Enantioselective Synthesis of the Originally Proposed Usneoidone Structure: Evidence for a Structural Revision

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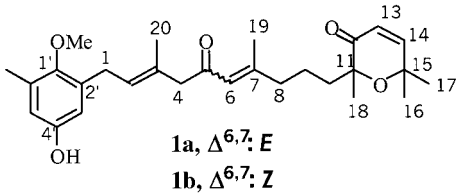
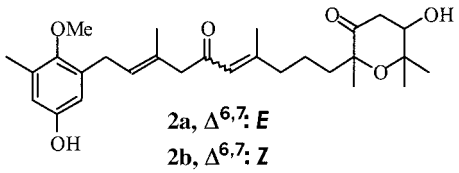
The enantioselective synthesis of the initially proposed structure of usneoidone has been completed according to a convergent strategy in which the key steps were an enantioselective Michael addition involving chiral imines to set up the C12 quaternary center, and the final assembly of the chiral pyran moiety with the aromatic subunit through a cyanohydrin anion alkylation step. The obtained product displays spectroscopic data that significantly differ from the reported values. A putative revised structure in which the pyran ring is opened is proposed for usneoidones.

Introduction

A few years ago, Urones and co-workers reported the isolation and the structure determination of four new meroterpenes — (*E*)- and (*Z*)-usneoidones (**1a** and **1b**, Figure 1) and (*E*)- and (*Z*)-usneoidols (**2a** and **2b)** — from the brown seaweed *Cystoseira usneoides* found off the West Coast of the Iberian Peninsula. These compounds displayed significant antiherpes and antitumoral activities, but also showed some cytotoxicity against normal cells.[1a,1b] The most striking feature of usneoidones is the 2,2,6,6-tetrasubstituted-6*H*-pyran-3-one moiety, which is found in only a few marine natural products. Following the isolation, Urones et al. described a synthetic approach of the crucial pyran core, based on phenylselenium-mediated cyclization of geranyl acetate.[2] Later on the same group reported the total synthesis of an analogue of (*E*)-usneoidol devoid of the C12 carbonyl.[3] The structural novelty and the relevant biological activities of usneoidones present an exciting challenge for chemical synthesis. Our aim was to develop a convergent synthesis whose strategy was readily amenable to the synthesis of analogues. Furthermore, an enantioselective synthesis should permit the elucidation of the absolute configuration of these compounds. Herein we report the enantioselective synthesis of compounds **1a**,**b**, providing evidence that the structure of usneoidones was wrongly assigned.



1a, $\Delta^{6,7}$: *E*
1b, $\Delta^{6,7}$: Z



2a, $\Delta^{6,7}$: *E*
2b, $\Delta^{6,7}$: Z

Figure 1. Structures of usneoidones and usneoidols, as proposed by Urones et al.

Results and Discussion

Our plan for preparing **1a**,**b**, arbitrarily targeting the (11*R*)-enantiomer, was based on the convergent coupling of the anion of the silylated cyanohydrin **3** with the aromatic subunit **5**. The chiral cyanohydrin **3** can be obtained from the alkyne **4** by zirconocene-catalyzed carboalumination and cyanohydrin formation. Compound **4**, in turn, could be assembled from keto ester (*R*)-**7b** through side-chain homologation and introduction of the C13−C14 double bond. In such an approach, the key synthetic issue was the stereoselective elaboration of the densely functionalized pyran nucleus. We have established in earlier studies that the asymmetric Michael addition of chiral imine **8a** with methyl acrylate afforded the Michael adduct **7a** regio- and stereoselectively.[4] Assuming that the C6 *gem*-dimethyl group

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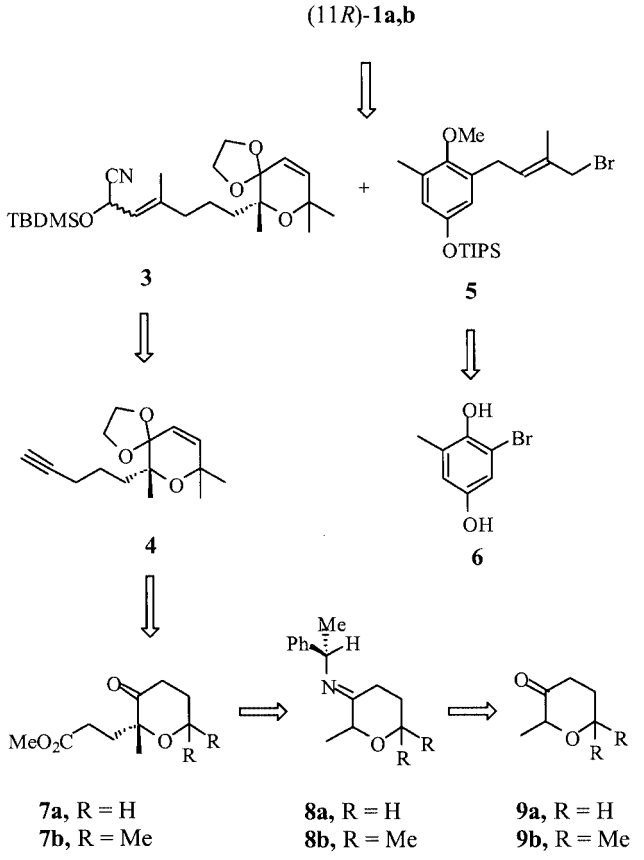
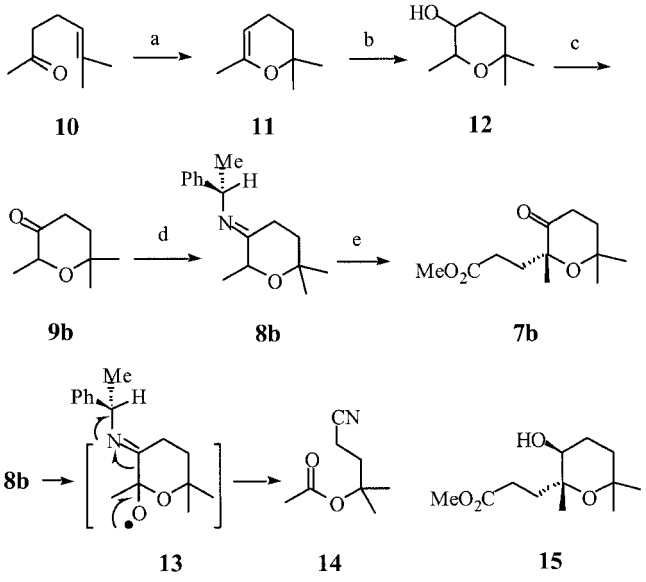
should not interfere with the Michael addition step, we chose to prepare the keto ester **7b** from the chiral imine **8b**, derived from pyranone **9b** and (*S*)-1-phenylethylamine. The aromatic subunit **5** could be prepared from the known bromohydroquinone **6**, in a sequence involving chemoselective protection, prenylation, and allylic functionalization (Scheme 1).



Scheme 1. Retrosynthetic analysis of usneoidones

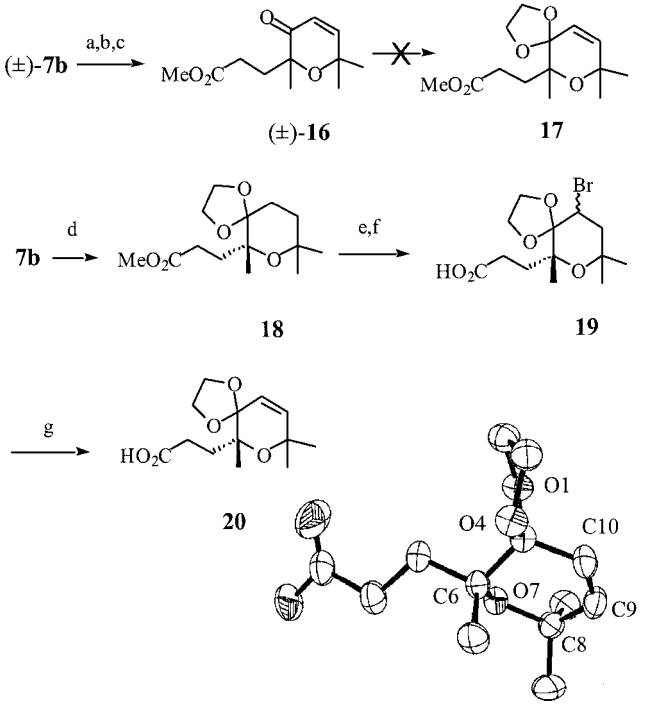
To implement this synthetic plan, we required a viable, large-scale preparation of 2,6,6-trimethyl-pyran-3-one (**9b**). This was secured by a hydroboration-Swern oxidation reaction sequence of 2,2,6-trimethyl-3,4-dihydro-2*H*-pyran (**11**), easily accessible by acid-catalyzed cyclization of 6-methylhept-5-en-2-one (**10**).[5] This sequence routinely furnished pyranone **9b** in a 53% overall yield from **10** on a twenty five-gram scale. When **9b** was subjected to standard imination conditions [(*S*)-PhCH(Me)NH_2, TsOH, toluene, azeotropic removal of water] none of the desired imine was obtained due to competitive rearrangements, as previously observed with other α-alkoxy-substituted imines.[6] However, upon treatment with a catalyst made by mixing 5-Å molecular sieves, silica and basic alumina, the desired imine **8b** was obtained smoothly. Subsequent Michael addition with methyl acrylate delivered, after acidic work up, the Michael adduct (*R*)-**7b** in 62% overall yield from **9b**, along with several minor components. One of them (ca. 8−10%) was identified as nitrile **14**, the formation of which might be tentatively explained by oxidation of the imine at C2, followed by ring opening of the putative radical intermediate **13**. Careful deoxygenation of the reaction medium reduced the formation of **14**, but did not completely suppress it. The mechanistic aspects of the Michael addition involving chiral imines have been extensively studied on the basis of both experimental and theoretical investigations. Both the unusual regioselectivity and the high stereoselectivity were explained by invoking a cyclic transition state and a concerted proton transfer from the nitrogen atom of the secondary enamine to the electrophilic alkene.[7,4a] In the present case, it must be emphasized that the intrinsic regioselectivity of the Michael addition toward the formation of the more substituted adduct **7b** overcomes the steric hindrance due to the additional quaternary carbon center lodged in the proximity of the reactive enamine carbon. The direct evaluation of the enantiomeric excess of keto ester **7b** by ^1H NMR shift experiments failed. However, the enantiomeric excess was finally evaluated to be 95% by studying the corresponding alcohol **15** with an equatiorial OH group[8] in the presence of $Eu(hfc)_3$ (Scheme 2). The (2*R*) absolute configuration of **7b** was not demonstrated but was assigned according to the general empirical rule governing this type of enantioselective Michael addition.[7]



Scheme 2. Enantioselective synthesis of the chiral pyran **7b**: a) *i*: 40% H_2SO_4, 20 °C, 45 min, *ii*: distillation, 85%; b) *i*: $BH_3.SMe_2$, cyclohexane, 0 °C, 3 h *ii*: NaOH, H_2O_2, EtOH, 80 °C, 2 h, 93%; (c) *i*: DMSO, ClCOCOCl, CH_2Cl_2, −78 °C *ii*: Et_3N, 68%; d) (*S*)-PhCH(Me)NH_2, 5-Å molecular sieves-SiO_2−Al_2O_3, cyclohexane, 48 h, 20 °C; e) H_2C=$CHCO_2Me$, 48 h, 50 °C, 62% overall from **9b**

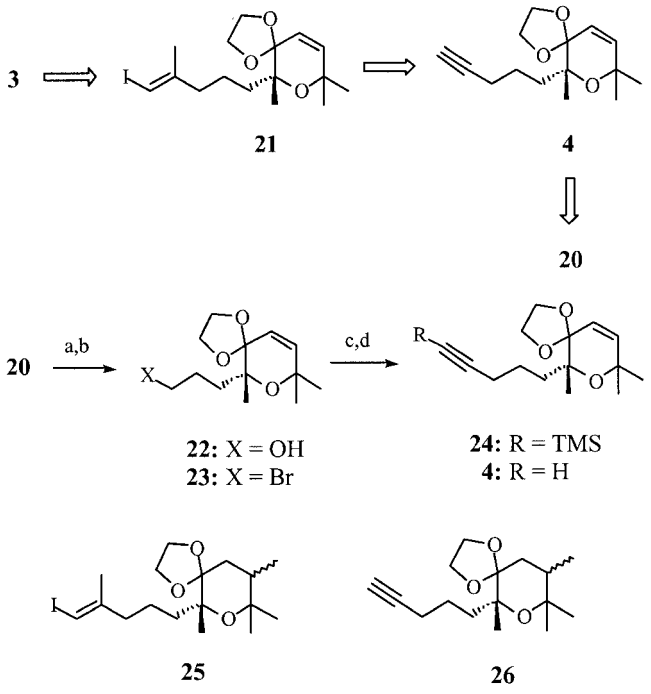
With the key pyran **7b** in hand, we turned to the introduction of the $\Delta^{4,5}$ double bond. In the event, bromination of the trimethylsilyl enol ether derived from racemic **7b**, followed by dehydrobromination by treatment with lithium bromide and lithium carbonate in DMF, gave enone **16** in 54% overall yield. Unfortunately, all attempts to protect the highly hindered ketonic group of **16** as a dioxolane or 1,3-dithiolane failed. Assuming that the carbonyl group in **7b** should be more reactive we decided to protect the C3 car-

bonyl group before introducing the double bond. To our delight, treatment with ethylene glycol under the standard conditions of **7b** afforded the corresponding ketal **18** in 84% yield,[9] which was then brominated (Br_2, CCl_4, 40 °C, quantitative). Attempts to perform the elimination with various bases, including DBU, failed repeatedly. Finally, saponification of the ester group of **18**, followed by treatment with an excess of *t*BuOK in DMSO at 110 °C, smoothly delivered the desired enone **20** in 75% overall yield from **18**. The structure of this compound was secured by means of an X-ray diffraction analysis (Scheme 3).



