Solid Phase Synthesis of Highly Substituted Tetrahydropyrans by Tandem ene-Reaction/Intramolecular Sakurai Cyclization

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A solid-phase tandem ene-reaction/intramolecular Sakurai cyclization sequence has been developed to synthesize highly substituted tetrahydropyran derivatives in two steps from aldehydes and with complete control of the relative stereochemistry of the three newly formed stereocenters. The compounds are obtained with high purity after release from the solid support and can be easily isolated in multimilligram amounts. Moreover, we have shown that asymmetric induction is possible on solid phase and that enantiomerically pure tetrahydropyrans containing four stereocenters can be effectively synthesized with this method.

Introduction

Syntheses of natural products and analogues thereof embodying substituted tetrahydropyrans are of substantial interest to organic chemistry and chemical biology.[1,2] In particular, 4-exo-methylene[3] and 4-hydroxy tetrahydropyrans[4] occur widely in nature and are endowed with pronounced biological activities. For example the macrolide zampanolide[5] (Figure 1) shows significant activity against a variety of tumor cell lines and the cyclic diarylheptanoid family (including the blepharocalyxins and (−)-centrolobine analogs, for an example, see Figure 1) includes inhibitors of NO production and platelet aggregation as well as natural products with antiproliferative activity against human and murine colon carcinoma cells.[6] Substituted 4-exo-methylene and 4-hydroxy tetrahydropyrans also occur as substructures of fairly complex molecules like phorboxazole.[7]

We have recently introduced a structural classification of natural products (SCONP)[8] and protein structure similarity clustering (PSSC)[9] as hypothesis generating approaches for the selection and synthesis of compound collections populating regions of biologically relevant structure space. The combined use of these concepts led us to forward biology oriented synthesis (BIOS)[10] as concept for the synthesis of focused compound collections. Within this concept efficient methods for the synthesis of natural-product-derived and -inspired compound collections based on privileged scaffolds occurring in major natural product classes are required.[11]

In this paper, we report on a solid-phase synthesis of polysubstituted tetrahydropyrans. The tandem ene-reaction/intramolecular Sakurai cyclization developed by Markó et al.[12] gives rapid and efficient access to the 4-*exo*-methylene tetrahydropyran scaffold. We envisioned a synthetic route in which the tetrahydropyran derivatives **5** are generated by the tandem reaction starting from a polymer-bound aldehyde **1**, the allylsilane **2**[13] and a second aldehyde (Scheme 1). The

execution of the decisive ene-reaction on a polymeric carrier appeared advantageous since it would guarantee for straightforward removal of excess of unreacted starting material **2**. The stereoselectivity of the intramolecular Sakurai cyclization can be explained by a six-membered transition state in which all the substituents are in equatorial position.[12a] The regioselectivity observed in the ene-reaction can be explained by considering the stabilizing β-silicon effect and the repulsive 1,3-diaxial interactions in the six-membered transition state **3**.

Initial experiments to establish the sequence were carried out in solution as shown in Scheme 2. Aldehyde **7** bearing a protected phenol group for possible immobilization to a solid support was synthesized from commercially available 3-(4-hydroxyphenyl)propionic acid and subjected to ene-reaction with allylsilane **2** as described by Marko et al.[12a] Intermediate **8** was obtained in 70% yield and converted to product **11** by Sakurai cyclization (80% yield) and deprotection of the hydroxyl groups. Compound **11** was formed as a single diastereomer, its relative stereochemistry was confirmed by analysis of the ^{1}H NMR coupling constants.[14]

The reaction conditions were then adapted to the solid phase. The synthesis was carried out using the IRORI MacroKan system. The solid support bound aldehyde **14** was obtained from the ester **13** after reduction with LiBH$_4$ and reoxidation with IBX. The loading of the immobilized aldehyde **4** was determined to be 0.7 mmol/g after reaction with dinitrophenylhydrazine and release from the solid support by treatment with TBAF (1M) in THF. Initially only low yields were obtained for the key carbonyl ene-reaction, caused by the presence of small amounts of water in the resin (which could not be removed, even when dried overnight with heating and under high vacuum). However, in the presence of molecular sieves 4Å full conversion was observed for the ene-reaction (a MAS NMR spectrum of the resin **15** showed complete disappearance of the characteristic aldehyde peak at ca. 10 ppm). The tetrahydropyran **11** was obtained after the intramolecular Sakurai cyclization and cleavage from solid support in high purity and in 52% yield

