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Reinvestigation of the Dimerisation Process Forming Isoglaucanic Acid

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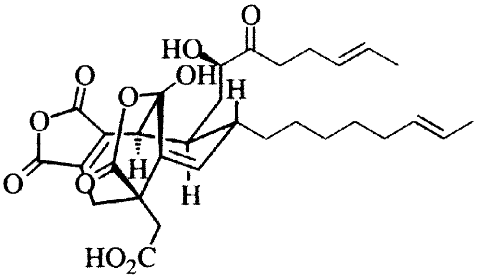
Abstract: The base catalysed dimerisation of 2-[(*E*)-1'-pentenyl]-3-methyl maleic anhydride has been extensively reinvestigated and the relative stereochemistry of an isoglaucanic acid derivative product has been determined by X-ray crystallography. The dimerisation process has been improved and the work up has been simplified, doubling the yield. Further co-products have been isolated and characterised from which a stepwise mechanism is proposed. © 1999 Elsevier Science Ltd. All rights reserved.

Recently two new natural products, CP-225,917 (**1**) and CP-263,114 (**2**), have been isolated at the Pfizer Central Research Laboratories from an unidentified fungus.[1] They are inhibitors of the squalene synthase and the Ras-farnesyl transferase,[2] thus they are of great interest for cancer chemotherapy as well as in the control of the cholesterol levels. Indeed their unusual structure and the important biological activity of these compounds has inspired several different total synthetic approaches to simplified model compounds with a similar core.[3-7]



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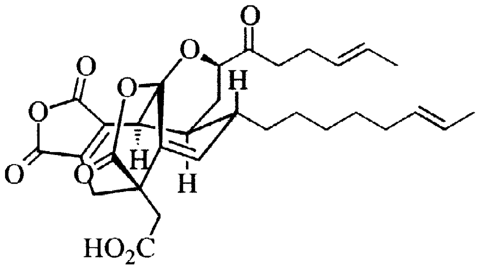

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Scheme 1

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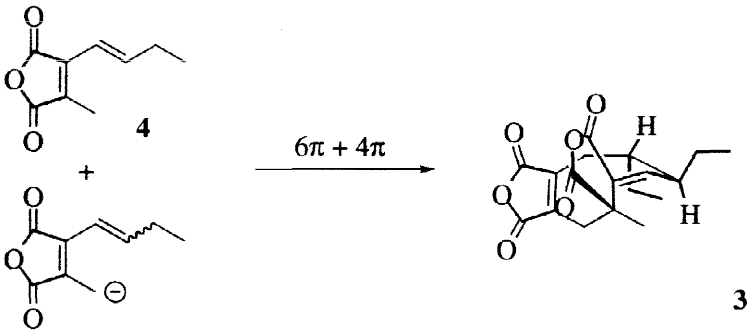
The main core of CP-225,917 (**1**) and CP-263,114 (**2**) consists of an isomeric form of the isoglaucanic acid structure (**3**), stabilised by an additional C-C bond, joining the nine membered ring on to one of the anhydride carbonyls.[9] In the isoglaucanic acid molecule the relative stereochemistry is different from the one of the 'CP'- compounds (**1** and **2**). In **3** the methyl side chain is ***trans*** to the first ethyl side chain, whereas the corresponding substituents are *cis* in the molecules **1** and **2**.

A biomimetic approach to CP-225,917 (**1**) and CP-263,114 (**2**) would be to construct the nine membered ring via an analogous 6π + 4π cyclodimerisation as proposed by Sutherland for the simpler nonadride isoglaucanic acid (**3**) (Scheme 2).[8,9] Likewise (**1**) and (**2**) contain a (*Z*)-trisubstituted alkene whereas the trisubstituted double bond in isoglaucanic acid (**3**) is of (*E*)-geometry.