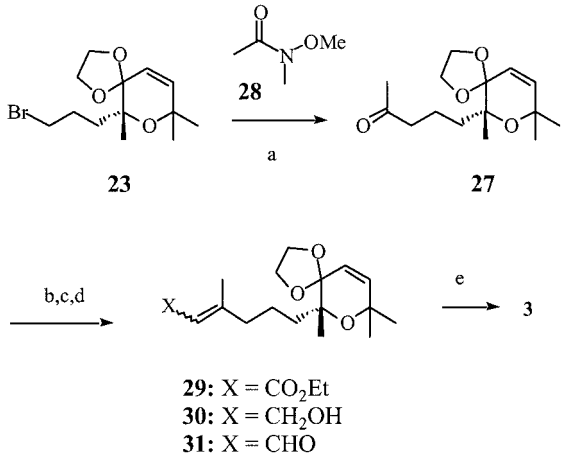
Scheme 3. Elaboration of the pyran core and ORTEP drawing of the crystal structure of **20**: a) TMSCl, Et_3N, DMF, 12 h, 100 °C, 87%, b) Br_2, CCl_4, 0 °C, 77%; c) LiBr, Li_2CO_3, DMF, 100 °C, 12 h, 81%; d) $(CH_2OH)_2$, TsOH, toluene, reflux, 8 h, 84%; e) Br_2, CCl_4, 40 °C, 45 min; f) 2 N NaOH, MeOH, 20 °C, 18 h; g) *t*BuOK, DMSO, 110 °C, 4 h, 75% from **18**

Once we had developed an efficient access to the chiral pyranone subunit, we turned our attention to the side-chain elongation. We first envisaged a two-carbon homologation via alkyne **4**, followed by Negishi-type carboalumination[10] to form **21** (Scheme 4). Thus, reduction of the acid group of **20** with $LiAlH_4$ gave alcohol **22** with a 84% yield, which was converted into bromide **23** upon treatment with CBr_4/PPh_3. Nucleophilic substitution with the lithium derivative of trimethylsilylacetylene, followed by desilylation with nBu$_4$NF provided the requisite alkyne **4** in 70% overall yield from **22**. Next, the stereocontrolled formation of the trisubstituted double bond C6−C7 was investigated. However, the zirconium-catalyzed carboalumination of **22** (*i*: $AlMe_3$, Cp_2ZrCl_2, 1.5 equiv. H_2O, CH_2Cl_2, −20 °C, 10 min, *ii*: I_2, THF, 20 °C)[11] afforded none of the desired iodoalkene **21**, but a mixture of iodoolefin **25** (ca. 5%) and alkyne **26** (25−30%) resulting from an apparent 1,4-type addition of a methyl group to the unsaturated ketal moiety,[12] along with several other unidentified products (Scheme 4).

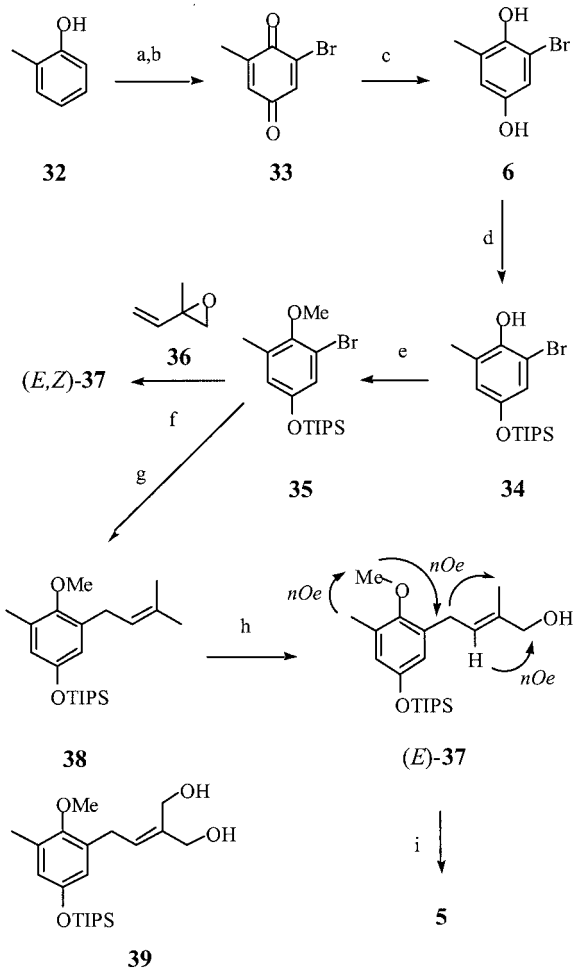


Scheme 4. Attempted functionalization of the side chain through zirconocene-catalyzed carboalumination: a) LAH, Et_2O, 20 °C, 30 min, 84%; b) CBr_4, PPh_3, pyridine, Et_2O, 4 h, 20 °C, 80%; c) TMSCCLi, THF, DMPU, 12 h, 20 °C, 76%; d) nBu$_4$NF, THF, 20 °C, 1 h, 92%

To overcome this problem, an alternative strategy was investigated to set up the C5−C6 fragment based on a Horner−Emmons olefination. Thus, treatment of bromide **23** with *t*BuLi, followed by reaction of the intermediate lithio derivative with the Weinreb amide **28**,[13] afforded the desired ketone **27** in 46% yield. Condensation of the latter with triethyl phosphonoacetate in THF using *n*BuLi as base furnished the unsaturated ester **29** in 83% yield as a 4:1 (*E*)/(*Z*) mixture.[14,15] The major isomer exhibited an NOE between the vinylic proton (δ = 5.65 ppm) and the allylic methylene (δ = 2.09 ppm), thus supporting the (*E*)-geometry of its double bond. Attempts to improve this selectivity by using NaH as base in various solvents were unsuccessful. Since the separation of the two isomers turned out to be quite difficult, the following steps were therefore conducted on the mixture. Thus, DIBAL-H reduction of the ester group of **29**, followed by manganese dioxide oxidation of the allylic alcohol **30**, uneventfully afforded the desired aldehyde **31** in 85% overall yield. Due to the presence of the acetal group, we preferred to avoid the use of a Lewis acid for the formation of the silylated cyanohydrin **3**. Thus, heating **31** with *tert*-butyldimethylsilyl cyanide in acetonitrile without the use of any catalyst[16] delivered the expected silylated cyanohydrin **3** in 80% yield (Scheme 5).



Scheme 5. Elaboration of the side chain of cyanohydrin **3**: a) *i*: *t*BuLi, Et_2O, −78 °C, 15 min, *ii*: **28**, THF, 3 h, 20 °C, 46%; b) $EtO_2CCH_2PO(OEt)_2$, *n*BuLi, THF, 20 °C, 24 h, 83%, (*E*)/(*Z*) = 4:1; c) DIBAL-H, THF, −70 °C, 2 h, 95%; d) MnO_2, CH_2Cl_2, 20 °C, 8 h, 90%; e) *t*$BuMe_2SiCN$, CH_3CN, 80 °C, 10 h, 80%



Scheme 6. Synthesis of the aromatic subunit **5**: a) Br_2, AcOH, 20 °C, 96%; b) CrO_3, AcOH, 0 °C, 5 h, 95%; c) $Na_2S_2O_4$, EtOH, 20 °C, 2 h, 52%;%; d) TIPSCl, Imidazole, DMF, 18 h; e) CH_3I, K_2CO_3, acetone, reflux, 4 h, 70% from **6**; f) *i*: *n*BuLi, Et_2O, −78 °C *ii*: CuCN, LiCl, −30 °C, 30 min *iii*: **36**, −78 °C to 20 °C, 1 h, 67%; g) *i*: PhLi, Et_2O, 0 °C, ii: $BrCH_2CH{=}C(CH_3)_2$, DMPU, 20 °C, 18 h, 91%; h) *i*: SeO_2, dioxane, water, 100 °C, 1 h, *ii*: $NaBH_4$, EtOH, 15 min, 20 °C, 60%; i) Br_2, $Ph_2PCH_2CH_2PPh_2$, CH_2Cl_2, 20 °C, 2 h, 88%

With the desired chiral cyanohydrin **3** in hand, the next task was to develop a suitable strategy for the preparation of the aromatic fragment **5**. The sequence was initiated with the selective protection of the less-hindered phenol group of bromo-hydroquinone **6**, which is easily available from *o*-cresol (**32**) in a three-step sequence.[17] Thus, monosilylation of **6** with triisopropylsilyl chloride and methylation of the remaining phenol group afforded almost exclusively the aryl bromide **35** in 70% overall yield. Metalation of **35** with *n*BuLi, followed by transmetalation of the intermediate aryllithium derivative with copper cyanide, and addition of 2-methyl-2-vinyloxirane **36**, gave the desired allylic alcohol **37** in 67% yield, but with a disappointing 2.5:1 *E*/*Z* ratio.[18] To solve this problem selenium dioxide allylic oxidation was chosen as the key step to control the stereochemistry of the double bond. Thus, the aryllithium reagent derived from **35** was alkylated with prenyl bromide to yield **38** (91%). Selenium dioxide allylic oxidation of **38** turned out to be somewhat capricious. When the reaction was conducted with a catalytic amount of SeO_2 in the presence of *t*BuO_2H[19] the desired alcohol (*E*)-**37** was obtained in 44% yield but was unexpectedly accompanied by diol **39** (25%). The formation of the latter was suppressed, and the yield of **37** was improved to 60%, upon using a stoichiometric amount of SeO_2 in refluxing dioxane, followed by reduction with $NaBH_4$.[20] The relative position of the butenol side-chain with respect to the methoxy group on the aromatic ring, as well as the double bond geometry, were unequivocally established as given by NOESY analysis. Alcohol (*E*)-**37** was finally transformed into bromide **5** upon treatment with 1,1,2,2,-tetrabromo-1,2-bis(diphenylphosphanyl)ethane[21] (Scheme 6).