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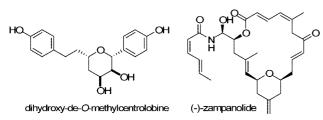
Figure 1. Tetrahydropyran containing natural products.
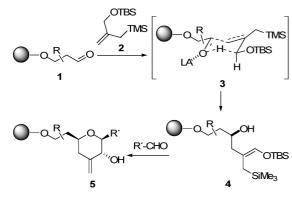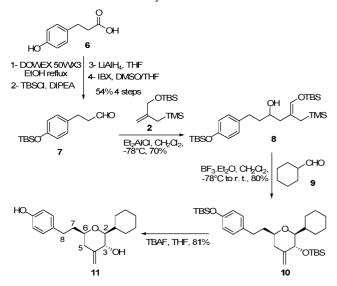
dihydroxy-de-*O*-methylcentrolobine   (-)-zampanolide

Scheme 1

Scheme 2. Solution Phase Synthesis Of **11**

Scheme 3. Solid-Phase Synthesis of Tetrahydropyran Derivatives

RCHO	$\overset{O}{\underset{H}{\bigvee}}$ cyclohexanal	$\overset{EtO}{\underset{OEt}{\bigvee}}$	benzaldehyde	crotonaldehyde	p-OTBS benzaldehyde
R (yield)	cyclohexyl **11** (52%)	butenyl **17** (33%)	phenyl **18** (38%)	propenyl **19** (24%)	OTBS-aryl **20** (27%)

based on loaded aldehyde (Scheme 3). Spectral data for this compound were identical with those obtained for the compound synthesized in solution. Impurities (mainly tetrabutylammonium salts) could easily be removed by flash chromatography or by preparative HPLC.

To explore the scope of the tandem solid phase reaction different aldehydes were employed in the Sakurai cyclization step; including aliphatic (cyclohexanal), aromatic (benzaldehyde), and unsaturated (crotonaldehyde) aldehydes (Scheme 3). The desired products were obtained in useful overall yields and with high purity. The use of the diethylacetal of 3-butenal as a masked aldehyde allowed the introduction of a double bond into **17** that may be used in metathesis reactions as described by Ding and Jennings in their formal synthesis of zampanolide.[15] The possibility to introduce *p*-hydroxybenzaldehyde is also of particular interest because it gives an access to the diarylheptanoid family scaffold in **20**.[6]
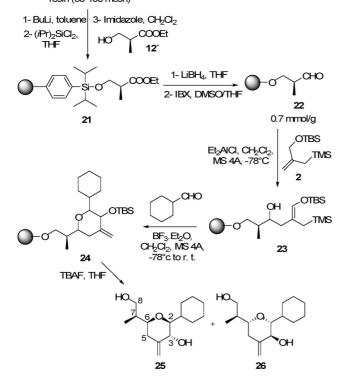
To extend the scope of the method, an aliphatic solid support bound aldehyde was synthesized. In addition, a stereogenic center was introduced to give access to enantiomerically enriched THP derivativatives, by directing the face selectivity of the attack on the double bond during the ene-reaction. For this purpose, (+)-methyl-L-*β*-hydroxy-isobutyrate was linked to the solid support using the same silyl linker (Scheme 4). Reduction to the alcohol and oxidation as described above yielded solid phase bound aldehyde **22** with a loading of 0.7 mmol/g, (determined by reaction with DNPH followed by cleavage). The tandem ene-reaction/Sakurai cyclization gave, as expected, the desired THP derivatives **25** and **26** as a mixture of only two diastereoisomers with a diastereomeric ratio of 75:25. Analysis of the coupling constants in the ^{1}H-NMR spectrum revealed that the relative configuration of the stereocenters in the tetrahydropyran ring was as described above for compound **11**. The absolute configuration of **25** and **26** was assigned by analogy to the observations of Markó et al. for a closely related case.[12a] Felkin Ahn type addition predicts in this case that **25** is the major isomer.