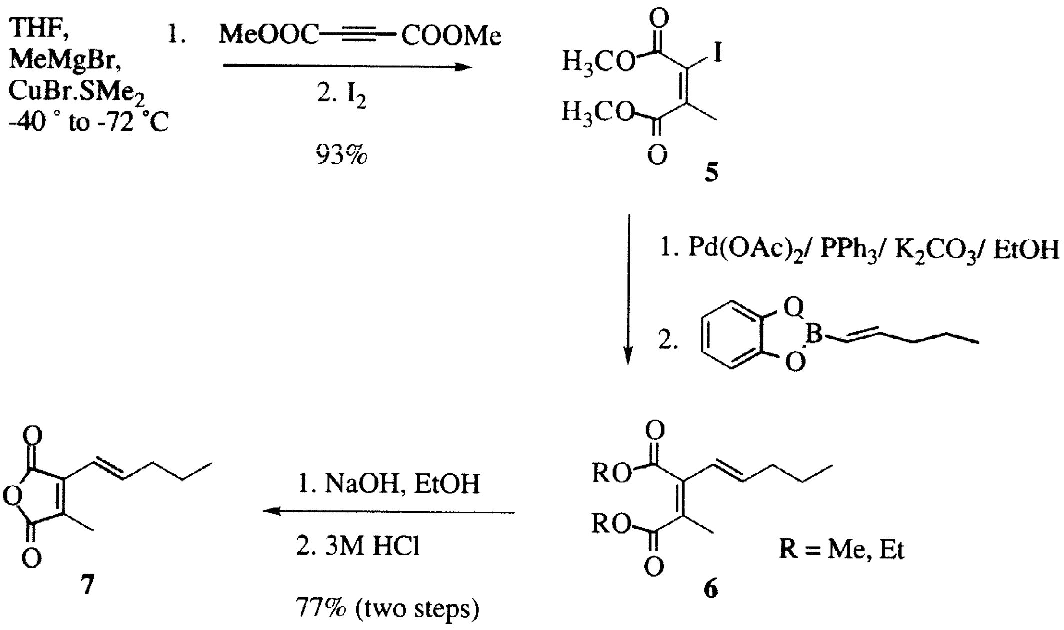


Scheme 2

As the relative stereochemistry of Sutherland's isoglaucanic acid has not been absolutely proven and only little was known about the reaction mechanism we have reinvestigated this dimerisation step, with a view to establishing its potential for a biomimetic synthesis of CP-225,917 (**1**) and CP-263,114 (**2**). Sutherland proposed the stereochemistry of **3** based on comparison to a stereoisomer, naturally occurring glaucanic acid (*cis* relative stereochemistry for ethyl groups).

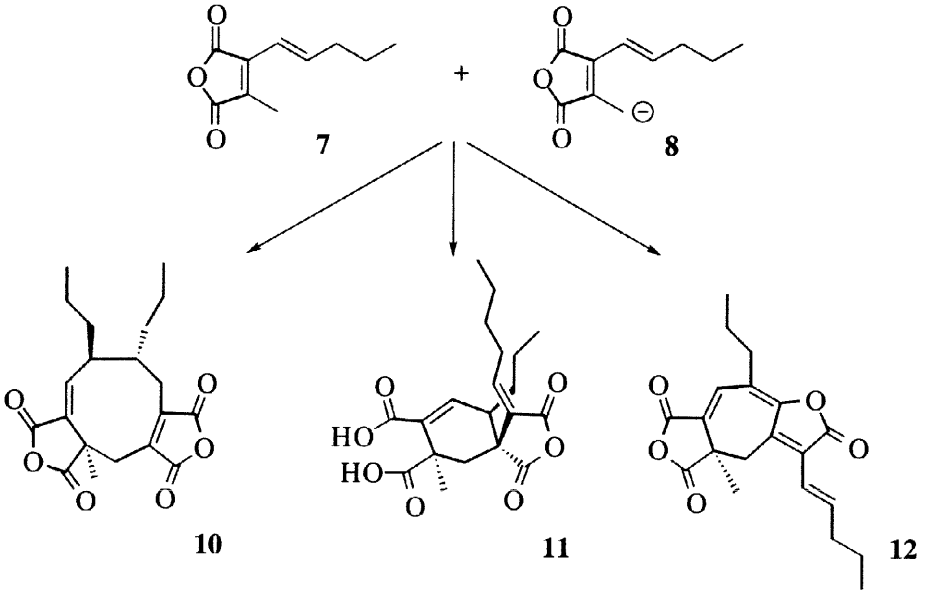
Results and discussion

A shorter and more efficient route to an anhydride having a pentenyl (**7**) side chain instead of butenyl (**4**), as employed by Sutherland, was sought. Starting from commercial dimethyl acetylene dicarboxylate, 2-iodo-3-methyl dimethyl maleate (**5**) was obtained in 93 % yield via a modified synthesis based upon known organocopper chemistry.[10] The iodide (**5**) was converted into the 2-[(*E*)-1'-pentenyl]-3-methyl dimethyl maleate (**6**) by a palladium cross coupling reaction with [(*E*)-1'-pentenyl]-1,3,2-benzodioxaborole.[11,12] During the reaction partial trans-esterification occurred, resulting in a mixture of dimethyl, diethyl and methyl ethyl ester. In an attempt to avoid trans-esterification the reaction was also carried out in methanol, however only very low yield (26%) was obtained. The mixture of esters was transformed into the desired anhydride **7** under basic reaction conditions with subsequent acidic work up.[9] The anhydride was stable and could be stored for several weeks at RT, however, decomposition was seen on silica gel even when adding formic acid to the eluent.



Scheme 3

The dimerisation reaction reported by Sutherland was carried out in DMF with sodium hydride or triethylamine as a base with 2% and 4% yield respectively.[9] In our hands different parameters in the reaction were varied: solvent, temperature, base and the addition of metal salts in an attempt to optimise dimerisation of **7**. Experimental results are summarised in Table 1. In all cases polymerisation of **7** was found to be the major pathway, however three compounds (**10**, **11** and **12**) were isolated (Scheme 4).



Scheme 4

From Table 1 it can be seen that the polarity of the solvent was an important factor. On changing to DMSO (entry a, Table 1) from DMF (entry b), better results were obtained. Less polar solvents appeared to disfavour the formation of the anion **8** (deep purple colour), thus impeding any reaction. Temperature dependence was investigated for the triethylamine and DMF/ DMSO system. In DMF the reaction seemed to reach completion after a shorter reaction time at higher temperature (within 3 hours at 80 °C). Cooling to 0 - 10 °C however not only slowed down the reaction but also favoured the formation of the spiro compound **11** (entry c). Heating the reaction in DMSO did not show any improvement and almost no dimeric products could be detected by ^1H NMR.

