-6a), 161.6 (s, C-5). − CIMS: 329 [M + H]$^+$. − C$_{20}$H$_{24}$O$_4$: calcd. C 73.15, H 7.37; found C 73.26, H 7.33.

**(2*R**,4*R**)-4-Ethenyl-2-ethoxy-4-methyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (13):** IR (KBr disk): $\tilde{\nu}$ = 1715, 1615, 1390, 1325, 1150, 995 cm$^{-1}$. − $^1$H NMR (CDCl$_3$): $\delta$ = 1.61 (s, 4-Me), 1.34 (t, $J$ = 6.6 Hz, 2-Et), 2.01 (m, $J$ = 13.6, 8.8 Hz, 3b-H), 2.16 (dd, $J$ = 13.6, 1.9 Hz, 3a-H), 4.13 (m, 2-Et) 3.77 (m, 2-Et), 4.95 (d, $J$ = 17.6 Hz, 2′b-H), 5.15 (d, $J$ = 10.4 Hz, 2′a-H), 5.22 (dd, $J$ = 8.8, 1.9 Hz, 2-H), 6.01 (dd, $J$ = 17.6, 10.4 Hz, 1′-H), 7.30 (m, 7 and 9-H), 7.51 (br. t, $J$ = 8.0 Hz, 8-H), 7. 81 (br. d, $J$ = 8.0 Hz, 10-H). − $R_f$ = 0.44 (hexane/EtOAc, 8:2).). − $^{13}$C NMR (CDCl$_3$) $\delta$ = 162.6 (s, C-5), 24.0 (q, C-4 acetyl), 28.2 (q, *tert*-butoxy), 36.1 (s, C-4), 36.3 (t, C-3), 77.2 (s, *tert*-butoxy), 99.1 (d, C-2), 116.1 (s, C-10a), 113.0 (t, C-4 vinyl), 116.4 (d, C-7), 123.0 (d, C-9), 124.1 (d, C-10), 132.2 (d, C-8), 140.6 (s, C-4 vinyl), 151.0 (s, C-6a), 158.7 (s, C-10b). − CIMS: 287 [M + H]$^+$. − C$_{17}$H$_{18}$O$_4$: calcd. C 71.31, H 6.34; found C 71.26, H 6.32.

**Hydrolysis of the Ethyl Acetal Adducts:** Treatment of **10a** is given as representative. H$_2$SO$_4$ (50%, 120 mL) was added to a solution of **10a** (18.0 g, 60 mmol) in THF (80 mL), and the reaction mixture was refluxed for 5 h. After cooling, this mixture was diluted with water (200 mL) and extracted with EtOAc. The organic phase was washed with sat. Na$_2$CO$_3$ and brine, and then concentrated to give a solid residue. Washing with ether removed some coloured impurities, eventually affording **15** (12.0 g, 73%) as a white powder.

**(2*S**,3a*R**,10a*R**)-2-Hydroxy-3a,10a-dimethyl-2,3,3a,10a-tetrahydro-4*H*-furo[3′,2′:4,5]furo[2,3-*c*]chromen-4-one (15):** IR (KBr disk): $\tilde{\nu}$ = 1715, 1615, 1390, 1325, 1150, 995 cm$^{-1}$. − $^1$H NMR (CDCl$_3$): $\delta$ = 1.34 (t, $J$ = 6.6 Hz, Me), 1.61 (s, 4-Me), 2.01 (m, $J$ = 13.6, 8.8 Hz, 3b-H), 2.16 (dd, $J$ = 17.3, 3.6, 1.9 Hz, 3a-H), 3.77 (m, OCH$_2$), 4.13 (m, OCH$_2$), 4.95 (d, $J$ = 17.6 Hz, 2′b-H), 5.15 (d,

$J$ = 10.4 Hz, 2′a-H), 5.22 (dd, $J$ = 8.8, 1.9 Hz, 2-H), 6.01 (dd, $J$ = 17.6, 10.4 Hz, 1′-H), 7.51 (br. t, $J$ = 8.0 Hz, 8-H), 7. 81 (br. d, $J$ = 8.0 Hz, 10-H). − $R_f$ = 0.44 (hexane/EtOAc, 8:2). − CIMS: 275 $[M + H]^+$. − $C_{15}H_{14}O_5$: calcd. C 65.69, H 5.15; found C 65.76, H 5.15.