These results demonstrate that the tandem ene-reaction/intramolecular Sakurai cyclization can be successfully adapted to the solid phase synthesis, starting from immobilized aldehydes. To the best of our knowledge, this is the first carbonyl-ene reaction carried out on solid support.[16] This methodology allows the synthesis of highly substituted THP derivatives in two steps from the aldehydes and with complete control of the relative stereochemistry of the three newly formed stereocenters. Moreover, the compounds are

Scheme 4. Asymmetric Induction on Solid-Phase

obtained with high purity after release from the solid support and can be easily isolated in multimilligram amounts by reverse-phase HPLC or silica gel chromatography purification. This finding indicates that solid phase chemistry is advantageous for this tandem sequence. Indeed, by adding excess of reagents most of the aldehyde reacts in the carbonyl ene-reaction (as compared to 60–70% in the solution phase). We have also shown that asymmetric induction is possible on solid phase and that enantiomerically pure tetrahydropyrans containing four stereocenters can be effectively synthesized with this method.

Experimental Section

General Methods. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Mercury 400 or Bruker DRX 500 spectrometers and were referenced to residual solvent peaks. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. MAS-NMR spectra were recorded on a Varian Merury 400 with a Varian 400 gHX nano probe. High resolution fast atom bombardment spectra (Hrms-FAB) were measured on a Jeol SX102A spectrometer using *m*-nitrobenzylalcohol as a matrix. Optical rotations were measured on a Schmidt + Haensch Polartronic HH8 polarimeter at 589 nm. Concentrations are given in g/100 mL solvent. Preparative HPLC-MS was performed on an Agilent Series HPLC 1100 system with a LC/MSD VL (ESI-MS) mass detector (negative ionization), using a VP 125/21 Nocleodor C18 Gravity 5 μm column (Macherey–Nagel). Eluent: H$_2$O/acetonitrile, flow = 25 mL/min, gradient: 10% acetonitrile for 1 min; from 10 to 80% acetonitrile in 6 min; from 80 to 100% acetonitrile in 10 min; 100% acetonitrile in 17 min; from 100 to 10% acetonitrile in 17.1 min; 10%

acetonitrile in 18.0 min. For ESI mass detection 0.1% of the solvent flow was diluted with 10 mM ammonia in H$_2$O/ acetonitrile 1:1. GC-MS spectra were recorded on a Hewlett Packard 6890 system with HP-5MS, 25 m × 0.2 mm; 0.33 μm column (Agilent), helium as carrier gas and a mass detector Hewlett Packard 5973. The temperature profile starts at 100 °C keeping this temperature for 1 min and heats to 300 °C within 5 min, remaining at this temperature for further 5 min. For solid phase synthesis IRORI MacroKans (obtained from Discovery Partners) were used.

Materials. TLC was performed on Merck silica gel 60F$_{254}$ aluminium sheets. For flash chromatography silica gel (35–70 μm) was used. *p*-Bromophenylpolystyrene resin (1.9 mmol/ g, 50–100 mesh) was purchased from Novabiochem. All reactions utilizing dry solvents were performed under argon atmosphere. Dichloromethane was dried over calciumhydride and freshly distilled before use. All other commercially available reagents and solvents were purchased in the given quality and used without further purification.

Experimental Procedures for the Synthesis of Tetrahydropyrans Using IRORI MacroKans. Preparation of the MacroKans. The MacroKans were loaded with (250 ± 10) mg dry *p*-bromophenylpolystyrene resin.

Washing Cycle. The MacroKans were shaken vigorously for 2 min in a separation funnel with the desired solvent. The solvent was removed and the funnel was then shaken vigorously for a few seconds to force solvent out of the MacroKans, and additional solvent was removed again. The MacroKans could then either be washed with a new solvent or dried in vacuo.

Washing Cycle Using Dry Solvents. The MacroKans were placed into a reaction vessel, which was evacuated and flushed with argon. The vessel was sealed with a septum cap and dry solvent was added via canula. The vessel was shaken for 2 min, and the solvent was removed via canula. The vessel was then shaken vigorously several times until no significant additional solvent could be removed.