Sutherland and co-workers reported an increase of the dimerisation yield using triethylamine instead of sodium hydride. Experiments using dimethylaminopyridine showed only little dimeric product upon heating to 100 °C, whereas use of pyridine or dimethylaniline as a base didn't form any dimeric material.

A further possibility, that the anhydride may undergo metal complexation to assist dimerisation at the expense of polymerisation, was investigated. This was tried with anhydrous $MgCl_2$, being added to the anhydride in DMSO prior to the base. As listed in Table 1 (entry a and d), a clear influence is evident.

The best result to bias dimerisation to **10** was obtained using a ratio of 1:2 ($MgCl_2$/ anhydride, entry d). A similar effect could also be observed using DMF as a solvent, however a much longer reaction time was required. Other anhydrous magnesium salts ($MgBr_2$ and $Mg(OTf)_2$) were tested with less success. To show that a coordinative effect was involved, the reaction was repeated with LiCl to check the effect of the ionic strength of the reaction. This showed no influence on the product distribution compared to the system without any addition of metal salts (entry a).

exp.	condition	product ratio			isolated yield
		10	**11**	**7**	
a	DMSO/ NEt_3 (0.66 eq.)	1	1.5	1.8	4.5 % of **10**
b	DMF/ NEt_3 (0.66 eq.)	1	2.3	4.2	12.5 % of **11**
c	DMF/ NEt_3 (0.66 eq.), 0-10 °C, 90 h	1	2.9	2.1	not isolated
d	DMSO/ NEt_3 (0.66 eq.)/ $MgCl_2$ (0.5 eq.)	1	0.7	1.1	8.5 % of **10**
e	DMSO/ NEt_3 (0.66 eq.)/ $CaCl_2$ (0.5 eq.)	1	<0.1	2.5	not isolated
f	DMSO/ $MgBr((CH_3)_2CHNC_6H_{13})$ (0.25 eq.)	1	0.4	1.6	6.5 % of **10**
g	DMSO/ CaH_2 (0.66 eq.)	1	<0.1	4.8	not isolated

Table 1: The ratio between the different products is determined comparing the integrals of the clearly separated olefinic signals between 6.9 and 6.2 ppm in the ^1H NMR of the crude product. All reactions were stirred at RT for 24 h unless otherwise stated.

However it was found that adding small amounts of water had a detrimental effect to the influence of $MgCl_2$. This is a clear hint to the coordination of the anhydride. Water, being a better ligand for Mg^{2+}, will occupy the free coordination sites and therefore block a further coordination to weaker ligands. Ca^{2+} also usually shows a strong coordination tendency to acids,[13] so anhydrous $CaCl_2$ was tested too (entry e). In this case almost no formation of the spiro compound (**11**) could be observed.

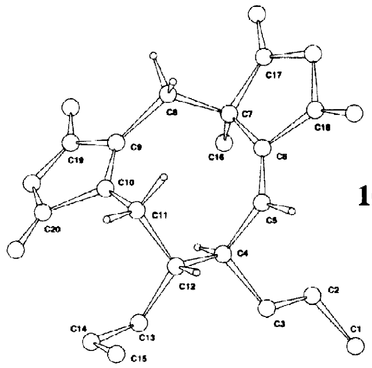
A further proposal that a metal salt should act as a base at the same time as a coordinating species was investigated. Thus it was found with both substances CaH_2 and bromomagnesium(isopropylcyclohexylamide), a higher selectivity towards the desired product in the ratio isoglaucanic acid (**10**)/ spiro compound (**11**) was observed (entry g and f).

Attempted dimerisation starting from the more stable ester **6** gave no dimeric products at all. Instead the anhydride **7** was partially formed, along with unchanged starting material. Some of the discussed results are listed in Table 1.

From adding known amounts of naphthalene to the crude mixture, the total yield of the isoglaucanic acid in the reaction using $MgCl_2$ in DMSO (entry d) was estimated by ^1H NMR to be around 10 %. This matched the reported isolated yields after chromatography (Table 1).

Purification of **10** was simplified by using flash chromatography and slow crystallisation from ether after an aqueous work up instead of the much more complicated purification process as published.[8]

From a slowly evaporating ether solution rhombohedral crystals of the isoglaucanic acid derivative **10** were obtained. The crystals consisted of a 1:1 mixture of enantiomers as demonstrated by X-ray crystallography which likewise gave proof of the relative stereochemistry of this nonadride.[14] One of the enantiomers is shown below (Scheme 5).