The critical coupling of the subunits **3** and **5** was achieved by condensation of the lithio derivative of **3**, prepared by reaction with LDA, with **5** in the presence of DMPU.[22] The resulting adduct **40** was obtained as a mixture of geometric isomers at $\Delta^{6,7}$ and diastereomers at the C5 cyanohydrin center. Treatment with *n*Bu_4NF smoothly cleaved the phenolic protecting group and caused the reversion of the cyanohydrin to the parent carbonyl compound. Finally, acidic hydrolysis of the ketal group afforded **1a**,**b** [3:1 (*E*)/(*Z*) ratio] in 51% overall yield from **3**. Surprisingly, the ^1H, ^{13}C NMR and MS data of our sample did not match the reported values for **1a**,**b**.[1a] Although most of the signals of both the aromatic nucleus and the linker are very close to the ones described for the natural product, large discrepancies existed for the two vinylic protons 13-H and 14-H of the pyran core (see Table 1). Since the structure of this moiety in our sample has been unambiguously established, the assigned structure of the usneoidones came into doubt. The misattribution of the pyran system of usneoidones was reinforced by the ^1H NMR spectroscopic data reported for the pyranone **41**,[2] which are very close to our own values

Table 1. Selected spectroscopic data of usneoidones and derivatives

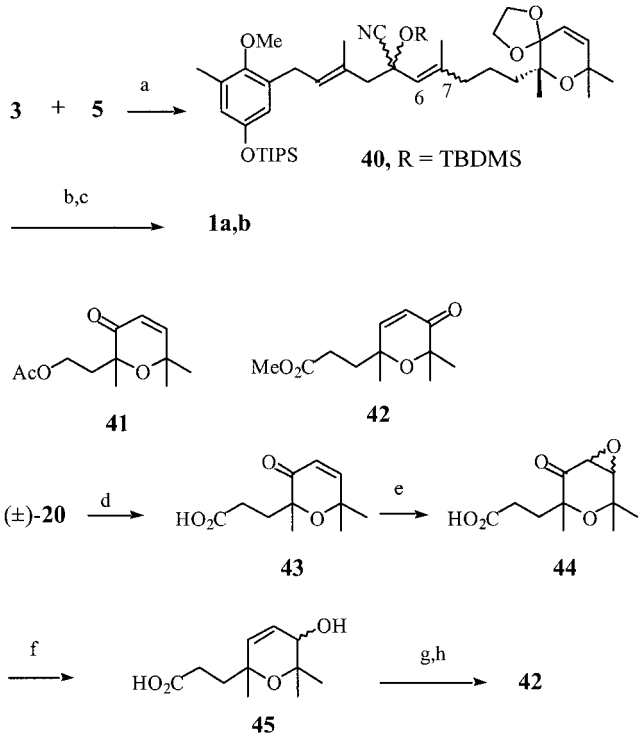
Entry	δ, 13-H (ppm)	δ, 14-H (ppm)	$J_{13\text{-H},14\text{-H}}$ (Hz)	δ, C13 (ppm)	δ, C14 (ppm)	δ, C12 (ppm)
(*E*)-Usneoidone[a]	6.60	7.20	15.1	118.4	156.3	202.9
(*Z*)-Usneoidone[a]	6.86	7.16	15.6	119.3	155.7	203.3
1a	5.94	6.85	10.4	122.2	155.5	199.6
1b	5.90	6.83	10.5	123.5	155.4	199.5
16	5.90	6.82	10.2	122.2	154.9	197.4
41	5.91	6.82	10.5	122.1	154.7	197.7
42	5.96	6.72	10.5	123.5	153.0	198.8
46	6.64	7.13	17.1	118.3	156.2	200.0
47 (in [D_6]acetone)	6.91	7.04	15.5			

[a] Data reported for the natural product in ref.[1a]

for **1a**,**b**. To assess the origin of this discrepancy, our first feeling was to consider a 5-oxo-tetrahydropyranyl system as a possible alternative structure for the pyran core of usneoidone. To explore this point we decided to prepare the pyranone **42** as a model of this putative structure. Thus acetal (±)-**20** was hydrolyzed and the resulting unsaturated ketone **43** was epoxidized by treatment with hydrogen peroxide in the presence of sodium hydroxide providing α,β-epoxy ketone **44** as a mixture of diastereomers in 77% yield. Wharton rearrangement[23] of **44** delivered the expected allylic alcohols **45**, which were subsequently oxidized by using Dess−Martin periodinane and esterified with diazomethane into enone **42**. Once again, however, the two vinylic protons of **42** were found to resonate upfield from those in the natural product (Scheme 7).[1a]

This result led us to reconsider the structure of the chiral part of usneoidones. Indeed, we became quite suspicious of the abnormally downfield chemical shift of 14-H, and the 15.1 Hz coupling constant between 13-H and 14-H, featuring a *cis*-enone reported for the natural product. However such values are commonly found for acyclic *trans*-enones. For example, compound **46**, which has been extracted as a minor polar component together with usneoidones from *Cystoseira usneoides*,[1c] displays ^{1}H NMR spectra that are remarkably similar to the values reported for the usneoidones, as did the synthetic diol **47**[24] (See Table 1). These striking similarities led us to propose the putative structures **48a**,**b** for usneoidones. Such a structure, however, should show a molecular ion at *m*/*z* = 472 in the MS, while the reported value is *m*/*z* = 454. This apparent contradiction can easily be solved considering that the molecular ion in the MS of **46** at *m*/*z* = 458 is of very low abundance (0.2%). Indeed the exact mass was measured on the $M^+ - H_2O$ ion at *m*/*z* = 440. Accordingly, the mass spectra of **48a**,**b** might display a very weak molecular ion peak at *m*/*z* = 472, which was not observed and a higher $M^+ - H_2O$ peak at *m*/*z* = 454 as reported (Figure 2).

In summary, we have achieved a stereocontrolled and convergent synthesis of the structures **1a**,**b** originally assigned to usneoidones. We have found that the spectroscopic data of the pyran moiety are different from those of the natural product. In addition, we have outlined a synthesis of the alternative pyran **42**, but once again the spectral characteristics were completely at variance with those

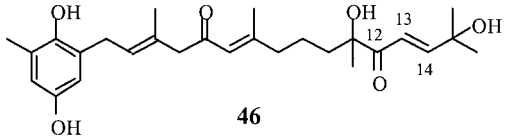


Scheme 7. Completion of the synthesis of **1a**,**b** and Wharton rearrangement of **44**: a) *i:* LDA, −78 °C, THF, 15 min, *ii*: 2 equiv. **5**, DMPU, 4 h, 20 °C, 80%; b) 1 M nBu$_4$NF, THF, 2 h, 20 °C; c) 0.5 N HCl, THF, 2 h, 20 °C, 64% overall from **40**; d) 1 N HCl, THF, 1 h, 20 °C, 85%; e) H_2O_2, 1 N NaOH, MeOH, 30 min, 0 °C, 77%; f) H_2NNH_2, MeOH, AcOH, 60 °C, 2 h, 40%; g) Dess−Martin periodinane, CH_2Cl_2, 1 h, h) CH_2N_2, Et_2O, 0 °C, 52% from **45**

of usneoidones. These observations and a careful scrutiny of the reported spectroscopic data led us to surmise that usneoidones do not possess a pyran ring in their structure. The open-chain structure **48a**,**b** was thus proposed. Validation of this proposal through synthesis is required.

Experimental Section

General: Melting points were recorded with a Büchi capillary tube melting point apparatus, and are uncorrected. IR spectra were obtained as solids or neat liquids with a Fourier Transform Bruker Vector 22 spectrometer. Only significant absorptions are listed. Op-



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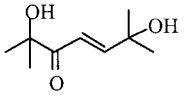

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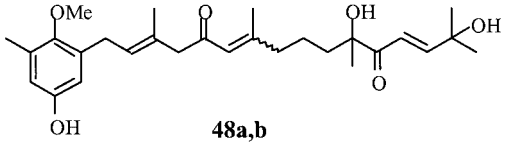

48a,b

Figure 2. Structure of meroterpene **51** and putative structures of usneoidones

tical rotations were measured with a Perkin−Elmer 241 Polarimeter at 589 nm. The ^1H and ^{13}C NMR spectra were recorded with Bruker AC 200 P (200 MHz and 50 MHz, for ^1H and ^{13}C, respectively) or Bruker ARX 400 (400 MHz and 100 MHz, for ^1H and ^{13}C, respectively) spectrometers. Assignment of methyl, methylene, methine, and quaternary carbon nuclei in the ^{13}C NMR spectra rests on the *J*-modulated spin-echo sequence. Mass spectra were recorded with a Hewlett−Packard G 1019 A (70 eV). Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). Column chromatography was performed with Merck silica gel 60 (230−400 mesh ASTM). Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methanol and ethanol were dried with magnesium and distilled. Benzene, toluene, DMF, and CH_2Cl_2 were distilled from calcium hydride, under nitrogen. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-dried under a positive pressure of nitrogen. Chemicals obtained from commercial suppliers were used without further purification. Elemental analyses were performed by the Service de microanalyse, Centre d′Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin−Elmer 2400 analyzer.

2,6,6-Trimethyl-3,4-dihydro-2*H*-pyran (11): Sulfuric acid (40% w/w, 400 g) was placed in an ice-chilled 1 L flask. 6-Methylhept-5-en-2-one (**10**; 40 g, 0.317 mol) was added dropwise at 0 °C with vigorous stirring. The temperature was then raised to 20 °C and the mixture was stirred until a homogeneous solution was obtained (ca. 45 min). The mixture was cooled to 0 °C and 50% aqueous sodium hydroxide was added until neutrality. Diethyl ether was added (500 mL) and the mixture was filtered. The solid was washed thoroughly with diethyl ether. The ethereal layer was separated and the aqueous phase was extracted with diethyl ether (5 × 200 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated at atmospheric pressure until the volume of the solution was reduced to ca 100 mL. Amberlite® IR 120 (2 g) was then added and the mixture was stirred for 8 h at room temperature. The acidic resin was filtered off and the mixture was slowly distilled to give a two-phase distillate. Pentane (50 mL) was added and the organic phase was separated, dried with Na_2CO_3, filtered and concentrated at atmospheric pressure. Distillation afforded the dihydropyran **11** (34 g, 85%) as a colorless oil; b.p. 125−130 °C (Ref.[5] b.p. 127−129 °C). ^1H NMR (200 MHz, [D_6]benzene): δ = 4.39 (t, *J* = 1.8 Hz, 1 H, *H*C=), 1.95−1.80 (m, 2 H, =CHCH_2), 1.71 (s, 3 H, CH_3C=CH), 1.55 (t, *J* = 6.6 Hz, 2 H, HC=CCH$_2$CH_2), 1.15 [s, 6 H, OC(CH_3)$_2$] ppm. ^{13}C NMR (50 MHz, [D_6]benzene): δ = 150.2 (C, CH_3C=CH), 93.9 (CH, CH_3C=*C*H), 73.7 [C, O*C*(CH$_3$)$_2$], 33.6 (CH_2, C5), 27.2 (2 CH_3, OC(*C*H$_3$)$_2$], 21.4 (CH_3, *C*H$_3$C=CH), 19.5 (CH_2, C4) ppm.

2,6,6-Trimethyltetrahydropyran-3-ol (12): Borane−dimethyl sulfide complex (10 M, 10 mL 0.10 mol) was added dropwise to an ice-cooled solution of the dihydropyran **11** (34.0 g, 0.27 mol) in cyclohexane (140 mL). The mixture was stirred at 20 °C for 3 h and 200 mL of 95% ethanol was carefully added. A condenser was adapted and 3 M sodium hydroxide (100 mL, 0.3 mol), and 35% hydrogen peroxide (27 mL, 0.3 mol) were sequentially added dropwise. A vigorous reaction took place and the mixture was refluxed for a further 2 h. The mixture was cooled to 20 °C and partially concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phases were washed with aqueous sodium bisulfite and brine, dried with $MgSO_4$, filtered and concentrated. The residue was distilled under reduced pressure to give the alcohol **12** as a colorless oil 36.3 g, 93% yield; b.p. 105−110 °C/22 Torr (oil-bath temperature). IR (film): $\tilde{\nu}$ = 3600−3200 (OH), 1448, 1380, 1366, 1233, 1051 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.50−3.35 (m, 1 H, 2-H), 3.25−3.10 (m, 1 H, 3-H), 1.95−1.60 (m, 1 H, 4-H), 1.80 (s, 1 H, OH), 1.75−1.45 (m, 3 H, 4-H and 5-H), 1.25−1.20 (m, 9 H, 3 × CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 72.7 (CH, C3), 71.4 (C, C6), 71.0 (CH, C2), 36.0 (CH_2, C5), 31.0 [CH_3, OC(*C*H$_3$)$_2$], 29.3 (CH_2, C4), 21.7 [CH_3, OC(*C*H$_3$)$_2$], 18.7 (CH_3, *C*H$_3$CHOC) ppm. MS (EI): *m*/*z* (%) = 144 (1.8) [M$^+$], 130 (1.2), 129 (19), 116 (5.6), 111 (5.2), 99 (8.2), 88 (73.5), 71 (20.3), 59 (25.7), 57 (64.2), 56 (100). 3,5-Dinitrobenzoate of **12**: M.p. 161−162 °C. $C_{15}H_{18}N_2O_7$ (338.3): calcd. C 53.25, H 5.36, N 8.28; found C 53.24, H 5.40, N 8.19.