Immobilization of Esters. To a suspension of *p*-bromophenylpolystyrene resin (2 g, 8 MacroKans, 250 mg each) in dry toluene (30 mL) was added under argon atmosphere *n*-BuLi (10M, 3 mL, 30 mmol), and the mixture was shaken at 65 °C for 6 h. The yellow toluene solution was removed via canula, and the orange resin was washed twice with 20 mL of dry THF. Then 20 mL of dry THF and neat di-*iso*-propyldichlorosilane (3 mL, 16 mmol) was added. The resin rapidly became colorless. After 1 h, the solution was removed via canula, and the resin was washed with dry THF (20 mL) and dry dichloromethane (20 mL). Dry dichloromethane was added (30 mL), followed by solid imidazole (817 mg, 12 mmol) and the corresponding alcohol (8 mmol) as solution in the minimum amount of dry dichloromethane. The mixture was shaken at room temperature overnight. The MacroKans were washed with dichloromethane and methanol and dried in vacuo. The FT-IR spectra showed a strong C=O stretching band at 1730 cm^{-1} for both esters **13** and **21**.

Synthesis of Aldehydes. The 8 MacroKans were swollen in THF (20 mL) and lithium borohydride (2 M in THF, 15 mL, 30 mmol) was added. After 48 h at room temperature, the MacroKans were washed with THF, a saturated solution

of ammonium chloride in water and THF (1:4), water, THF, methanol and THF, and dried in vacuo. The FT-IR spectra showed complete disappearance of the C=O stretching band at 1730 cm^{-1}. The 8 MacroKans were then swollen in a solution of DMSO and THF (15 mL/15 mL) and IBX (1.8 g) was added. After 18 h at room temperature, the Macro-Kans were washed with DMSO, THF, methanol, THF and dichloromethane, and dried in vacuo. The FT-IR spectra showed a strong C=O stretching band at 1730 cm^{-1} for both aldehydes **14** and **22**. The immobilized aldehydes were also analyzed by MAS ^{1}H-NMR spectroscopy. In both cases, a characteristic aldehyde signal at ca. 10 ppm was detected.

Determination of the Loading. The loading was determined for the esters and the aldehydes.

Resin loaded with ester (100 mg) was swollen in 10 mL THF, and treated with 100 μL TBAF 1 M in THF (3 mL). After 1 h, the resin was washed twice with THF and ether. The organic phases were pooled and washed with water, dried, and evaporated in vacuo. The residue was purified by silica gel column chromatography to yield 15 mg of ester (0.077 mmol), loading = 0.8 mmol/g.

The aldehyde **14** was treated with dinitrophenylhydrazine (DNPH) (30 mg resin, 20 mg DNPH in 30 mL THF and 5 drops TFA for 2h at r.t.) to yield a yellow resin. The resin was washed three times with THF and treated with TBAF (1M) in THF. After 1 h, the resin was washed twice with THF and ether. The organic phases were pooled and washed with water, dried and evaporated to dryness. The residue was purified by silica gel column chromatography to yield 7 mg of the hydrazone (0.021 mmol), loading = 0.7 mmol/g. The same procedure gave a loading of 0.7 mmol/g for the aldehyde **22**.

Tandem Carbonyl-ene Reaction/Sakurai Cyclization on Solid Support. Carbonyl-ene Reaction. A MacroKan was loaded with 200 mg of resin bound aldehyde **14** or **22** (0.14 mmol). The MacroKan and activated molecular sieves 4 Å in a 50 mL flask were submitted to three cycles of vacuum/flushing with argon. Dry dichloromethane (15 mL) was added, and the resin and molecular sieves were swollen for 15 min at room temperature. The solution was cooled to −78 °C and the allylsilane **2** (180 mg, 0.7 mmol) was added, followed by dropwise addition of diethylaluminium chloride (1 M in hexane, 0.7 mL, 0.7 mmol). The mixture was shaken at −78 °C for 90 min. The MacroKans were washed with dichloromethane, methanol, dichloromethane, MeOH, and twice with dichloromethane and dried in vacuo. 300 mg of resin bound homoallylic alcohol **15** were obtained for each MacroKan. A MAS ^{1}H-NMR spectrum of the solid phase bound homoallylic alcohol **15** was recorded, showing the disappearance of the aldehyde peak at 10 ppm and appearance of the characteristic alkene and TBS signals: ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 0.1 (SiMe$_2$), 1.1 (Si-*t*Bu), 6.1 (C=CH).