**(2*R**,4*S*ξ,5*S**)-4,5-Dimethyl-4,5-dihydro-2*H*,6*H*-2,5-methano-[1,3]dioxepa[5,4-*c*]chromen-6-one (14):** IR (KBr disk): $\tilde{\nu}$ = 1713, 1610, 1325, 1150, 970 cm$^{-1}$. − $^1$H NMR ($CDCl_3$): $\delta$ = 1.29 (d, $J$ = 6.2 Hz, 13-H), 1.65 (s, 14-H), 2.18 (d, $J$ = 8.8 Hz, 3b-H), 2.31 (d, $J$ = 11.7 Hz, 3a-H), 4.08 (q, $J$ = 6.2 Hz, 12-H), 5.86 (d, $J$ = 3.3 Hz, 2-H), 7.26 (m, 7 and 9-H), 7.50 (br. t, $J$ = 7.3 Hz, 8-H), 7. 72 (d, $J$ = 7.7 Hz, 10-H). − $R_f$ = 0.60 (hexane/EtOAc, 1:1). − CIMS: 259 $[M + H]^+$. − $C_{15}H_{14}O_4$: calcd. C 69.76, H 5.46; found, 69.70, H 5.44.

**Oxidation of Lactol 15 to Lactone 16:** PCC (14.0 g, 64.9 mmol) was added to a solution of lactol **15** (12.8 g, 43.8 mmol) in dry $CH_2Cl_2$, (155 mL), and the reaction mixture was stirred at room temp. for 24 h. At this point, additional PCC (14.0 g) was added, and 6 h later the reaction was worked up by addition of ether (100 mL) and filtration through Celite. The cake was washed with ether, and the pooled filtrates were concentrated to afford a residue that crystallised spontaneously. After washing with ether, 4.9 g of **16** (41%) were obtained as white powder.

**(2*S**,3a*R**,10a*R**)-3a,10a-Dimethyl-2,3,3a,10a-tetrahydro-2*H*,4*H*-furo[3′,2′:4,5]furo[2,3-*c*]chromene-2,4-dione (16):** White powder, m.p. 191 °C. − IR (KBr disk): $\tilde{\nu}$ = 1780, 1710, 1650, 1610, 1400, 1070, 990, 950, 770 cm$^{-1}$. − $^1$H NMR ($CDCl_3$): $\delta$ = 1.57 (s, Me), 1.88 (s, Me), 2.73 (d, $J$ = 18.0, Hz, 3b-H), 3.36 (d, $J$ = 18.0 Hz, 3a-H), 7.34 (br. t, $J$ = 8.0 Hz, 8-H), 7.41 (br. d, $J$ = 8.0 Hz, 6-H), 7.63 (br. t, $J$ = 8.0 Hz, 7-H), 7. 71 (dd, $J$ = 8.0, 1.5 Hz, 9-H). − $^{13}$C NMR ($CDCl_3$): $\delta$ = 20.3 (2 × q, C-3a-Me and C-10a-Me), 21.1, 43.7 (t, C-3), 51.9 (s, C-3a), 96.2 (d, C-2), 108.6 (s, C-10a), 112.6 (s, C-9a), 116.7 (d, C-6), 122.6 (d, C-9), 123.6 (d, C-8), 124.7 (s, C-9a), 131.8 (d, C-7), 159.6 (s, C-9b), 154.7 (s, C-5b), 162.8 (s, C-4). − $R_f$ = 0.34 (hexane/EtOAc, 6:4). − CIMS: 273 $[M + H]^+$. − $C_{15}H_{12}O_5$: C,66.17, H 4.44; found C 66.27, H 4.32.

**Hydrolysis of the *tert*-Butyl Acetal Adducts:** Treatment of **23** is given as representative. Trifluoroacetic acid (500 µL) was added to a solution of **23** (92 mg, 0.28 mmol) in dry $CH_2Cl_2$. The reaction mixture was stirred for 3 h at room temperature, and then worked up by treatment with a saturated solution of $NaHCO_3$ and extraction with EtOAc. The organic phase was washed with brine and dried with $MgSO_4$. The residue was purified by CC (PE/EtOAc, 8:2) to give **5** (65 mg, 85%) as a pale yellow powder.