2,6,6-Trimethyldihydropyran-3-one (9b): Anhydrous DMSO (36 mL, 0.50 mol) in CH_2Cl_2 (60 mL) was added dropwise at −78 °C to a solution of oxalyl chloride (40 g, 0.315 mol) in CH_2Cl_2 (100 mL). After stirring for five minutes, a solution of the alcohol **12** (30.0 g, 0.208 mol) in CH_2Cl_2 (60 mL) was added dropwise. After stirring at −78 °C for a further 30 min, Et_3N (200 mL, 1.40 mol) was added. The reaction mixture was then slowly raised to room temperature over a 3 h period. Water (250 mL) was added, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic phases were washed with 3 N HCl (3 × 20 mL) and brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure (below 30 °C). The residue was taken up in diethyl ether and filtered through a pad of silica. The filtrate was concentrated and distilled to give the pyranone **9b** (21 g, 68%) as a pale yellow oil; b.p. 56−58 °C/20 Torr. IR (film): $\tilde{\nu}$ = 1731 (CO), 1448, 1370 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.05 [q, *J* = 7.0 Hz, 1 H, OC*H*(CH$_3$)C=O], 2.54 (ddd, *J* = 16.5, 9.5, 5.7 Hz, 1 H, 4-H), 2.37 (ddd, *J* = 16.5, 5.7, 5.1 Hz, 1 H, 4-H), 1.99 (dt, *J* = 14.2, 5.7 Hz, 1 H, 5-H), 1.83 (ddd, *J* = 14.2, 10.1, 5.1 Hz, 1 H, 5-H), 1.34 [s, 3 H, OC(CH_3)$_2$], 1.31 [s, 3 H, OC(CH_3)$_2$], 1.26 (d, *J* = 7.0 Hz, 3 H, OCH(CH_3)C=O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 212.1 (*C*O), 72.1 (CH, C2), 71.9 (C, C6), 34.4 [CH_3, OC(*C*H$_3$)$_2$], 34.3 [CH_3, OC(*C*H$_3$)$_2$], 29.1 (CH_2, C4), 24.4 (CH_2, C5), 15.5 [CH_3, OCH(*C*H$_3$)C=O)] ppm. MS (EI): *m*/*z* (%) = 142 (32.0) [M$^+$], 127 (4.4), 109 (2.5), 99 (5.7), 98 (26.4), 81 (4.3), 70 (91.4), 56 (100). Semicarbazone of **9b**: M.p. 208−209 °C. $C_9H_{17}N_3O_2$ (199.2): calcd. C 54.25, H 8.60, N 21.09; found C 54.31, H 8.30, N 21.09.

Methyl (*R*)-3-(2,6,6-Trimethyl-3-oxo-tetrahydro-2*H*-pyran-2-yl)propanoate (7b): A mixture of 44 g of 5-Å molecular sieves, 11 g of basic alumina and 6 g of silica was activated by heating for a few minutes at 0.05 Torr with a Bunsen burner. After cooling, 100 mL of cyclohexane was added followed by optically pure (*S*)-(+)-1-phenylethylamine (24.0 g, 0.198 mol) and the ketone **9b** (21.1 g, 0.148 mol) in 20 mL of cyclohexane. The suspension was stirred vigorously at 20 °C for 18 h. The reaction mixture was then filtered and the solid residue was washed repeatedly with dry diethyl ether. The filtrate was concentrated under reduced pressure (0.05 Torr, 40 °C) to give the crude imine **8b** (1:1 diastereomeric mixture, 37.0 g, quantitative) as a pale-yellow oil. IR (film): $\tilde{\nu}$ = 1666 (C=N) cm^{-1}. Freshly distilled methyl acrylate (26.0 g, 0.3 mol) and hydroquinone (0.05 g) were added to the crude imine **8b** (37.0 g, 0.148 mol). The stirred mixture was heated at 50 °C for 4 days. After cooling to 20 °C, 20% aqueous acetic acid (100 mL) and THF (300 mL) were added, and the mixture was stirred at 20 °C for 3 h. Solvents were removed under reduced pressure and 1 N hydrochloric acid (100 mL) was added. The mixture was extracted with diethyl ether (4 × 50 mL) and the collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Chromatography (cyclohexane/EtOAc, 4:1) gave the keto ester **7b** (20.9 g, 62% overall yield from **9b**). Distillation afforded an analytical sample as a colorless oil: b.p. 110 °C/0.05 Torr. $[\alpha]_D^{20}$ = +50.6 (*c* = 7, EtOH). IR (film): $\tilde{\nu}$ = 1740 (CO_2Me), 1720 (CO), 1439, 1370, 1297 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3 H, OCH_3), 2.48 (t, *J* = 6.7 Hz, 2 H, $CH_3O_2CCH_2CH_2$), 2.39 (ddd, *J* = 15.7, 9.6, 6.2 Hz, 1 H, 4-H), 2.27 (ddd, *J* = 15.7, 9.8, 5.6 Hz, 1 H, 4-H), 2.12−1.94 (m, 3 H, $CH_3O_2CCH_2CH_2$ and 5-H), 1.87 (ddd, *J* = 13.9, 9.8, 6.2 Hz, 1 H, 5-H), 1.33 [s, 3 H, $OC(CH_3)_2$], 1.32 [s, 3 H, $CH_2C(CH_3)O$], 1.28 [s, 3 H, $OC(CH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.1 (CO), 173.8 (CO_2Me), 81.0 (C, C2), 71.8 (C, C6), 51.4 (CH_3, OCH_3), 35.0 (CH_2, C5), 33.8 (CH_2, $CH_2CO_2CH_3$), 33.4 (CH_2, $CH_2CH_2CO_2CH_3$), 29.5 [CH_3, $OC(CH_3)_2$], 29.2 [CH_3, $OC(CH_3)_2$], 28.8 (CH_2, C4), 26.0 [CH_3, O=CC(CH_3)CH_2] ppm. $C_{12}H_{20}O_4$ (228.3): calcd. C 63.14, H 8.83; found C 62.95, H 8.99.

Methyl (±)-3-(2,6,6-Trimethyl-3-oxo-3,6-dihydro-2*H*-pyran-2-yl)-propanoate (16): Chlorotrimethylsilane (1.47 g, 13.5 mmol) and Et_3N (2.75 g, 27.2 mmol) were added to a solution of the keto ester (±)-**7b** [prepared as (*R*)-**7b** using racemic 1-phenylethylamine, 1.03 g, 4.51 mmol] in dry DMF (5 mL). The mixture was stirred at 100 °C for 16 h. After cooling the mixture was diluted with pentane (50 mL), and washed with water (2 × 5 mL), dried with $MgSO_4$ and concentrated under reduced pressure to leave a yellow oil (1.18 g, 87%). The crude silyl enol ether (1.18 g, 3.92 mmol) was taken up in CCl_4 (20 mL) and a solution of bromine (640 mg, 4.0 mmol) in 2 mL of CCl_4 was added dropwise at −78 °C. When the addition was complete, aqueous sodium thiosulfate was added and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give a yellow oil which was used directly in the next step. The crude mixture of bromoketones obtained above (1.16 g) was taken up in dry DMF (17 mL). Lithium carbonate (558 mg, 7.55 mmol) and lithium bromide (656 mg, 7.55 mmol) were added and the resulting mixture was heated at 80 °C for 16 h. After cooling to 20 °C the reaction mixture was poured into 1 N hydrochloric acid, and extracted with diethyl ether. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to leave an oil which was purified by chromatography over silica gel (cyclohexane/EtOAc, 4:1) to give the enone **16** as a colorless oil 550 mg, 54% overall yield from **7b**. IR (film): $\tilde{\nu}$ = 1740 (CO_2Me), 1683 (CO), 1438, 1373, 1260 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.82 (d, *J* = 10.2 Hz, 1 H, *H*C=CHCO), 5.90 (d, *J* = 10.2 Hz, 1 H, HC=C*H*CO), 3.64 (s, 3 H, CO_2CH_3), 2.50−2.10 (m, 3 H, $CH_2CH_2CO_2CH_3$), 1.98−1.80 (m, 1 H, $CH_2CH_2CO_2CH_3$), 1.45 (s, 3 H, HC=CHCOCH_3), 1.35 [s, 6 H, $OC(CH_3)_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.4 (CO), 173.9 (CO_2CH_3), 154.9 (CH, H*C*=CHCO), 122.2 (CH, HC=*C*HCO), 79.6 (C, C2), 71.7 [C, $OC(CH_3)_2$], 51.4 (CH_3, OCH_3), 34.5 (CH_2, $CH_2CH_2CO_2CH_3$), 30.3 (CH_2, $CH_2CH_2CO_2CH_3$), 28.9 [2 CH_3, $OC(CH_3)_2$], 26.2 [CH_3, $CH_2C(CH_3)O$] ppm. $C_{12}H_{18}O_4 \cdot 1/4H_2O$ (230.8): calcd. C 62.45, H 8.08; found C 62.21, H 8.30.

Methyl (*R*)-3-(6,8,8-Trimethyl-1,4,7-trioxaspiro[4.5]dec-6-yl)propionoate (18): Keto ester **7b** (3.20 g, 14.0 mmol), ethylene glycol (8.70 g, 140 mmol), *p*-toluenesulfonic acid (0.1 g, 0.58 mmol) and 150 mL of toluene were placed into a round-bottomed flask equipped with a Dean−Stark apparatus. The reaction mixture was heated at reflux for 9 h, and two additional portions of *p*-toluenesulfonic acid (0.1 g, 0.58 mmol) were added. The reaction mixture was taken up in EtOAc (250 mL), washed with saturated aqueous sodium hydrogencarbonate and brine and dried with $MgSO_4$. After concentration under reduced pressure the residue was taken up in anhydrous methanol (10 mL) and added dropwise to a solution of sodium methoxide in methanol (from 0.25 g of sodium in 100 mL of MeOH). The reaction mixture was stirred at 20 °C for 1 h, and most of the methanol was removed in vacuo. A saturated aqueous ammonium chloride solution was added to the residue and the mixture was extracted with EtOAc (4 × 50 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Chromatography (cyclohexane/EtOAc, 5:1 + 0.5% Et_3N) gave the acetal **18** (3.2 g, 84%); colorless oil. $[\alpha]_D^{20}$ = +4.9 (*c* = 5, EtOH). IR (film): $\tilde{\nu}$ = 1734 (CO_2Me), 1436, 1369, 1256, 1206 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.85 (s, 4 H, OCH_2CH_2O), 3.55 (s, 3 H, CO_2CH_3), 2.55 (m, 2 H, $CH_2CO_2CH_3$), 2.00 (m, 1 H, 10-H), 1.88−1.55 (m, 5 H, $CH_2CH_2CO_2CH_3$, 9-H, 10-H), 1.12 [s, 3 H, $CH_2C(CH_3)O$], 1.08 [s, 6 H, $OC(CH_3)_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.7 (CO_2CH_3), 108.8 (C, C5), 77.2 (C, C6) 71.1 (C, C8), 64.7 (CH_2, OCH_2CH_2O), 64.5 (CH_2, OCH_2CH_2O), 51.1 (CH_3, OCH_3), 34.9 (CH_2), 31.7 (CH_2), 30.5 [CH_3, $OC(CH_3)_2$], 29.1 [CH_3, $OC(CH_3)_2$], 28.4 (CH_2), 25.8 (CH_2), 22.5 [CH_3, $CH_2C(CH_3)O$] ppm. $C_{14}H_{24}O_5$ (272.3): calcd. C 61.76, H 8.82; found C 61.86, H 8.99.

(6*R*,10 *R*)- and (6*R*,10*S*)-3-(10-Bromo-6,8,8-trimethyl-1,4,7-trioxaspiro[4.5]dec-6-yl)propionic Acid (19): A solution of bromine (1.55 g, 9.8 mmol) in CCl_4 (5 mL) was added dropwise to a solution of the acetal **18** (2.4 g, 8.8 mmol) in CCl_4 (20 mL) at 40 °C. The resulting dark-red solution was heated at 40 °C for 45 min, while the color progressively faded. After cooling, aqueous sodium thiosulfate was added, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were sequentially washed with sodium hydrogencarbonate and brine, dried with $MgSO_4$ and concentrated in vacuo to give a yellow oil (3.1 g) which was taken up in methanol (20 mL). 2 M Sodium hydroxide (15 mL, 30 mmol) was added and the reaction mixture was stirred at 20 °C for 18 h. Most of the methanol was removed under reduced pressure and 3 N hydrochloric acid was added at 0 °C until pH 3. The mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude acid **19** (2.8 g, 94%) as a yellow oil which was used in the next step without further purification. IR (film): $\tilde{\nu}$ = 3500−2500 (OH), 1705 (CO_2H), 1446, 1415, 1367, 1339, 1312, 1209, 1098 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) the presence of a 2:1 mixture of diastereomers induced the splitting of some signals, δ = 4.78−4.74 (m, 1 H, C*H*Br), 4.37−4.33 (m, 2 H, OCH_2CH_2O), 4.10−4.01 (m, 2 H, OCH_2CH_2O),

CH_2O), 2.57−1.30 (m, 6 H), 1.34 and 1.32 (2 s, 3 H), 1.30 and 1.24 (2 s, 3 H), 1.21 and 1.07 (2 s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) only the major isomer is described δ = 180.1 (CO_2CH_3), 109.4 (C, C5), 80.1 (C, C6) 73.6 (C, C8), 67.7 (CH_2, OCH_2CH_2O), 67.0 (CH_2, OCH_2CH_2O), 52.5 (CH, CHBr), 47.1 (CH_2, C9), 32.8 (CH_2, $CH_2CH_2CO_2H$), 32.2 [CH_3, $OC(CH_3)_2$], 28.6 (CH_2, $CH_2CH_2CO_2H$), 27.6 [CH_3, $OC(CH_3)_2$], 23.4 (CH_3, $CH_2C(CH_3)O$] ppm.