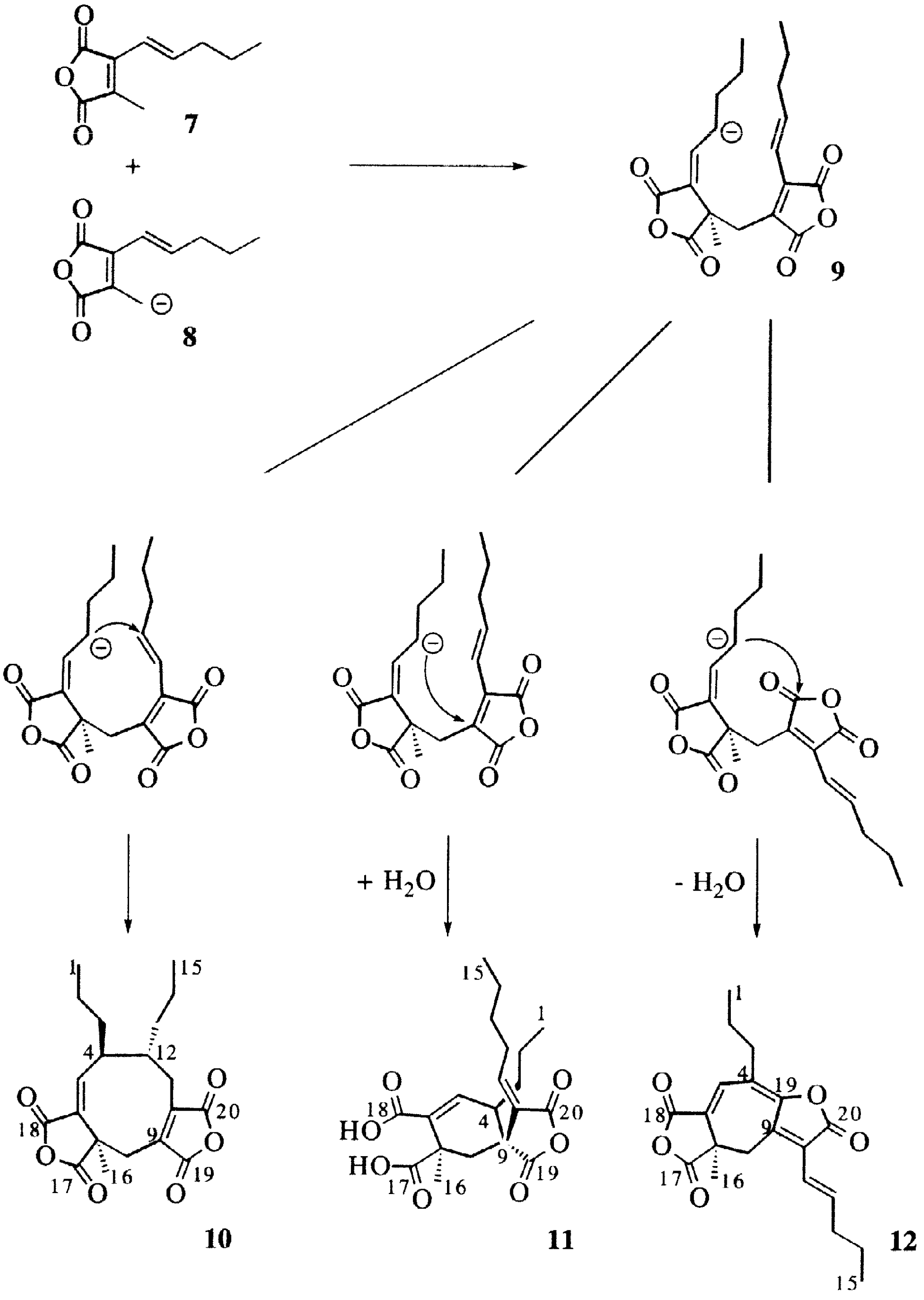


10

Scheme 5

As Sutherland and co-workers suggested for isoglaucanic acid (**3**), the two alkyl side chains are situated *trans* to each other, while the one closer to the methyl group (C1 to C3) is *trans* to (C16). So the stereochemistry for this analogue of isoglaucanic acid is clearly different to the one of CP-225,917, where the acetic acid residue and the nearest side chain are *cis* to each other.

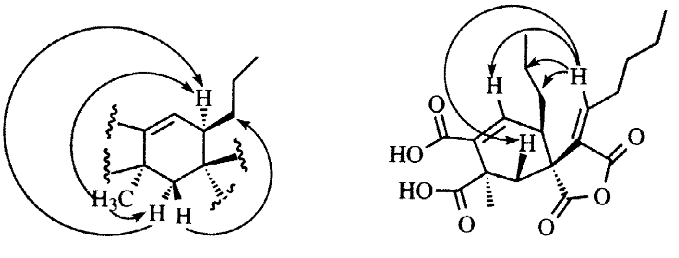
From the various crude reaction mixtures, three different dimers have been successfully isolated and characterised spectroscopically (Scheme 6). The two major products are the isoglaucanic acid derivative **10** and a new spiro compound **11**, where one anhydride has opened to the diacid. A third product has been tentatively assigned as **12**. However about 70 % of all crude reaction material remained on the column, which showed no olefinic protons in the ^1H NMR when washed from the column.



Scheme 6

In the spiro compound **11** the ring opened anhydride is situated on the six membered ring whereas the spiro anhydride remains unchanged, consistent with evidence which was obtained from heteronuclear long range coupling experiments (interaction from C17 to H16). In principle four different stereoisomers are possible within the six membered ring. Analysis by ROESY experiment[15] gave the observed enhancements shown in Scheme 7. From this data one isomer is strongly suggested. As in the isoglaucanic acid derivative **10** the propyl group of **11** is *trans* to the C16-methyl next to the anhydride.