Typical Procedure for the Sakurai Cyclization. A MacroKan loaded with 200 mg of the resin bound homoallylic alcohol **15** (0.093 mmol) was swollen in dry dichloromethane (15 mL), in the presence of activated molecular sieves 4 Å, for 15 min at room temperature and under argon atmosphere. The solution was cooled to −78 °C and

cyclohexanecarboxaldehyde (or other aldehydes or acetals) (0.157 mL, 1.3 mmol) and boron trifluoride (0.082 mL, 0.65 mmol) were added. The mixture was allowed to warm to room temperature overnight and the MacroKans were washed with dichloromethane, methanol, dichloromethane, MeOH and twice with dichloromethane and dried in vacuo. In the case of the aldehyde **22**, the mixture was only allowed to warm to −30 °C over 4h to avoid significant cleavage from the resin. A MAS ^{1}H-NMR spectrum of the solid phase bound mixture of 2-cyclohexyl-tetrahydro-6-((S)-1-hydroxypropan-2-yl)-4-methylene-2H-pyran-3-ol **25** and **26** was recorded, showing in particular the characteristic signals of the *exo*-methylene group at 4.9 and 5.1 ppm. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 0.1 (SiMe$_2$), 1.1 (Si-*t*Bu), 4.9 (C=CH$_2$), 5.1 (C=CH$_2$).

Cleavage of Tetrahydropyrans from the Solid Support. A MacroKan (or the resin) in a 50 mL flask was swollen in 10 mL THF, and a solution of TBAF/THF 1 M (0.3 mL, 0.3 mmol) was added. The flask was shaken for 2 h (only cleavage) or overnight (deprotection of the secondary TBS protected alcohol) at ambient temperature. The THF was removed, and the MacroKan was washed twice with 5 mL THF and diethyl ether. The combined washing and cleavage solutions were washed with saturated NaHCO$_3$ solution, dried over MgSO$_4$, evaporated, and dried in vacuo. The residue was dissolved in 1 mL acetonitrile and purified by HPLC or dissolved in cyclohexane and purified by flash silica gel column chromatography.

Spectroscopic Data. 2-Cyclohexyl-6-(4-hydroxyphenethyl)-4-methylenetetrahydro-2H-pyran-3-ol (11). Fifteen mg (yield based on the solid phase bound aldehyde: 52 %). ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.15–1.40 and 1.50–1.80 (m, 13H, H7, and Cy), 2.04 (dd, $^2J_{5,5'}$ = 13.3 Hz, $^3J_{6,5'}$ = 12.5 Hz, 1H, H5′), 2.30 (dd, $^2J_{5',5}$ = 13.3 Hz, $^3J_{6,5}$ = 2.1 Hz, 1H, H5), 2.58–2.75 (m, 2H, H8), 2.84 (dd, $^3J_{3,2}$ = 9.4 Hz, $^3J_{Cy,2}$ = 2.1 Hz, 1H, H2), 3.19 (m, 1H, H6), 3.99 (d, $^3J_{2,3}$ = 9.6 Hz, 1H, H3), 4.57 (br. s, 1H, OH), 4.80 (d, ^2J = 1.8 Hz, 1H, =CH$_2$), 4.97 (d, ^2J = 2.0 Hz, 1H, =CH$_2$), 6.74 (d, ^3J = 8.4 Hz, 2H, Ph), 7.04 (d, ^3J = 8.6 Hz, 2H, Ph). ^{13}C-NMR (101 MHz, CDCl$_3$): δ = 25.8, 26.7, 26.9, 27.1, 31.0, 31.1 (Cy), 37.9, 38.7, 41.5 (C5, C7, C8), 70.5, 77.2, 86.4 (C2, C3, C6), 105.2 (C=$\underline{C}$H$_2$), 115.4 (phenol), 129.8 (phenol), 134.6 (phenol), 148.7 (C4), 153.8 (phenol). LC-MS(ESI): t$_R$ = 8.5 min, *m/z* = 315.1 [M–H]$^-$. Hrms(FAB) *m/z* calc. for C$_{20}$H$_{28}$O$_3$ 316.2038, found 316.2051 [M]$^+$.