(*R*)-3-(6,8,8-Trimethyl-1,4,7-trioxaspiro[4.5]dec-9-en-6-yl)propionic Acid (20): A solution of the bromoacetal **19** (3.37 g, 10 mmol) in DMSO (30 mL) was added dropwise to a solution of potassium *tert*-butoxide (5.2 g, 46.4 mmol) in dry DMSO (25 mL). The resulting mixture was heated at 110 °C for 4 h. After cooling to 0 °C, 1 M oxalic acid was added until pH 3. The mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. Chromatographic purification (cyclohexane/EtOAc, 1:1) gave the acid **20** (2.05 g, 80%) as colorless crystals; m.p. 72−73 °C. $[\alpha]_D^{20}$ = −18.2 (*c* = 5, EtOH). IR (film): $\tilde{\nu}$ = 2800−2600 (OH), 1705 (CO_2H), 1415, 1371, 1252, 1148, 1101, 1080 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.80 (d, *J* = 10.4 Hz, 1 H, 9-H), 5.61 (d, *J* = 10.4 Hz, 1 H, 10-H), 4.04−3.85 (m, 4 H, OCH_2CH_2O), 2.70−2.40 (m, 2 H, $CH_2CH_2CO_2H$), 2.20−2.05 (m, 1 H, $CH_2CH_2CO_2H$), 1.90−1.70 (m, 1 H, $CH_2CH_2CO_2H$), 1.25 [s, 6 H, $OC(CH_3)_2$], 1.20 [s, 3 H, $CH_2C(CH_3)O$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.8 (CO_2H), 136.7 (CH, C9), 123.0 (CH, C10), 104.8 (C, C5), 77.0 (C, C6), 71.8 (C, C8), 65.2 (CH_2, OCH_2CH_2O), 65.0 (CH_2, OCH_2CH_2O), 30.4 [CH_3, $OC(CH_3)_2$], 30.2 (CH_2, $CH_2CH_2CO_2H$), 29.2 [CH_3, $OC(CH_3)_2$], 28.6 (CH_2, $CH_2CH_2CO_2H$), 21.6 [CH_3, $CH_2C(CH_3)O$] ppm. $C_{13}H_{20}O_5$ (256.3): calcd. C 60.90, H 7.81; found C 60.93, H 7.92. Crystal data: White crystal of 0.20 × 0.24 × 0.27 mm. $C_{13}H_{20}O_5$, *M* = 256.30. Orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 8.618(7), *b* = 10.372(4), *c* = 15.207(6)Å, α = β = γ = 90°, *V* = 1359.3(13)Å^3, *d* = 1.252 g·cm^{-3}, *F*(000) = 552, λ = 0.710693 Å (Mo-K_α), μ = 0.0957 mm^{-1}; 3330 reflections measured (0 ≤ *h* ≤ 11, 0 ≤ *k* ≤ 13, 0 ≤ *l* ≤ 20) on a Nonius CAD4 diffractometer. The structure was solved with SIR92[25] and refined with CRYSTALS[26] with hydrogen atoms riding. Refinement converged to *R*(*gt*) = 0.0439 for the 1808 reflections having *I* = 2σ(*I*), and *wR*(*gt*) = 0.0555, goodness-of-fit *S* = 1.0873. Residual electron density: − 0.28 and 0.23 e·Å^3. The crystal cohesion is ensured by one hydrogen bond involving O_{37}, [for $O_{37}-H_{38}\cdots O_{1i}$: 1.936(3)Å, 174.4° (symmetry code i: *x* −1/2, −*y* +1/2, −*z*)]. CCDC-226013 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK: Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

(*R*)-3-(6,8,8-Trimethyl-1,4,7-trioxaspiro[4.5]dec-9-en-6-yl)propan-1-ol (22): A solution of the acid **20** (2.0 g, 7.8 mmol) in Et_2O (10 mL) was added to an ice-cooled suspension of $LiAlH_4$ (600 mg, 15.8 mmol) in Et_2O (20 mL). The resulting mixture was stirred at 0 °C for 30 min, and a further 30 min at 20 °C. Water was added until most of the salts precipitated. Filtration and concentration under reduced pressure gave an oil which was chromatographed over silica gel (cyclohexane/EtOAc, 1:1 + 0.5% Et_3N) to provide the alcohol **22** as a colorless oil (1.6 g, 84%). $[\alpha]_D^{20}$ = −11.2 (*c* = 5.7, EtOH). IR (film): $\tilde{\nu}$ = 3500−3300 (OH), 1469, 1370, 1251, 1149, 1118 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.75 (d, *J* = 10.4 Hz, 1 H, 9-H), 5.55 (d, *J* = 10.4 Hz, 1 H, 10-H), 4.00−3.80 (m, 4 H, OCH_2CH_2O), 3.60−3.40 (m, 2 H, CH_2OH), 2.70 (br. s, 1 H, OH), 1.90−1.50 (m, 4 H, $CH_2CH_2CH_2OH$), 1.25 [s, 3 H, $OC(CH_3)_2$], 1.22 [s, 3 H, $OC(CH_3)_2$], 1.20 [s, 3 H, $CH_2C(CH_3)O$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 136.4 (CH, C9), 123.1 (CH, C10), 104.9 (C, C5), 77.5 (C, C6), 71.8 (C, C8), 65.1 (CH_2, OCH_2CH_2O), 64.8 (CH_2, OCH_2CH_2O), 63.1 (CH_2, CH_2OH), 31.5 (CH_2, $CH_2CH_2CH_2OH$), 30.7 [CH_3, $OC(CH_3)_2$], 28.8 [CH_3, $OC(CH_3)_2$], 26.2 (CH_2, $CH_2CH_2CH_2OH$), 21.2 [CH_3, $CH_2C(CH_3)O$] ppm. $C_{13}H_{22}O_4$ (242.3): calcd. C 64.44, H 9.15; found C 64.23, H 9.24.

(*R*)-6-(3-Bromopropyl)-6,8,8-trimethyl-1,4,7-trioxaspiro[4.5]dec-9-ene (23): Pyridine (1.58 g, 20 mmol), CBr_4 (3.0 g, 9.0 mmol) and a solution of PPh_3 (2.4 g, 9.1 mmol) in diethyl ether (12 mL) were added sequentially to a solution of the alcohol **22** (1.10 g, 4.5 mmol) in dry diethyl ether (16 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 4 h and was then filtered through a sintered glass funnel containing a large pad of silica. The solid was washed with diethyl ether, the filtrate was concentrated and the resulting oil was triturated with a mixture of diethyl ether/pentane 2:1. The solid was filtered and the filtrate concentrated to leave a colorless oil which was used directly in the next step (1.1 g, 80%). $[\alpha]_D^{20}$ = −19.8 (*c* = 5, EtOH). IR (film): $\tilde{\nu}$ = 1467, 1437, 1370, 1259, 1168, 1146 cm^{-1}. ^1H NMR (200 MHz, [D_6]benzene): δ = 5.51 (d, *J* = 10.4 Hz, 1 H, 9-H), 5.44 (d, *J* = 10.4 Hz, 1 H, 10-H), 3.50−3.30 (m, 4 H, OCH_2CH_2O), 3.18−2.98 (m, 2 H, CH_2Br), 2.30−1.45 (m, 4 H, $CH_2CH_2CH_2Br$), 1.22 (s, 3 H), 1.20 (s, 3 H), 1.18 (s, 3 H) ppm. ^{13}C NMR (50 MHz, [D_6]benzene): δ = 137.1 (CH, C9), 124.4 (CH, C10), 105.8 (C, C5), 77.9 (C, C6), 72.2 (C, C8), 65.6 (CH_2, OCH_2CH_2O), 65.4 (CH_2, OCH_2CH_2O), 35.6 (CH_2, CH_2Br or $CH_2CH_2CH_2Br$), 35.4 (CH_2, CH_2Br or $CH_2CH_2CH_2Br$), 31.4 [CH_3, $OC(CH_3)_2$], 30.1 [CH_3, $OC(CH_3)_2$], 28.0 (CH_2, CH_2CH_2 CH_2Br), 22.6 [CH_3, $CH_2C(CH_3)O$] ppm.

(*R*)-6,8,8-Trimethyl-6-(pent-4-ynyl)-1,4,7-trioxaspiro[4.5]dec-9-ene (4): A solution of *n*-butyllithium (2.5 M in hexane, 0.65 mL, 1.6 mmol) was added to a solution of (trimethylsilyl)acetylene (158 mg, 1.6 mmol) in dry THF (2 mL) at −78 °C. The mixture was stirred at −78 °C for 5 min and the temperature was raised to 20 °C. After stirring for a further 15 min at room temperature the mixture was cooled to −50 °C, and a solution of the bromide **23** (250 mg, 0.82 mmol) in THF (1 mL) and DMPU (0.3 mL) was added. The reaction mixture was stirred at −50 °C for 15 min and the temperature was raised to 20 °C. After 12 h saturated aqueous ammonium chloride was added and the mixture was extracted with diethyl ether (4 × 15 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. The residue was taken up in THF (2 mL) and a THF solution of tetrabutylammonium fluoride (1 M, 1 mL, 1 mmol) was added at 0 °C. After stirring at room temperature for 1 h, saturated aqueous ammonium chloride was added and the mixture was extracted with diethyl ether (4 × 10 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Chromatography (cyclohexane/EtOAc, 10:1 + 0.5% Et_3N) gave compound **4** (142 mg, 69% overall yield from **23**) as a colorless oil. $[\alpha]_D^{20}$ = −17 (*c* = 3.7, EtOH). IR (film): $\tilde{\nu}$ = 3292 (C≡C−H), 2116 (weak, C≡C), 1466, 1370, 1251 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.80 (d, *J* = 10.4 Hz, 1 H, 9-H), 5.68 (d, *J* = 10.4 Hz, 1 H, 10-H), 4.00−3.75 (m, 4 H, OCH_2CH_2O), 2.25−2.05 (m, 2 H, $CH_2C{\equiv}CH$), 1.90 (t, *J* = 2.5 Hz, 1 H, ≡C−H), 1.80−1.40 (m, 4 H, $CH_2CH_2CH_2C{\equiv}$), 1.30 [s, 6 H, $OC(CH_3)_2$], 1.20 [s, 3 H, $CH_2C(CH_3)O$] ppm. ^{13}C NMR (50 MHz, [D_6]benzene): δ = 137.1 (CH, C9), 124.5 (CH, C10), 105.9 (C, C5), 84.3 (C≡CH), 78.1 (C, C6), 72.0 (C, C8), 69.4 (C≡CH), 65.6 (CH_2, OCH_2CH_2O), 65.3 (CH_2, OCH_2CH_2O), 35.7 (CH_2, $CH_2CH_2CH_2C{\equiv}$), 31.2 [CH_3, $OC(CH_3)_2$], 30.2 [CH_3, $OC(CH_3)_2$], 23.4 (CH_2, $CH_2CH_2CH_2C{\equiv}$

or $CH_2CH_2CH_2C\equiv$), 22.3 (CH_2, $CH_2CH_2CH_2C\equiv$ or $CH_2CH_2CH_2C\equiv$), 20.0 [CH_3, $CH_2C(CH_3)O$] ppm. $C_{15}H_{22}O_3$ (250.3): calcd. C 71.97, H 8.86; found C 71.71, H 9.03.