**(2*R**,4*R**)-4-Ethenyl-2-hydroxy-4,10-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (5):** M.p. 131 °C. − IR (KBr disk): $\tilde{\nu}$ = 3400, 1717, 1684, 1613, 1566, 1034, 756 cm$^{-1}$. − **Major Isomer:** $^1$H NMR ($CDCl_3$): $\delta$ = 1.68 (s, 4-Me), 1.96 (m, 3b-H), 2.18 (m, 3a-H), 2.73 (s, 10-Me), 4.99 (d, $J$ = 17.9 Hz, 2′b-H), 5.13 (d, $J$ = 11.0 Hz, 2′a-H), 5.78 (dd, $J$ = 6.9, 2.9 Hz, 2-H), 6.05 (dd, $J$ = 17.3, 10.5 Hz, 1′-H), 7.00 (d, $J$ = 7.6 Hz, 9-H), 7.10 (d, $J$ = 8.0 Hz, 7-H), 7.32 (dd, $J$ = 8.0, 7.5 Hz, 8-H). − $R_f$ = 0.63 (hexane/EtOAc, 6:4). − **Minor Isomer:** $^1$H NMR ($CDCl_3$): $\delta$ = 1.74 (s, 4-Me), 2.07 (m, 3b-H), 2.08 (m, 3a-H), 2.79 (s, 10-Me), 4.93 (d, $J$ = 17.9 Hz, 2′b-H), 5.20 (d, $J$ = 11.0 Hz, 2′a-H), 5.72 (dd, $J$ = 6.9, 2.9 Hz, 2-H), 6.22 (dd, $J$ = 17.3, 10.5 Hz, 1′-H), 7.01 (d, $J$ = 7.6 Hz, 9-H), 7.14 (d, $J$ = 8.0 Hz, 7-H), 7.30 (dd, $J$ = 8.0, 7.5 Hz, 8-H). − $R_f$ = 0.63 (hexane/EtOAc, 6:4). − CIMS: 273 $[M + H]^+$. − $C_{16}H_{16}O_4$: calcd. C 70.57, H 5.92; found C 70.54, H 5.90.

**Treatment of the Side-Chain Alcohol 19 with Burgess Reagent:** A solution of **19** (1.33 g, 4.0 mmol) in dry benzene (20 mL) was added dropwise to a solution of Burgess reagent (1.08 g, 4.2 mmol, 1.05 mol. equiv.) in 5 mL of dry benzene. The reaction mixture was then stirred at 50 °C for 4 h, and worked up by dilution with EtOAc (50 mL) and washing with brine. After drying ($MgSO_4$) and removal of the solvent, the residue was purified by CC (hexane/EtOAc, 9:1) to give, in order of elution, 80 mg of **20**, 68 mg of **17** and 40 mg of **21**.

**(2*R**,3*S**)-3-(2-*tert*-Butoxyethenyl)-2,3-dimethyl-2,3-dihydro-4*H*-furo[2,3-*b*]chromen-5-one (20):** IR (KBr disk): $\tilde{\nu}$ = 1637, 1622, 1460, 1441, 1146, 1059 cm$^{-1}$. − $^1$H NMR ($CDCl_3$): $\delta$ = 1.21 (s, *t*Bu), 1.39 (s, 2-Me), 1.58 (s, 3-Me), 4.83 (q, $J$ = 6.6 Hz, 2-H), 4.93 (d, $J$ = 16.0 Hz, 1′-H), 5.58 (d, $J$ = 16.0 Hz, 2′-H), 7.36 (br. d, $J$ = 7.8 Hz, 8-H), 7.40 (m, 6-H), 7.55 (m, 7-H), 8.20 (d, $J$ = 8.0 Hz, 5-H). − $^{13}$C NMR ($CDCl_3$): $\delta$ = 15.75 (q, C-2),24.8 (q, C-3 Me), 27.9 (q, *tert*-butoxy), 76.2 (s, *tert*-butoxy), 91.7 (d, C-2), 101.0 (s, C-3a), 108.2 (d, C-3 vinyl), 124.65 (s, C-4a), 125.3 (d, C-6), 125.8 (d, C-5), 117.25 (d, C-8), 132.15 (d, C-7), 142.6 (d, C-3 vinyl), 153.3 (s, C-8a), 168.0 (s, C-9a), 174.0 (s, C-4). − $R_f$ = 0.50 (hexane/EtOAc, 6:4). − CIMS: 315 $[M + H]^+$. − $C_{19}H_{22}O_4$: calcd. C 72.59, H 7.05; found C 72.59, H 7.00.

**(2*R**,3*S**)-2,3-Dimethyl-3-(2-oxoethyl)-2,3-dihydro-4*H*-furo[2,3-*b*]-chromen-5-one (21):** IR (KBr disk): $\tilde{\nu}$ = 1725, 1645, 1614, 1564, 1476, 1078, 789, 760 cm$^{-1}$. − $^1$H NMR ($CDCl_3$): $\delta$ = 1.41 (d, $J$ = 6.8 Hz, 2-Me), 1.58 (s, 3-Me), 3.17 (m, 1′a-H), 2.84 (1′b-H), 4.82 (q, $J$ = 6.8 Hz, 2-H),7.4 (m, 8-H and 6-H), 7.59 (m, 7-H), 8.18 (d, $J$ = 8.0 Hz, 5-H), 9.83 (t, $J$ = 3.0 Hz, 2′-H). − $^{13}$C NMR ($CDCl_3$): $\delta$ = 24.6 (C-3 Me), 15.25 (C-2 Me), 44.5 (s, C-3), 48.4 (t, C-1′), 91.0 (d, C-2), 94.0 (s, C-3a), 125.6 (d, C-5 and C-6), 124.3 (s, C-4a), 132.6 (d, C-7), 153.4 (s, C-8a), 117.45 (d, C-8), 168.1 (s, C-9a), 175.1 (s, C-4), 201.2 (s, C-2′), − $R_f$ = 0.25 (hexane/EtOAc, 6:4). − CIMS: 259 $[M + H]^+$. − $C_{15}H_{14}O_4$: calcd. C 69.76, H 5.46; found C 69.81, H 5.34.