This structure for **11** is consistent with no J-coupling from the olefinic proton in the six membered ring to the neighbouring aliphatic one because with this configuration the dihedral angle is almost 90°. This would not be the case if the propyl and methyl groups were of *cis* relative stereochemistry.



Scheme 7

The olefinic proton adjacent to the intact anhydride shows ROESY[14] enhancement to the other olefinic proton and to the propyl side chain but none to the methyl group. Therefore the C_{10}-C_{15} side chain is proposed to point into the same direction as the C_1-C_3 propyl group.

The third isolated product showed a strong yellow fluorescence and was only isolated in small amounts (< 2%). It was proposed to be a dimer, formed after an elimination of one water molecule (Scheme 6). In this case there is only possible isomer because the seven membered ring consists of five sp^2 carbon centres. The structure proposed was consistent with heteronuclear long range coupling experiments and UV/vis data (λ_{max}: 368 nm).

Comparing the three isolated dimeric products one can easily see that they all show the same partial structure linking the two anhydride moieties via a CH_2 bridge. A stepwise Michael addition is an alternative reaction mechanism to a concerted $6\pi + 4\pi$ cycloaddition and this seems even more reasonable because the anion intermediate **9** is able to attack at different electrophilic positions, forming the observed three different products (Scheme 6). The same relative stereochemistry between the propyl and the methyl group in the spiro compound (**11**) is also seen in the nine membered isoglaucanic acid derivative **10**.

The reversibility of the reaction was also checked by treating the dimers **10** and **11** with base. The spiro compound **11** remained unchanged after work up, however the isoglaucanic acid derivative decomposed partially, giving different products, the major product being the anhydride **7**. Hence the dimerisation step to give **10** is seen to be reversible.

In summary an efficient and short synthesis of an anhydride **7** was developed, which under basic conditions gave an isoglaucanic acid derivative (**10**) whose structure was proven by X-ray crystallography. This proves Sutherland's original assignment of isoglaucanic acid (**3**). The presence of isolated biproducts (**11**, **12**) during the base induced dimerisation to **10** suggests a stepwise mechanism via Michael addition for the formation of **10**.

Further investigations to a biomimetic approach to the compounds **1** and **2** are underway.

Experimental

Melting points were obtained using a Büchi 510 capillary apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Paragon 1000 Fourier transform spectrometer with major absorbances only being quoted. The following abbreviations are used: w, weak; m, medium; s, strong.

^{1}H NMR spectra were recorded at 200 and 400 MHz using Varian Gemini 200, Bruker AC200, and Bruker DPX400 instruments. For ^{1}H spectra recorded in $CDCl_3$, chemical shifts are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are quoted to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 50.3 and 100.6 MHz using Varian Gemini 200 and Bruker DPX400 instruments. Special experiments (300 ms ROESY, HMBC, HMQC, DQF-COSY, DEPT) to assist structural assignment of **10**, **11** and **12** were carried out on Bruker DPX400 Bruker AMX500 and Bruker AM500 instruments.[15] Chemical shifts are quoted in parts per million and are referenced to $CDCl_3$.

Low resolution mass spectra were recorded on V.G. Micromass ZAB 1F (FAB / CI / DCI) and V.G. Masslab 20-250 (CI / DCI) instruments as appropriate with only molecular ions, fragments from molecular ions and other major peaks being reported. High resolution mass spectra were recorded on a VG ZAB-E instrument.

Microanalyses were performed in the Dyson Perrins Laboratory. UV/vis measurements were carried out on a Perkin Elmer Lambda 2 instrument.

Flash chromatography was carried out using Sorbsil™ C60 (40-63 μm, 230-40 mesh) silica gel as stationary phase. Thin layer chromatography was carried out on aluminium plates pre-coated with Merck silica gel 60 F_{254} which were visualised by quenching of UV fluorescence or by staining with iodine vapour or 10% w/v ammonium molybdate in 2M sulphuric acid (followed by heat) as appropriate.

All solvents and reagents were purified by standard techniques or used as supplied from commercial sources as appropriate.[16] Light petroleum refers to the fraction of light petroleum ether boiling between 40-60 °C.

2-Iodo-3-methyl dimethyl maleate (5)

In a 500 ml three necked flask fitted with a dropping funnel and low temperature thermometer, a suspension of copper(I) bromide-dimethyl sulphide complex (4.52 g/ 22.0 mmol) in dry THF (120 ml) was set under argon and cooled to -40 °C. A MeMgBr solution (7.3 ml/ 3.0M solution in ether/ 22.0 mmol) was added and the yellow mixture was stirred for 30 minutes. After cooling to -72 °C a solution of dimethyl acetylene dicarboxylate (2.46 ml/ 2.84 g/ 20.0 mmol) in THF (30 ml) was added dropwise over a period of 30 minutes without exceeding an internal temperature of -67 °C. A colour change from yellow to red occurred. After 40 minutes additional stirring at this temperature iodine (5.84 g/ 23.0 mmol), dissolved in THF (60 ml), was added dropwise over a period of approximately 30 minutes, maintaining the same internal temperature. The mixture turned dark. After additional stirring for 90 minutes at -70 °C, a aqueous solution of ammonium chloride (9.6 g) in water (100 ml) was added and the mixture was allowed to warm to RT. The mixture was poured onto a further portion of water (50 ml) and extracted four times with ether (75 ml). The combined organic layers were washed with 0.2M $Na_2S_2O_3$ (2 x 100 ml), water (100 ml) and saturated brine (50 ml). After drying over $MgSO_4$ the solvent was removed in vacuo and the crude yellowish liquid was purified by flash chromatography (SiO_2, light petroleum/ ether: 4:1 v/v; R_f 0.20). A colourless liquid was obtained (5.30 g/ 18.7 mmol/ 93%).