(*R*)-5-(6,8,8-Trimethyl-1,4,7-trioxaspiro[4.5]dec-9-en-6-yl)pentan-2-one (27): A solution of *t*BuLi (1.7 M in pentane, 4.3 mL, 7.3 mmol) was added dropwise at −78 °C to a solution of bromide **23** (1.0 g, 3.3 mmol) in a diethyl ether/THF mixture (9:1, 20 mL). The resulting orange solution was stirred for 15 min at −78 °C, and a solution of *N*-methoxy-*N*-methylacetamide (**28**) (0.75 g, 7.27 mmol) in THF (10 mL) was added. The mixture was stirred for 15 min at −78 °C and slowly warmed up to room temperature. After 3 h, saturated aqueous ammonium chloride was added, the ethereal layer was separated, and the aqueous phase extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated to give an oil which was chromatographed on silica gel (cyclohexane/EtOAc, 8:1 + 0.5% Et_3N, then 4:1 + 0.5% Et_3N) to give ketone **27** as a yellow oil (0.40 g, 46%). $[\alpha]_D^{20} = -18.0$ (c = 5.1, EtOH). IR (film): $\tilde{\nu}$ = 1714 (C=O), 1466, 1368, 1251, 1148, 1112 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.79 (d, J = 10.4 Hz, 1 H, 9-H), 5.58 (d, J = 10.4 Hz, 1 H, 10-H), 4.05−3.85 (m, 4 H, OCH_2CH_2O), 2.50−2.35 (m, 2 H, CH_3COCH_2), 2.12 (s, 3 H, CH_3COCH_2), 1.84−1.48 (m, 4 H, $CH_3COCH_2CH_2CH_2$), 1.27 [s, 3 H, $OC(CH_3)_2$], 1.26 [s, 3 H, $OC(CH_3)_2$], 1.22 [s, 3 H, $CH_2C(CH_3)O$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.9 (CO), 136.7 (CH, C9), 122.9 (CH, C10), 104.9 (C, C5), 77.2 (C, C6), 71.3 (C, C8), 65.0 (CH_2, OCH_2CH_2O), 64.8 (CH_2, OCH_2CH_2O), 44.2 (CH_2, CH_3COCH_2), 34.5 (CH_2, $CH_3COCH_2CH_2CH_2$), 30.3 [CH_3, $OC(CH_3)_2$], 29.6 (CH_3, CH_3COCH_2), 29.3 [CH_3, $OC(CH_3)_2$], 21.0 [CH_3, $CH_2C(CH_3)O$], 17.5 (CH_2, $CH_3COCH_2CH_2CH_2$) ppm. $C_{15}H_{24}O_4$ (268.3): calcd. C 67.16, H 8.95; found C 66.83, H 9.18.

Ethyl (*R*)-(*E*,*Z*)-3-Methyl-6-(6,8,8-trimethyl-1,4,7-trioxaspiro[4.5]-dec-9-en-6-yl)hex-2-enoate (29): A slight excess of a *n*BuLi solution (2.5 M in hexane, 0.84 mL, 2.1 mmol) was added dropwise to a solution of triethyl phosphonoacetate (450 mg, 2.0 mmol) in THF (2 mL) cooled to −60 °C. The mixture was warmed up to −20 °C and stirred for 20 min at this temperature. A solution of ketone **27** (270 mg, 1.0 mmol) in THF (0.5 mL) was then added in one portion to the clear phosphonoacetate anion solution at −20 °C, and the reaction mixture was stirred for 24 h at room temperature. Saturated aqueous ammonium chloride (10 mL) was then added, the mixture was extracted with diethyl ether (4 × 50 mL) and the collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Chromatography (cyclohexane/EtOAc, 6:1 + 0.5% Et_3N) gave ester **29** (280 mg, 83%) as an oil. IR (film): $\tilde{\nu}$ = 1714 (CO_2Et), 1648 (C=C), 1465, 1369, 1221, 1147 cm^{-1}. A 4:1 (*E*)/(*Z*) ratio was determined by NMR spectroscopy, only the main (*E*) isomer is described. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.77 (d, J = 10.3 Hz, 1 H, 9-H), 5.65 (s, 1 H, $=CHCO_2Et$), 5.56 (d, J = 10.3 Hz, 1 H, 10-H), 4.11 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.05−3.85 (m, 4 H, OCH_2CH_2O), 2.12 [s, 3 H, $(CH_3)C=CHCO_2Et$], 2.15−2.00 [m, 2 H, $CH_2(CH_3)C=CHCO_2Et$], 1.80−1.40 [m, 4 H, $CH_2CH_2CH_2(CH_3)C=$], 1.22 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.24 [s, 3 H, $OC(CH_3)_2$], 1.22 [s, 3 H, $OC(CH_3)_2$], 1.17 [s, 3 H, $CH_2C(CH_3)O$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8 (CO_2Et), 160.1 (C, $C=CHCO_2Et$), 136.8 (CH, C9), 123.0 (CH, C10), 115.4 (CH, $C=CHCO_2Et$), 105.0 (C, C5), 77.3 (C, C6), 71.4 (C, C8), 65.1 (CH_2, OCH_2CH_2O), 64.9 (CH_2, OCH_2CH_2O), 59.3 (CH_2, OCH_2CH_3), 41.5 [CH_2, $CH_2(CH_3)C=$], 34.8 [CH_2, $CH_2CH_2CH_2(CH_3)C=$], 30.2 [CH_3, $OC(CH_3)_2$], 29.6 [CH_3, $OC(CH_3)_2$], 21.0 [CH_2, $CH_2CH_2(CH_3)C=$], 20.9 [CH_3, $CH_2C(CH_3)O$], 18.7 [CH_3, $CH_2(CH_3)C=C$], 14.3 (CH_3, OCH_2CH_3) ppm. $C_{19}H_{30}O_5$ (338.4): calcd. C 67.43, H 8.93; found C 67.37, H 8.79.

(*R*)-(*E*,*Z*)-3-Methyl-6-(6,8,8-trimethyl-1,4,7-trioxaspiro[4.5]dec-9-en-6-yl)hex-2-en-1-ol (30): A toluene solution of DIBAH (1.5 M, 13 mL, 19.5 mmol) was added to a solution of the enoate **29** [4:1 (*E*)/(*Z*) mixture] (1.68 g, 5.0 mmol) in THF (75 mL) at −78 °C. The reaction was stirred for 2 h at −78 °C. Saturated aqueous ammonium chloride was then added and the mixture was warmed to room temperature. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with an aqueous solution of tartaric acid sodium potassium salt, dried with $MgSO_4$, evaporated and chromatographed on silica gel (cyclohexane/EtOAc, 2:1 + 0.5% Et_3N), to give alcohol **30** (1.40 g, 95%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3600−3400 (OH), 1667 (C=C), 1466, 1443, 1370, 1251, 1169, 1148, 1115, 1007 cm^{-1}. A 4:1 (*E*)/(*Z*) ratio was determined by NMR, only the main (*E*) isomer is described. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.76 (d, J = 10.4 Hz, 1 H, 9-H), 5.55 (d, J = 10.4 Hz, 1 H, 10-H), 5.37 (t, J = 6.7 Hz, 1 H, $C=CHCH_2OH$), 4.09 (d, J = 6.7 Hz, 2 H, $C=CHCH_2OH$), 4.05−3.80 (m, 4 H, OCH_2CH_2O), 1.95 [t, J = 7.2 Hz, 2 H, $CH_2(CH_3)C=CHCH_2OH$], 1.70−1.30 [m, 5 H, OH, $CH_2CH_2CH_2(CH_3)C=$], 1.65 [s, 3 H, $(CH_3)C=CHCH_2OH$], 1.22 [s, 3 H, $OC(CH_3)_2$], 1.20 [s, 3 H, $OC(CH_3)_2$], 1.16 [s, 3 H, $CH_2C(CH_3)O$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.6 (C, $C=CHCH_2OH$), 136.6 (CH, C9), 124.2 (CH, $C=CHCH_2OH$), 123.3 (CH, C10), 105.1 (C, C5), 77.4 (C, C6), 71.4 (C, C8), 65.1 (CH_2, OCH_2CH_2O), 65.0 (CH_2, OCH_2CH_2O), 59.1 (CH_2, $C=CHCH_2OH$), 40.1 [CH_2, $CH_2(CH_3)C=$], 34.8 [CH_2, $CH_2CH_2CH_2(CH_3)C=C$], 29.9 [CH_3, $OC(CH_3)_2$], 29.5 [CH_3, $OC(CH_3)_2$], 21.1 [CH_2, $CH_2CH_2(CH_3)C=C$], 20.8 [CH_3, $CH_2C(CH_3)O$], 16.1 [CH_3, $CH_2(CH_3)C=$] ppm. $C_{17}H_{28}O_4$ (296.4): calcd. C 68.89, H 9.52; found C 68.64, H 9.60.

(*R*)-(*E*,*Z*)-3-Methyl-6-(6,8,8-trimethyl-1,4,7-trioxaspiro[4.5]dec-9-en-6-yl)hex-2-enal (31): A mixture of the alcohol **30** [4:1 (*E*)/(*Z*) mixture] (300 mg, 1.01 mmol) and MnO_2 (610 mg, 7.0 mmol) in dichloromethane (10 mL) was stirred at 20 °C for 12 h. Filtration through Celite and concentration afforded a yellow oil. Flash chromatography (cyclohexane/ethyl acetate, 4:1) furnished the pure aldehyde **31** (270 mg, 90%) as a colorless oil. IR (film): $\tilde{\nu}$ = 1672 (CO), 1630 (C=C), 1466, 1371, 1251, 1169, 1149, 1122, 1082 cm^{-1}. A 4:1 (*E*)/(*Z*) ratio was determined by NMR, only the main (*E*) isomer is described. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.98 (d, J = 7.9 Hz, 1 H, $CH=O$), 5.90 (m, 1 H, $C=CHCHO$), 5.79 (d, J = 10.0 Hz, 1 H, 9-H), 5.58 (d, J = 10.0 Hz, 1 H, 10-H), 4.05−3.80 (m, 4 H, OCH_2CH_2O), 2.20 [t, J = 7.2 Hz, 2 H, $CH_2(CH_3)C=CHCHO$], 2.16 [s, 3 H, $(CH_3)C=CHCHO$], 1.90−1.40 [m, 4 H, $CH_2CH_2CH_2(CH_3)C=$], 1.22 [s, 3 H, $OC(CH_3)_2$], 1.20 [s, 3 H, $OC(CH_3)_2$], 1.16 [s, 3 H, $CH_2C(CH_3)O$] ppm. $C_{17}H_{26}O_4$ (294.3): calcd. C 69.36, H 8.90; found C 69.38, H 8.94.

(6*R*)-(*E*,*Z*)-2-(*tert*-Butyldimethylsilyloxy)-4-methyl-7-(6,8,8-trimethyl-1,4,7-trioxaspiro[4.5]dec-9-en-6-yl)hept-3-enenitrile (3): *tert*-Butyldimethylsilyl cyanide (400 g, 2.88 mmol) was added to a solution of the aldehyde **31** (200 mg, 0.68 mmol) in acetonitrile (5 mL) and the resulting mixture was heated at reflux for 10 h. Concentration under reduced pressure afforded a crude oil. Chromatographic purification (cyclohexane/EtOAc, 10:1 + 0.5% Et_3N) gave the cyanohydrin **3** as a colorless oil (235 mg, 80%). IR (film): $\tilde{\nu}$ = 1666 (C=C), 1472, 1369, 1254, 1149, 1119, 1102, 1083 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) the presence of two diastereomers in a 1:1 ratio, and a 4:1 ratio of (*E*)/(*Z*) geometric isomers induced the splitting of some signals δ = 5.80 (d, J = 10.3 Hz, 1 H, 9-H), 5.59 (d, J = 10.3 Hz, 1 H, 10-H), 5.33 [m, 1 H, C=

C*H*CH(CN)OSi], 5.08 [d, *J* = 8.1 Hz, 1 H, C=CHC*H*(CN)OSi], 4.05−3.80 (m, 4 H, OCH_2CH_2O), 2.04 [broad t, *J* = 7.0 Hz, 2 H, CH_2(CH_3)C=CH(CN)OSi], 1.80−1.30 [m, 4 H, CH_2CH_2CH_2(CH_3)C=], 1.78 and 1.70 [2 s, 3 H, (CH_3)C=CHCH_2OH], 1.26 [s, 3 H, OC(CH_3)$_2$], 1.24 [s, 3 H, OC(CH_3)$_2$], 1.19 [s, 3 H, CH_2C(CH_3)O], 0.90 [s, 9 H, (CH_3)$_3$CSi], 0.18 [s, 3 H, (CH_3)$_2$SiO], 0.12 [s, 3 H, (CH_3)$_2$Si]) ppm. ^{13}C NMR (50 MHz, [D_6]benzene) the presence of two diastereomers in a 1:1 ratio, and (*E*)/(*Z*) geometric isomers in a 4:1 ratio induced the splitting of some signals δ = 142.9 and 142.8 [C, HC=*C*(CH_3)CH_2], 136.5 (CH, C9), 124.0 (CH, C10), 122.2, 122.0 121.5 and 121.4 [CH, C=*C*HCH(CN)OSi], 119.5 (C, *C*N), 105.3 (C, C5), 77.5 (C, C6), 71.4 (C, C8), 65.1 (CH_2, OCH_2CH_2O), 64.8 (CH_2, OCH_2CH_2O), 59.3 and 59.0 [CH, =CH*C*H(CN)OSi], 40.0 [CH_2, *C*H_2(CH_3)C=], 35.2 and 35.1 [CH_2, *C*H_2CH_2CH_2(CH_3)C=], 30.8 and 30.7 [CH_3, OC(CH_3)$_2$], 29.7 and 29.6 [CH_3, OC(CH_3)$_2$], 26.2, 25.7, and 25.5 [3 CH_3, (*C*H_3)$_3$CSiO], 21.7 [CH_3, CH_2C(*C*H_3)O], 21.1 [CH_2, *C*H_2CH_2(CH_3)C=], 18.2 [C, (*C*H_3)$_3$*C*SiO], 16.4 and 16.5 (CH_3, CH_2(*C*H_3)C=], −4.8, −6.3 and −8.7 [2 CH_3, (*C*H_3)$_2$SiO] ppm. $C_{24}H_{41}NO_4Si$ (435.6): calcd. C 66.16, H 9.49, N 3.21; found C 66.16, H 9.68, N 3.06.