6-(4-Hydroxyphenethyl)-2-allyl-tetrahydro-4-methylene-2H-pyran-3-ol (17). Twelve mg (33 %). ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 0.02 and 0.07 (2s, 6H, SiMe$_2$), 0.92 (s, 9H, Si-*t*Bu), 1.60–1.83 (m, 2H, 2xH7), 2.04 (dd, $^2J_{5,5'}$ = 12.1 Hz, $^3J_{6,5'}$ = 12.1 Hz, 1H, H5′), 2.14 (m, 1H, H9), 2.28 (dd, $^2J_{5',5}$ = 13.1 Hz, $^3J_{6,5}$ = 2.1 Hz, 1H, H5), 2.53–2.70 (m, 3H, 2xH8 and H9′), 3.04 (ddd, $^3J_{3,2}$ = 8.8 Hz, $^3J_{9,2}$ = 10.0 Hz, $^3J_{9',2}$ = 2.6 Hz, 1H, H2), 3.18 (m, 1H, H6), 3.69 (d, $^3J_{2,3}$ = 8.8 Hz, 1H, H3), 4.62 (s, 1H, OH), 4.73 (d, ^2J = 1.8 Hz, 1H, =CH$_2$), 4.95 (d, ^2J = 1.4 Hz, 1H, =CH$_2$), 5.05 (dq, $^3J_{10,11}$ = 10.2 Hz, $^4J_{9,11}$ = 2.0 Hz, 1H, H11), 5.09 (dq, $^3J_{10,11'}$ = 17.2 Hz, $^4J_{9,11'}$ = 2.0 Hz, 1H, H11′), 5.93 (tdd, $^3J_{11',10}$ = 17.0 Hz, $^3J_{11,10}$ = 10.2 Hz, $^3J_{9,10}$ = 6.8 Hz, 1H, H10), 6.70 (d, ^3J = 8.6 Hz, 2H, phenol), 7.01 (d, ^3J = 8.6 Hz, 2H,

phenol). ^{13}C-NMR (101 MHz, CDCl$_3$): δ = 0.0, 0.5 (SiMe$_2$), 23.0 (Cq, Si-*t*Bu), 30.6 (CH$_3$, Si-*t*Bu), 35.6, 41.9, 42.4, 46.4 (C5, C7, C8, C9), 79.5, 82.1, 87.8 (C2, C3, C6), 111.1 (C=$\underline{C}$H$_2$), 119.9 (CH, phenol), 121.0 (C11), 134.4 (CH, phenol), 139.1 (C10), 140.6 (Cq, phenol), 152.0 (C4), 158.3 (Cq, phenol). GC-MS: t$_R$ = 7.15 min, *m/z* = 388 [M]$^+$. Hrms(FAB) *m/z* calc. for C$_{23}$H$_{36}$O$_3$Si 388.2434, found 388.2413 [M]$^+$.

6-(4-Hydroxyphenethyl)-tetrahydro-4-methylene-2-phenyl-2H-pyran-3-ol (18). Eleven mg (38 %). ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.75–1.82 and 1.87–1.94 (2m, 2H, H7), 2.26 (dd, $^2J_{5,5'}$ = 13.2 Hz, $^3J_{6,5'}$ = 11.6 Hz, 1H, H5′), 2.46 (dd, $^2J_{5',5}$ = 13.6 Hz, $^3J_{6,5}$ = 2.2 Hz, 1H, H5), 2.55–2.75 (m, 2H, H8), 3.46 (m, 1H, H6), 3.99 (s, 2H, H3 and H2), 4.72 (br. s, 1H, OH), 4.92 (d, ^2J = 1.4 Hz, 1H, =CH$_2$), 5.13 (d, ^2J = 1.4 Hz, 1H, =CH$_2$), 6.71 (d, ^3J = 8.6 Hz, 2H, PhOH), 7.01 (d, ^3J = 8.6 Hz, 2H, PhOH), 7.30–7.50 (m, 5H, Ph). ^{13}C-NMR (101 MHz, CDCl$_3$): δ = 30.9, 37.8, 41.3 (C5, C7, C8), 74.6, 77.6, 85.4 (C2, C3, C6), 106.5 (C=$\underline{C}$H$_2$), 115.4 (phenol), 127.7 (Ph), 128.6 (Ph), 128.8 (Ph), 129.7 (phenol), 134.4 (phenol), 139.8 (Ph), 146.0 (C4), 153.8 (phenol). GC-MS: t$_R$ = 7.78 min, *m/z* = 310 [M]$^+$. Hrms(FAB) *m/z* calc. for C$_{20}$H$_{22}$O$_3$ 310.1563, found 310.1569 [M]$^+$.