**Norprenylation of Lactol 5:** Lithium wire with a high (1.5%) sodium content (138 mg, 19.9 mmol, 6 mol. equiv.) was added to a solution of 1-bromo-2-methylpropene (0.92 mL, 9.93 mmol, 3.0 mol. equiv.) in dry diethyl ether/THF (1:1, 40 mL), in a 100-mL two-necked flask equipped with a nitrogen inlet. The suspension was sonicated for 2 h at 0 °C in an ultrasound cleaner bath. The suspension was allowed to settle, and the supernatant was transferred by cannula to a 150-mL three-necked flask equipped with a pressure-equalising addition funnel, a magnetic stirrer and a nitrogen inlet. A solution of lactol **5** (900 mg, 3.31 mmol) in dry diethyl ether/THF (1:1, 30 mL) was slowly added dropwise at −78 °C and the mixture was stirred for 30 min at this temperature. After warming to 0 °C, stirring was continued for 50 min, and the reaction was then quenched by the addition of ice-cold sat. aq. $NH_4Cl$ (30 mL) and ethyl acetate (80 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$), and concentrated to give a yellowish oil. Purification by CC (PE/EtOAc, 9:1 as eluent) afforded **24** (217 mg, 20%) as a 2:1 mixture of isomers.

**3-(1-Ethenyl-3-hydroxy-1,5-dimethylhex-4-enyl)-4-hydroxy-5-methyl-2*H*-chromen-2-one (24):** White powder. − IR (KBr disk): $\tilde{\nu}$ = 1625, 1610, 1565, 1260, 1085, 990, 755 cm$^{-1}$. − $^1$H NMR ($CDCl_3$) (major diastereomer): $\delta$ = 1.54 (s, 1′-Me), 1.69, 1.58 (2 × s, 5′-Me), 2.04−1.69 (m, 2′-Ha,b), 2.82 (s, 5-Me), 4.30 (m, 3′-H), 5.05 (d, $J$ = 17.2 Hz, 1′-vinyl), 5.15 (d, $J$ = 10.1 Hz, 1′-vinyl), 5.22 (br. d, 4′-H), 6.18 (dd, $J$ = 17.0, 10.1 Hz, 1′-vinyl), 7.05 (m, 6-H), 7.15 (br. d, 8-H), 7.43 (m, 7-H). − $R_f$ = 0.48 (hexane/EtOAc, 6:4). − CIMS: 329 $[M + H]^+$. − $C_{20}H_{24}O_4$: calcd. C 73.15, H 7.37; found C 73.03, H 7.41.

**(2*S**,4*R**)-4-Ethenyl-4,10-dimethyl-2-(2-methylprop-1-enyl)-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromen-5-one [(±)-Preethulia Cou-**

**marin (3)]:** DEAD (29 mg, 0.166 mmol, 1.3 mol. equiv.) was added to a suspension of **24** (42 mg, 0.128 mmol) and triphenylphosphane (50 mg, 0.192 mmol, 1.5 mol. equiv.) in dry toluene (10 mL). After stirring for 3 h, the reaction mixture was worked up by filtration and dilution with EtOAc. After washing with brine and drying ($MgSO_4$), the solution was concentrated and the residue purified by CC (PE/EtOAc, 20:1, as eluent) affording 22 mg preethulia coumarin (**3**) (55%) as a foam. − IR (KBr disk): $\tilde{\nu}$ = 1650, 1620, 1610, 1395, 1320, 1150, 1105, 920 cm$^{-1}$. − $^1$H NMR ($CDCl_3$): $\delta$ = 1.64 (s, 4-Me), 1.68 (m, 3b-H), 1.96 (m, 3a-H), 1.84, 1.82 (2 × s, 2′-Me),), 2.84 (s, 10-Me), 5.07 (br. t, 3 H, $J$ = 8.5 Hz, 2-H), 5.36 (br. d, $J$ = 8.6, 1.3 Hz, 1′-H.5 Hz, 4-vinyl), 6.20 (dd, $J$ = 17.6, 10.6 Hz, 4-vinyl), 7.06 (br. d, 9-H), 7.17 (br. d, 7-H), 7.39 (m, 8-H). − $R_f$ (**3**) = 0.51 (hexane/EtOAc, 8:2). − CIMS: 311 [M + H]$^+$. − $C_{20}H_{22}O_3$: calcd. C 77.39, H 7.14; found C 77.30, H 7.22.

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