2-Bromo-6-methyl-4-(triisopropylsilyloxy)phenol (34): Triisopropylchlorosilane (8.69 g, 45.0 mmol) was added dropwise at −10 °C to a solution of 2-bromo-6-methylbenzene-1,4-diol (**6**)[17b] (8.36 g, 41.1 mmol) and imidazole (3.1 g, 45.0 mmol) in anhydrous DMF (125 mL). The temperature was slowly raised to 20 °C and stirring was continued for 18 h. The mixture was poured into ice-cooled water and extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure to give a yellowish oil which was used directly in the next step since substantial isomerization occurred on silica (14.5 g, quantitative). IR (film): ṽ = 3535 (OH), 1608, 1577, 1474, 1411, 1183 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.82 (m, 1 H, 3-H), 6.62 (m, 1 H, 5-H), 5.10 (broad s, 1 H, OH), 2.24 (s, 3 H, CH_3), 1.35−1.00 [m, 21 H, (CH_3)$_2$C*H*SiO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.2 (C, C1), 144.8 (C, C4), 125.9 (C, C6), 121.9 (CH, C3 or C5), 119.9 (CH, C3 or C5), 109.3 (C, C2), 18.0 [6 CH_3, OSiCH(*C*H_3)$_2$], 16.8 (CH_3, Ar*C*H_3), 12.6 [3 CH, OSi*C*H(CH_3)$_2$] ppm. $C_{16}H_{27}O_2SiBr{\cdot}1/4H_2O$ (362.9): calcd. C 52.81, H 7.62; found C 52.68, H 7.61.

(3-Bromo-4-methoxy-5-methylphenoxy)triisopropylsilane (35): Methyl iodide (11.3 g, 80 mmol) and potassium carbonate (11.3 g, 82 mmol) were added to a solution of the crude phenol **34** (14.5 g, 41 mmol) in acetone (180 mL). The mixture was stirred at reflux for 4 h. After cooling, saturated aqueous ammonium chloride was added and the mixture was extracted with diethyl ether (4 × 100 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Chromatographic purification (cyclohexane + 0.5% Et_3N, then cyclohexane/EtOAc, 10:1, + 0.5% Et_3N) gave **35** as a colorless oil (10.7 g, 70% overall from **6**). IR (film): ṽ = 1598, 1561, 1473, 1422, 1308, 1220, 1019 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.89 (d, *J* = 3.0 Hz, 1 H, 2-H), 6.63 (d, *J* = 3.0 Hz, 1 H, 6-H), 3.75 (s, 3 H, OCH_3), 2.26 (s, 3 H, ArCH_3), 1.35−1.00 [m, 21 H, (CH_3)$_2$C*H*SiO] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 152.3 (C, C4), 149.6 (C, C1), 133.1 (C, C5), 121.7 (CH, C2 or C6), 121.3 (CH, C2 or C6), 116.7 (C, C3), 60.2 (CH_3, OCH_3), 17.8 [6 CH_3, SiCH(*C*H_3)$_2$], 16.7 (CH_3, Ar*C*H_3), 12.3 [3 CH, Si*C*H(CH_3)$_2$] ppm. $C_{17}H_{29}BrO_2Si$ (372.9): calcd. C 54.68, H 7.83; found C 54.31, H 7.88.

Triisopropyl[4-methoxy-3-methyl-5-(3-methylbut-2-enyl)phenoxy]-silane (38): A dibutyl ether solution of PhLi (2.5 M, 11 mL, 27.5 mmol) was added to an ice-cooled solution of aryl bromide **35** (7.3 g, 19.6 mmol) in cyclohexane (40 mL) and the mixture was stirred at room temperature for 1 h. The clear solution was then cooled to −78 °C and dry diethyl ether (50 mL) was added, followed by 1-bromo-3-methylbut-2-ene (8.7 g, 58.4 mmol) and DMPU (7 mL). The temperature was gradually raised to 20 °C over a 1 h period, and the mixture was stirred at room temperature for 12 h. Saturated aqueous ammonium chloride was added and the mixture was extracted with diethyl ether (4 × 50 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Chromatography (cyclohexane + 0.5% Et_3N then cyclohexane/EtOAc, 99:1 + 0.5% Et_3N) gave compound **38** (6.45 g, 91%) as a colorless oil. IR (film): ṽ = 1599, 1499, 1466, 1326, 1219 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.51 (s, 2 H, 2-H, 6-H), 5.26 (broad t, *J* = 7.2 Hz, 1 H, ArCH_2C*H*=C), 3.67 (s, 3 H, OCH_3), 3.28 (d, *J* = 7.2 Hz, 2 H, ArCH_2CH=C), 2.22 (s, 3 H, ArCH_3), 1.74 [, 3 H, CH_2CH=C(CH_3)$_2$], 1.70 [s, 3 H, CH_2CH=C(CH_3)$_2$], 1.40−1.00 [m, 21 H, (CH_3)$_2$C*H*SiO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 151.7 (C, C4), 150.6 (C, C1), 134.9 [C, HC=*C*(CH_3)$_2$], 132.4 (C, C3 or C5), 131.4 (C, C3 or C5), 123.0 (CH, ArCH_2*C*H=C), 119.7 (CH, C2 or C6), 118.3 (CH, C2 or C6), 60.4 (CH_3, O*C*H_3), 28.1 (CH_2, Ar*C*H_2CH=), 25.6 [CH_3, HC=C(*C*H_3)$_2$], 17.9 [6 CH_3, SiCH(*C*H_3)$_2$], 17.7 [CH_3, HC=C(*C*H_3)$_2$], 16.1 (CH_3, Ar*C*H_3), 12.3 [3 CH, Si*C*H(CH_3)$_2$] ppm. MS (ESI): *m*/*z* (%) = 361.3 (100) [M^+ − 1], 291.1(66). $C_{22}H_{38}O_2Si$ (362.6): calcd. C 72.87, H 10.56; found C 72.81, H 10.58.

(*E*)-4-[2-Methoxy-3-methyl-5-(triisopropylsilyloxy)phenyl]-2-methylbut-2-en-1-ol (37): A mixture of **38** (3.1 g, 8.6 mmol) and selenium dioxide (1.14 g, 10.3 mmol) in 1,4-dioxane (33 mL) and water (2 mL) was refluxed for 1 h. After cooling the selenium was filtered off and the filtrate was washed with brine, dried and concentrated under reduced pressure. The oily residue was taken up in absolute ethanol (30 mL) and sodium borohydride (380 mg, 10.0 mmol) was added portionwise at 0 °C. When the addition was complete the mixture was stirred at 20 °C for 30 min. 1 M Hydrochloric acid was then added until neutrality, and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The organic layer was washed with brine, dried and concentrated in vacuo. The residue was chromatographed on silica gel (cyclohexane/EtOAc, 6:1 + 0.5% Et_3N) to give the allylic alcohol **37** (1.9 g, 60%) as a colorless oil. IR (film): ṽ = 3600−3200 (OH), 1599 (C=C), 1475, 1327, 1217 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53 (d, *J* = 2.9 Hz, 1 H, 4-H), 6.50 (d, *J* = 2.9 Hz, 1 H, 6-H), 5.55 (t, *J* = 7.1 Hz, 1 H, ArCH_2C*H*=C), 4.02 [br. s, 2 H, HC=C(CH_3)CH_2OH], 3.68 (s, 3 H, OCH_3), 3.35 (d, *J* = 7.1 Hz, 2 H, ArCH_2C*H*=C), 2.23 (s, 3 H, ArCH_3), 1.78 [s, 3 H, HC=C(CH_3)CH_2OH], 1.30 (s, 1 H, OH), 1.25−1.15 [m, 3 H, OSiC*H*(CH_3)$_2$], 1.08 [d, *J* = 8.5 Hz, 18 H, OSiCH(CH_3)$_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 151.8 (C, C2), 150.5 (C, C5), 135.6 [C, HC=*C*(CH_3)CH_2OH], 134.1 (C, C1), 131.5 (C, C3), 124.7 (CH, H*C*=C(CH_3)CH_2OH], 119.9 (CH, C4), 118.3 (CH, C6), 68.8 [CH_2, =C(CH_3)*C*H_2OH], 60.4 (CH_3, O*C*H_3), 28.0 (CH_2, Ar*C*H_2CH=C), 17.9 [6 CH_3, OSiCH(*C*H_3)$_2$], 16.2 (CH_3, Ar*C*H_3), 13.7 [CH_3, HC=C(*C*H_3)CH_2OH], 12.6 [3 CH, OSi*C*H(CH_3)$_2$] ppm. $C_{22}H_{38}O_3Si{\cdot}1/4H_2O$ (382.7): calcd. C 68.97, H 10.13; found C 68.98, H 9.86.

(*E*)-[3-(4-Bromo-3-methylbut-2-enyl)-4-methoxy-5-methylphenoxy]-triisopropylsilane (5): A solution of bromine (1.74 g, 10.9 mmol) in CH_2Cl_2 (5 mL) was added dropwise to an ice-cooled solution of 1,2-bis(diphenylphosphanyl)ethane (2.20 g, 5.45 mmol) in CH_2Cl_2 (25 mL). The addition was conducted at a rate to maintain the reaction temperature below 10 °C. A solution of alcohol **37** (1.65 g, 1.8 mmol), in CH_2Cl_2 (5 mL) was added and the resulting mixture was stirred at 20 °C for 2 h. Et_2O (70 mL) followed by *n*-pentane

(140 mL) were added to precipitate the by-products. The mixture was filtered through a thin pad of silica gel and the solids were washed with diethyl ether/pentane (1:2, 2 × 25 mL). The filtrate was concentrated under reduced pressure to afford the sensitive allylic bromide **5** as a colorless oil (1.70 g, 88%) which was used in the next step without further purification. IR (film): $\tilde{\nu}$ = 1600 (C=C), 1475, 1327, 1217, 1175 cm^{-1}. ^1H NMR (200 MHz, [D_6]benzene): δ = 6.74 (d, *J* = 2.6 Hz, 1 H, 2-H or 6-H), 6.69 (d, *J* = 2.6 Hz, 1 H, 2-H or 6-H), 5.52 (broad t, *J* = 7.4 Hz, 1 H, $ArCH_2CH$=C), 3.59 (s, 2 H, CH_2Br), 3.39 (s, 3 H, OCH_3), 3.24 (d, *J* = 7.4 Hz, 2 H, $ArCH_2CH$=C), 2.15 (s, 3 H, $ArCH_3$), 1.66 [s, 3 H, HC=C(CH_3)CH_2OH], 1.30−1.10 [m, 21 H, OSiC*H*(CH_3)$_2$] ppm. ^{13}C NMR (50 MHz, [D_6]benzene): δ = 152.0 (C, C2), 151.0 (C, C5), 133.4 (C, HC=*C*(CH_3)CH_2OH], 132.7 (C, C1), 131.6 (C, C3), 129.4 [CH, H*C*=C(CH_3)CH_2OH], 121.4 (CH, C4), 120.2 (CH, C6), 59.7 (CH_3, O*C*H_3), 40.6 [CH_2, =C(CH_3)*C*H_2Br], 28.5(CH_2, Ar*C*H_2CH=C), 17.8 [6 CH_3, OSiCH(*C*H_3)$_2$], 16.0 (CH_3, Ar*C*H_3), 14.2 [CH_3, HC=C(*C*H_3)CH_2OH], 12.7 [3 CH, OSi*C*H(CH_3)$_2$] ppm.