6-(4-Hydroxyphenethyl)-tetrahydro-4-methylene-2-((E)-prop-1-enyl)-2H-pyran-3-ol (19). Six mg (24 %). ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.70–1.95 (m, 2H, H7), 1.81 (dd, $^3J_{10,11}$ = 6.4 Hz, $^4J_{9,11}$ = 1.6 Hz, 3H, H11), 2.15 (dd, $^2J_{5,5'}$ = 12.3 Hz, $^3J_{6,5'}$ = 12.3 Hz, 1H, H5′), 2.40 (dd, $^2J_{5',5}$ = 13.4 Hz, $^3J_{6,5}$ = 2.3 Hz, 1H, H5), 2.60–2.75 (m, 2H, H8), 3.36 (m, 1H, H6), 3.46 (dd, $^3J_{9,2}$ = 8.4 Hz, $^3J_{3,2}$ = 8.4 Hz, 1H, H2), 3,81 (d, $^3J_{2,3}$ = 9.2 Hz, 1H, H3), 4.88 (d, ^2J = 2.0 Hz, 1H, =CH$_2$), 5.09 (d, ^2J = 1.8 Hz, 1H, =CH$_2$), 5.63 (ddq, $^3J_{10,9}$ = 15.2 Hz, $^3J_{2,9}$ = 7.4 Hz, $^4J_{11,9}$ = 1.6 Hz, 1H, H9), 5.92 (ddq, $^3J_{9,10}$ = 15.2 Hz, $^3J_{11,10}$ = 6.6 Hz, $^4J_{2,10}$ = 0.8 Hz, 1H, H10), 6.76 (d, ^3J = 8.6 Hz, 2H, phenol), 7.05 (d, ^3J = 8.4 Hz, 2H, phenol). ^{13}C-NMR (101 MHz, CDCl$_3$): δ = 18.3 (C11), 31.1, 37.7, 41.1 (C5, C7, C8), 72.9, 77.6, 84.3 (C2, C3, C6), 106.2 (C=$\underline{C}$H$_2$), 115.4, 129.7 (CH, phenol), 129.6, 131.8 (C9, C10), 134.2 (phenol), 145.9 (C4), 154.0 (phenol). GC-MS: t$_R$ = 6.35 min, *m/z* = 274 [M]$^+$. Hrms(ESI) *m/z* calc. for C$_{17}$H$_{22}$O$_3$ 274.1569, found 275.1642 [M+H]$^+$.