R_f 0.20 (SiO_2, light petroleum/ ether: 4:1 v/v); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.21 (3H, s, C-CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C 166.5 (COO), 165.0 (COO), 122.0 ($\underline{C}$=C-I), 100.2 (C=$\underline{C}$-I), 53.5 (OCH_3), 52.8 (OCH_3), 24.4 (C-$\underline{C}H_3$); IR (film): υ (cm^{-1}) 2953m, 1728s (COOR), 1610m, 1434m, 1249s, 1139m, 1050m; M/z (CI): 302 ($M+NH_4^+$), 285 ($M+H^+$), 253, 159, 137, 102, 85; Anal. Calcd. for $C_7H_9IO_4$: C, 29.60; H: 3.19. Found: C, 29.59; H, 3.04.

2-[(*E*)-1'-Pentenyl]-3-methyl dimethyl maleate (6)

In a 250 ml round bottom flask palladium acetate (125 mg/ 0.55 mmol), triphenylphosphine (306 mg/ 1.17 mmol) and potassium carbonate (4.64 g/ 33.6 mmol) were suspended in absolute ethanol (90 ml). Then the iodide **4** (5.30 g/ 18.7 mmol), dissolved in 20 ml ethanol, was added first, followed by [(*E*)-1'-pentenyl]-1,3,2-benzodioxaborole[11] (3.80 g/ 19.3 mmol) dissolved in 20 ml ethanol. The yellow mixture was heated to reflux for 3 h. The cooled green mixture was then poured onto 300 ml water and extracted with ether (3 x 100 ml). The combined organic layers were washed with water (2 x 150 ml) and saturated brine (50 ml). After drying over $MgSO_4$ the solvent was removed in vacuo yielding 4.42 g of crude material.

During this reaction trans-esterification occurred giving methyl ethyl (major) and diethyl ester. The crude product was purified by flash chromatography (SiO_2, light petroleum/ ether: 7:3 v/v). The fractions from R_f 0.50 to 0.30 were collected yielding 3.84 g of yellow liquid.

^{1}H NMR (methyl ethyl ester only) (200 MHz, $CDCl_3$): δ_H 6.34 (1H, d, J = 15.5 Hz, C$\underline{H}$=CH-CH_2), 5.92 (1H, dt, J_1 = 15.5 Hz, J_2 = 7 Hz, CH=C$\underline{H}$-CH_2), 4.17 (2H, q, J = 7 Hz, -OC$\underline{H}_2$-), 3.84 (3H, s, -OCH_3), 2.17 (2H, q, J = 7 Hz, =CH-C$\underline{H}_2$), 1.98 (3H, s, C-CH_3), 1.45 (2H, m, -CH_2-C$\underline{H}_2$-CH_3), 1.27 (3H, t, J = 7 Hz, -OCH_2-C$\underline{H}_3$), 0.90 (3H, t, J = 7.5 Hz, CH_2-C$\underline{H}_3$).

2-[(*E*)-1'-Pentenyl]-3-methyl maleic anhydride (7)

In a 1 l round bottom flask 3.84 g of ester mixture **6** was dissolved in 180 ml ethanol and 226 ml of 2M NaOH was added. The reaction was stirred under argon for 24 h at RT. Then 200 ml of 4 % Na_2SO_4 solution were added and the mixture was acidified to pH 2 using 3M HCl (ca. 120 ml). The mixture was extracted four times with ether (80 ml each). The combined organic layers were washed with water (100 ml) and saturated brine (100 ml), treated with activated charcoal, dried over $MgSO_4$ and the solvents evaporated in vacuo, 2.63 g (14.6 mmol) of slightly yellow liquid was obtained (77% over two steps from **5**). This anhydride was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$): δ_H 7.09 (1H, dt, J_1 = 16 Hz, J_2 = 7 Hz, $CH{=}C\underline{H}{-}CH_2$), 6.23 (1H, d, J = 16 Hz, $C\underline{H}{=}CH{-}CH_2$), 2.25 (2H, q, J = 7 Hz, $=CH{-}C\underline{H}_2$), 2.10 (3H, s, $C{-}CH_3$), 1.51 (2H, m, $-CH_2{-}C\underline{H}_2{-}CH_3$), 0.94 (3H, t, J = 7.5 Hz, $CH_2{-}C\underline{H}_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C 166.4 (COO), 164.5 (COO), 147.7 ($CH{=}\underline{C}H{-}CH_2$), 137.2 (C=C), 135.0 (C=C), 117.2 ($\underline{C}H{=}CH{-}CH_2$), 36.3 ($CH_2$), 21.6 ($CH_2$), 13.6 ($CH_3$), 9.2 ($CH_3$); IR (film): υ (cm^{-1}) 2962m, 2933m, 2874w, 1860w, 1766s (anhydride), 1652m, 1465w, 1390w, 1274s, 1140m, 974m, 926s, 897m, 731m; M/z (APCI$^-$): 179 (M-H$^+$), 153, 150, 129, 109; HRMS: calc.: 198.1130, found: 198.1125 for $C_{10}H_{16}NO_3$ (M+NH$_4^+$).