(11*R*)-(*E*,*Z*)-2-[10-(5-Hydroxy-2-methoxy-3-methylphenyl)-4,8-dimethyl-6-oxodeca-4,8-dienyl]-2,6,6-trimethyl-6*H*-pyran-3-one (1a,b): A solution of *n*-butyllithium (2.5 M in hexane, 0.65 mL, 1.6 mmol) was added at −5 °C to a solution of diisopropylamine (162 mg, 1.6 mmol) in THF (1 mL). The mixture was stirred at −5 °C for 15 min and cooled to −78 °C. A solution of the crude silylated cyanohydrin **3** (565 mg, 1.3 mmol) in THF (0.75 mL) was added dropwise. The resulting mixture was stirred at −40 °C for 30 min and a solution of bromide **5** (1.41 g, 3.2 mmol) in a mixture of THF (0.75 mL) and DMPU (2 mL) was then added. The reaction mixture was stirred while the temperature was gradually raised to room temperature. After 4 h at 20 °C, saturated aqueous ammonium chloride was added and the mixture was extracted with diethyl ether (4 × 15 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Filtration through a thin pad of silica (cyclohexane/EtOAc, 9:1 + 0.5% Et_3N) gave the cyanohydrin **40** (830 mg, 80%) as a yellow oil which was directly used in the next step without further purification.

A THF solution of tetrabutylammonium fluoride (1 M, 4 mL, 4 mmol) was added to a solution of the above product (830 mg, 1.04 mmol) in THF (5 mL). The resulting mixture was stirred at 20 °C for 2 h and 0.5 M aqueous oxalic acid (6 mL) was added. The mixture was extracted with diethyl ether (3 × 10 mL). The combined ethereal phases were dried with $MgSO_4$ and concentrated. The residue was taken up in THF (10 mL) and hydrochloric acid (0.5 M, 5 mL) was added. The reaction mixture was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried with $MgSO_4$ and concentrated. Chromatography on silica gel (cyclohexane/EtOAc, 4:1) afforded a 3:1 mixture of (*E*/*Z*)-**1a**,**b** (380 mg, 64%) as a colorless viscous oil. Attempts at separating the two isomers by HPLC failed due to the reconjugation of the $\Delta^{2,3}$ double bond. IR (film): $\tilde{\nu}$ = 3600−3300 (OH), 2978 (CH), 2934 (CH), 2826 (CH), 1681 (C=O), 1601 (C=C), 1464, 1374, 1320, 1215, 1175, 1093, 1013 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), only the main (*E*) isomer is described, δ = 6.85 (d, *J* = 10.4 Hz, 1 H, 14-H), 6.50 (s, 2 H, 3′-H and 5′-H), 6.20 (br. s, 1 H, O*H*), 6.10 (s, 1 H, 6-H), 5.94 (d, *J* = 10.4 Hz, 1 H, 13-H), 5.41 (t, *J* = 7.4 Hz, 1 H, 2-H), 3.67 (s, 3 H, O*C*H_3), 3.34 (d, *J* = 7.4 Hz, 2 H, 1-H), 3.09 (s, 2 H, 4-H), 2.23 (s, 3 H, Ar*C*H_3), 2.10 (d, *J* = 1.2 Hz, 3 H, 19-H), 2.10−2.00 (m, 2 H, 8-H), 1.70 (s, 3 H, 20-H), 1.70−1.40 (m, 4 H, 9-H, 10-H), 1.45 (s, 3 H, 16-H), 1.39 (s, 3 H, 17-H), 1.37 (s, 3 H, 18-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), only the main (*E*) isomer is described, δ = 199.8 (CO, C5), 199.6 (CO, C12), 159.4 (C, C7), 155.5 (C, C14), 152.1 (C, C1′), 150.1 (C, C4′), 134.6 (C, C2′), 134.3 (C, C6′), 130.8 (C, C3), 127.9 (CH, C2), 122.2 (2 CH, C6 and C13), 115.7 (CH, C5′), 113.8 (CH, C3′), 80.4 (C, C11), 71.7 (C, C15), 60.5 (CH_3, O*C*H_3), 55.5 (CH_2, C4), 41.2 (CH_2, C8), 39.4 (CH_2, C10), 30.4 (CH_3, C16), 29.1 (CH_3, C17), 28.1 (CH_2, C1), 26.6 (CH_3, C18), 21.7 (CH_2, C9), 19.2 (CH_3, C19), 16.5 (CH_3, C20), 16.2 (CH_3, Ar*C*H_3) ppm. MS (70 eV): *m*/*z* (%) = 454 (100) [M^+], 273 (8), 249 (36), 231 (38), 213 (34), 205 (20), 191 (21), 175 (39), 151 (22), 140 (52), 137 (22), 125 (28), 121 (21), 109 (21), 95 (60). HRMS: calcd. 454.2719; found 454.2724. $C_{28}H_{38}O_5 \cdot H_2O$ (472.6): calcd. C 71.16, H 8.53; found C 71.37, H 8.80.

(±)-3-(2,6,6-Trimethyl-3-oxo-3,6-dihydro-2*H*-pyran-2-yl)propionic Acid (43): 2 N Hydrochloric acid (10 mL) was added to a solution of acetal (±)-**20** (500 mg, 1.95 mmol) in THF (10 mL) and the resulting mixture was stirred at 20 °C for 1 h. The solvent was removed under reduced pressure and the aqueous residue was extracted with EtOAc (4 × 20 mL). The organic layers were dried with $MgSO_4$ and concentrated to leave a colorless oil (350 mg, 85%). IR (film): $\tilde{\nu}$ = 3600−2500 (CO_2H), 1709 (CO_2H), 1682 (CO), 1439, 1374, 1264, 1183, 1093 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.80−8.80 (m, 1 H, O*H*), 6.84 (d, *J* = 10.5 Hz, 1 H, 5-H), 5.92 (d, *J* = 10.5 Hz, 1 H, 4-H), 2.55−2.15 (m, 3 H, $CH_2CH_2CO_2H$), 1.95 (m, 1 H, $CH_2CH_2CO_2H$), 1.44 [s, 3 H, $CH_2(CH_3)CO$], 1.38 [s, 6 H, OC(CH_3)$_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.2 (C, *C*O), 179.4 (C, *C*O_2H), 155.1 (CH, C5), 122.1 (CH, C4), 79.6 (C, C2), 71.8 (C, C6), 34.1 (CH_2, *C*$H_2CH_2CO_2H$), 30.2 [CH_3, $CH_2(CH_3)CO$], 28.9 (CH_2, $CH_2CH_2CO_2H$), 28.8 [CH_3, OC(*C*H_3)$_2$], 26.2 [CH_3, OC(*C*H_3)$_2$] ppm. $C_{11}H_{16}O_4$ (212.2): calcd. C 62.25, H 7.60; found C 62.14, H 7.57.

(±)-3-(5-Hydroxy-2,6,6-trimethyl-5,6-dihydro-2*H*-pyran-2-yl)-propionic Acid (45): Hydrogen peroxide (35%, 480 mg, 4.9 mmol) and 1 N sodium hydroxide (2.8 mL, 2.8 mmol) were added sequentially to a solution of enone **43** (350 mg, 1.65 mmol) in methanol (12 mL). After stirring for 30 min at room temperature, 2 N hydrochloric acid was added until pH 5. The mixture was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with sodium hydrogen sulfite, dried with $MgSO_4$ and concentrated to leave a yellow oil (290 mg, 77%) which was taken up in methanol (5 mL). Hydrazine monohydrate (206 mg, 4.1 mmol) was added, followed by acetic acid (12 mg, 0.2 mmol), and the reaction mixture was heated at reflux for 2 h. After cooling, 2 N hydrochloric acid was added until pH 5. The mixture was extracted with EtOAc (4 × 15 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated. Chromatography on silica gel (cyclohexane/EtOAc, 2:1) gave the allylic alcohol **45** (as a 2:1 mixture of diastereomers, 110 mg, 40%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3600−3100 (OH), 1708 (CO_2H), 1366, 1286, 1193 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) major isomer δ = 6.80−6.00 (broad s, 2 H, OH), 5.99 (dd, *J* = 10.3, 5.6 Hz, 1 H, 4-H), 5.62 (d, *J* = 10.3 Hz, 1 H, 3-H), 3.56 (d, *J* = 5.6 Hz, 1 H, 5-H), 2.41−2.20 (m, 2 H, $CH_2CH_2CO_2H$), 2.05−1.85 (m, 1 H, $CH_2CH_2CO_2H$), 1.80−1.65 (m, 1 H, $CH_2CH_2CO_2H$), 1.26−1.15 [m, 9 H, $CH_2(CH_3)CO$ and OC(CH_3)$_2$]; minor isomer δ = 6.80−6.00 (broad s, 2 H, OH), 5.74 (dd, *J* = 10.4, 1.8 Hz, 1 H, 4-H), 5.52 (dd, *J* = 10.4, 2.2 Hz, 1 H, 3-H), 3.91 (dd, *J* = 2.2, 1.8 Hz, 1 H, 5-H), 2.41−2.20 (m, 2 H, $CH_2CH_2CO_2H$), 2.05−1.85 (m, 1 H, $CH_2CH_2CO_2H$), 1.80−1.65 (m, 1 H, $CH_2CH_2CO_2H$), 1.26−1.15 [m, 9 H, $CH_2(CH_3)CO$, and OC(CH_3)$_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$) major isomer δ = 179.5 (*C*O_2H), 134.0 (CH, C3), 125.8 (CH, C4), 74.6 (C, C2), 73.5 (C, C6), 67.6 (CH, C5), 37.3 (CH_2, *C*$H_2CH_2CO_2H$), 29.8 (CH_2, $CH_2CH_2CO_2H$), 27.5 [2 CH_3, OC(CH_3)$_2$], 25.1 [CH_3, $CH_2(CH_3)CO$] ppm; minor isomer δ = 179.2 (*C*O_2H), 132.4 (CH,

C3), 128.2 (CH, C4), 73.7 (C, C2), 73.5 (C, C6), 70.6 (CH, C5), 37.3 (CH_2, $CH_2CH_2CO_2H$), 29.0 (CH_2, $CH_2CH_2CO_2H$), 27.5 [2 CH_3, $OC(CH_3)_2$], 21.6 [CH_3, $CH_2(CH_3)CO$] ppm.

Methyl (±)-3-(2,6,6-Trimethyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl)-propionoate (42): A mixture of the alcohol **45** (100 mg, 0.48 mmol) and Dess−Martin periodinane reagent (285 mg, 0.67 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc, washed with saturated aqueous sodium thiosulfate and 1 N hydrochloric acid, dried with $MgSO_4$ and concentrated. The residue was taken up in dry diethyl ether (5 mL) and treated at 0 °C with an ethereal solution of diazomethane. After being stirred for 5 min the mixture was concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/EtOAc, 1:1) afforded the enone **42** (57 mg, 52%) as a colorless oil. IR (film): $\tilde{\nu}$ = 1735 (CO_2Me), 1685 (CO), 1437, 1393, 1373, 1292, 1165 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.72 (d, J = 10.5 Hz, 1 H, 3-H), 5.96 (d, J = 10.5 Hz, 1 H, 4-H), 3.63 (s, 3 H, OCH_3), 2.50−2.20 (m, 2 H, $CH_2CH_2CO_2H$), 2.10−1.75 (m, 2 H, $CH_2CH_2CO_2H$), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.8 (C, C2), 173.9 (CO_2Me), 153.0 (CH, C3), 123.5 (CH, C4), 78.2 (C, C2), 73.3 (C, C6), 51.6 (CH_3, OMe), 37.4 (CH_2, $CH_2CH_2CO_2H$), 28.8 (CH_2, $CH_2CH_2CO_2H$), 27.7 (CH_3), 27.4 (CH_3), 26.3 (CH_3) ppm. $C_{12}H_{18}O_4$ (226.3): calcd. C 63.70, H 8.02; found C 63.53, H 8.08.

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