Dimerisation of 2-[(*E*)-1'-pentenyl]-3-methyl maleic anhydride (7): Typical procedure

The anhydride **7** (720 mg/ 4.0 mmol) and anhydrous $MgCl_2$ (190 mg/ 2.0 mmol) were stirred under argon in dry DMSO (60 ml). After 5 min (370 µl/ 2.6 mmol) triethylamine was added. The solution turned purple and stirring was continued for 24 h at RT. The reaction was quenched by adding it to 200 ml of 3M HCl. The cooled orange reaction mixture was then extracted with ether (3 x 50 ml). The combined organic layers were washed with water (2 x 100 ml) and saturated brine (50 ml). After drying over $MgSO_4$ the solvent was removed in vacuo affording 739 mg of crude material.

The crude material was dissolved in a little dichloromethane and loaded onto a flash chromatography column (diameter: 32 mm, height: 36 cm) and eluted with light petroleum/ ether/ formic acid 28:12:1 v/v, collecting small fractions (5 - 7 ml). The fractions with R_f 0.15, containing the isoglaucanic acid derivative **10**, were combined and the solvent was removed in vacuo. The sticky yellow material was completely redissolved in ether and left for slow evaporation. Colourless crystalline material was obtained (62 mg/ 0.17 mmol/ 8.5 %).

The spiro compound **11** with R_f 0.10 (light petroleum/ ether/ formic acid 28:12:1 v/v) can, if necessary, be further purified using a second column of the same size and a solvent mixture of light petroleum/ ether/ formic acid 24:16:1 v/v (R_f 0.15). The yellow fluorescent biproduct **12** (R_f 0.40 in light petroleum/ ether/ formic acid 28:12:1 v/v) can be further purified with a less polar eluent (light petroleum/ ether/ formic acid 69:12:1 v/v (R_f 0.30)). The residue on the column was washed down with acetone yielding 510 mg/ ca. 70 % of sticky, acidic material which was not further investigated.

Isoglaucanic acid derivative 10

R_f 0.15 (SiO_2, light petroleum/ ether/ formic acid: 28:12:1 v/v); mp: 153-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.94 (1H, d, J = 11.5 Hz, 5-H), 3.26 (1H, d, J = 13.5 Hz, 8-H), 2.78 (1H, dd, J_1 = 13 Hz, J_2 = 3 Hz, 11-H), 2.65 (1H, d, J = 13.5 Hz, 8-H), 2.36 (1H, dd, J_1 = 13 Hz, J_2 = 4.5 Hz, 11-H), 2.02 - 1.81 (3H, m, 12-H, 4-H, 2-H), 1.71 - 1.54 (2H, m, 13-H, 3-H), 1.53 (3H, s, 16-H), 1.35 (1H, m, 2-H), 1.29 - 1.13 (3H, m, 3-H, 13-H, 14-H), 1.04 (1H, m, 14-H), 1.00 (3H, t, J = 7.5 Hz, 1-H), 0.90 (3H, t, J = 7 Hz, 15-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 173.7 (17-C), 165.5 (19-C), 165.2 (20-C), 164.1 (18-C), 152.2 (5-C), 147.2 (10-C), 141.3 (9-C), 129.7 (6-C), 48.6 (7-C), 44.1 (12-C), 42.9 (4-C), 34.0 (13-C), 32.6 (8-C), 31.8 (3-C), 26.7 (11-C), 21.3 (14-C), 21.0 (2-C), 20.2 (16-C), 14.4 (15-C), 13.9 (1-C); IR (KBr): υ (cm^{-1}) 2958m, 2872w, 1835m (anhydride), 1777s (anhydride), 1668w, 1453w, 1231m, 1158w, 952m, 938w; M/z (APCI$^-$): 359 (M-H$^+$), 347, 315, 288, 180, 179; HRMS: calc.: 378.1917, found: 378.1917 for $C_{20}H_{28}NO_6$ (M+NH$_4^+$); X-ray data available.[14]

Spiro compound 11

R$_f$ 0.10 (SiO$_2$, light petroleum/ ether/ formic acid: 28:12:1 v/v); ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 10.7 - 9.7 (2H, bs, COOH, concentration dependent), 7.31 (1H, s, 5-H), 6.56 (1H, dd, J_1 = 8.5 Hz, J_2 = 2 Hz, 11-H), 3.00 (1H, m, 4-H), 2.92 (1H, m, 12-H), 2.66 (1H, d, J = 14.5 Hz, 8-H), 2.50 (1H, m, 12-H), 2.21 (1H, d, J = 14.5 Hz, 8-H), 1.70 (3H, s, 16-H), 1.59 (1H, m, 2-H), 1.45 - 1.38 (3H, m, 13-H, 3-H), 1.38 - 1.31 (3H, m, 14-H, 2-H), 1.25 (1H, m, 3-H), 0.97 (3H, t, J = 7 Hz, 1-H), 0.94 (3H, t, J = 7 Hz, 15-H); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ_C 181.5 (17-C), 175.1 (19-C), 171.7 (18-C), 162.9 (20-C), 154.1 (11-C), 145.7 (5-C), 132.1 (6-C), 122.9 (10-C), 51.7 (9-C), 45.1 (8-C), 42.6 (7-C), 41.0 (4-C), 33.4 (3-C), 30.9 (13-C), 29.2 (12-C), 27.8 (16-C), 23.0 (14-C), 20.7 (2-C), 14.2 (1-C), 14.1 (15-C); IR (KBr): υ (cm^{-1}) 3433w, 2963m, 1832m (anhydride), 1774s (anhydride), 1703s (acid), 1666m, 1460m, 1261s, 1104m, 935m, 802w; M/z (APCI$^-$): 378 (M$^+$), 377 (M-H$^+$), 359 (M-H$_2$O-H$^+$), 333, 315, 289, 179; HRMS: calc.: 396.2025, found: 396.2022 for $C_{20}H_{30}NO_7$ (M+NH$_4^+$). Remarks: exists in CDCl$_3$ probably as dimer (NOE did not show clear results).

Lactone 12

R$_f$ 0.40 (SiO$_2$, light petroleum/ ether/ formic acid: 28:12:1 v/v); ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 7.26 (1H, s, 5-H), 7.18 (1H, m including J = 16 Hz, 12-H), 6.29 (1H, d, J = 16 Hz, 11-H), 3.43 (1H, d, J = 16 Hz, 8-H), 2.81 (1H, d, J = 16 Hz, 8-H), 2.61 (1H, m, 3-H), 2.55 (1H, m, 3-H), 2.32 (2H, m, 13-H), 1.68-1.58 (2H, m, 2-H), 1.61-1.55 (2H, m, 14-H), 1.47 (3H, s, 16-H), 1.01 (6H, m, 1-H, 15-H); ^{13}C NMR (125.7 MHz, CDCl$_3$): δ_C 173.9 (17-C), 165.9 (20-C), 163.1 (18-C), 153.2 (19-C), 144.8 (12-C), 136.9 (5-C), 129.5, 129.0 (6-C, 10-C), 124.0 (9-C), 121.1 (4-C), 117.1 (11-C), 44.5 (7-C), 36.5 (13-C), 34.2 (3-C), 30.7 (8-C), 22.4, 21.9 (2-C, 14-C), 18.3 (16-C), 13.8, 13.6 (1-C, 15-C); IR (KBr): υ (cm^{-1}) 2928m, 2868w, 1831w, 1769s, 1655w, 1578w, 1460w, 1241w, 1162w; M/z (CI): 360 (M+NH$_4^+$), 343 (M+H$^+$), 314, 300, 271, 256, 241, 227, 199, 185; HRMS: calc.: 343.1539, found: 343.1545 for $C_{20}H_{23}O_5$ (M+H$^+$); UV/vis (MeOH) λ_{max}: 368 nm.

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References and notes

1. Dabrah, T. T.; Kaneko, T.; Massefski, W. Jr.; Whipple, E.B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.
2. Dabrah, T. T.; Harwood, H. J. Jr.; Huang L. H.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1.
3. Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1737.
4. Nicolaou, K. C.; Härter, M. W.; Boulton, L.; Landeleit, B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1194.
5. Sgarbi, P. W. M.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157.
6. Armstrong, A.; Critchley, T. J.; Mortlock, A. A. *Synlett* **1998**, 552.
7. (a) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1877; (b) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1880.
8. (a) Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1769; (b) Barton, D. H. R.; Jackman, L. M.; Rodriguez-Hahn, L.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1773; (c) Barton, D. H. R.; Godinho, L. D. S.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1779; (d) Baldwin, J. E.; Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1787; (e) Bloomer, J. L.; Moppett, C. E.; Sutherland, J. K. *J. Chem. Soc.* **1968**, 588.
9. Huff, R. K.; Moppett, C. E.; Sutherland, J. K. *J. Chem. Soc.* **1972**, 2584.
10. Nishiyama, H.; Sasaki, M. *Chem. Lett.* **1981**, 905.
11. Miyaura, N.; Suginome, H.; Suzuki A. *Tetrahedron* **1983**, *39*, 3271.
12. Yanagi, T.; Oh-e, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3892.
13. Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th edition, John Wiley & Sons, New York, **1988**.
14. The atomic coordinates for **10** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW; the crystallographic numbering system differs from that used elsewhere in the text. Any request should be accompanied by the full literature citation for this paper.
15. Derome, A. E. *Modern NMR Techniques for Chemistry Research*, Pergamon Press, Oxford, **1987**.
16. Perrin, D. D.; Armarego, W. L. F., *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, Oxford, **1988**.