6-(4-Hydroxyphenethyl)-tetrahydro-2-(4-hydroxyphenyl)-4-methylene-2H-pyran-3-ol(TBS) (20). Eleven mg (27 %). ^{1}H-NMR (400 MHz, CDCl$_3$): δ = −0.46 and 0.00 (2s, 6H, SiMe$_2$), 0.99 (s, 9H, Si-*t*Bu), 1.85–2.10 (m, 2H, 2xH7), 2.40 (dd, $^2J_{5,5'}$ = 11.7 Hz, $^3J_{6,5'}$ = 11.7 Hz, 1H, H5′), 2.63 (dd, $^2J_{5',5}$ = 13.3 Hz, $^3J_{6,5}$ = 2.1 Hz, 1H, H5), 2.78–2.90 (m, 2H, 2xH8), 3.62 (m, 1H, H6), 4.00 (d, $^3J_{3,2}$ = 8.6 Hz, 1H, H3), 4.14 (d, $^3J_{2,3}$ = 8.8 Hz, 1H, H2), 5.06 (d, ^2J = 1.8 Hz, 1H, =CH$_2$), 5.27 (d, ^2J = 1.0 Hz, 1H, =CH$_2$), 6.92 (d, ^3J = 8.6 Hz, 2H, phenol), 7.01 (d, ^3J = 8.6 Hz, 2H, phenol), 7.21 (d, ^3J = 8.4 Hz, 2H, phenol), 7.46 (d, ^3J = 8.6 Hz, 2H, phenol). ^{13}C-NMR (101 MHz, CDCl$_3$): δ = −5.9, −4.8 (SiMe$_2$), 18.3 (Cq, Si-*t*Bu), 26.1 (CH$_3$, Si-*t*Bu), 31.0, 37.8, 41.5 (C5, C7, C8), 76.2, 78.1, 85.5 (C2, C3, C6), 107.0 (C=$\underline{C}$H$_2$), 114.9 and 115.4 (CH, phenol), 129.4 and 129.7 (CH, phenol), 133.4 and 134.5 (Cq, phenol), 147.5 (C4),

153.8 and 155.4 (Cq, phenol). GC-MS: t$_R$ = 10.65 min, *m/z* = 440 [M]$^+$. Hrms(FAB) *m/z* calc. for C$_{26}$H$_{36}$O$_4$Si 440.2383, found 440.2367 [M]$^+$.

(2S,3R,6S)-2-Cyclohexyl-tetrahydro-6-((S)-1-hydroxypropan-2-yl)-4-methylene-2H-pyran-3-ol (25). Eight mg (33 %). [α]$_D^{20}$ +35 ° (c 0.4, CHCl$_3$). ^{1}H-NMR (400 MHz, CDCl$_3$) δ = 0.89 (d, ^3J = 7.0 Hz, 3H, CH$_3$), 1.10–1.40 and 1.53–1.87 (m, 12H, Cyclohexyl and H7), 2.11 (dd, $^3J_{5,5'}$ = 11.6 Hz, $^3J_{6,5'}$ = 8.0 Hz, 1H, H5′), 2.48 (dd, $^3J_{5',5}$ = 13.3 Hz, $^3J_{6,5}$ = 2.2 Hz, 1H, H5), 2.92 (dd, $^3J_{3,2}$ = 9.4 Hz, $^3J_{Cy,2}$ = 2.0 Hz, 1H, H2), 3.21 (ddd, $^3J_{5',6}$ = 8.0 Hz, $^3J_{7,6}$ = 10.4 Hz, $^3J_{5,6}$ = 2.4 Hz, 1H, H6), 3.61 (d, $^3J_{7,8'}$ = 1.6 Hz, 1H, H8′), 3.63 (s, 1H, H8), 4.00 (d, $^3J_{2,3}$ = 9.6 Hz, 1H, H3), 4.88 (d, J = 1.6 Hz, 1H, =CH$_2$), 5.03 (s, J = 1.8 Hz, 1H, =CH$_2$). ^{13}C-NMR (101 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 25.9, 26.6, 26.7, 27.0, 31.1, 39.7 (6xCH$_2$, 5xCy and C5), 38.3, 40.4 (2xCH, Cy and C7), 67.9 (CH$_2$, C8), 69.9, 84.9, 87.1 (3xCH, C2, C3, C6), 106.0 (CH$_2$, C=$\underline{C}$H$_2$), 147.8 (Cq, C4). GC-MS: t$_R$ = 5.58 min, *m/z* = 254 [M]$^+$. Hrms(FAB) *m/z* calc. for C$_{15}$H$_{26}$O$_3$ 254.1882, found 254.1893 [M]$^+$.

(2R,3S,6R)-2-Cyclohexyl-tetrahydro-6-((S)-1-hydroxypropan-2-yl)-4-methylene-2H-pyran-3-ol (26). Three mg (12 %) [α]$_D^{20}$ −44 ° (*c* 0.4, CHCl$_3$). ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 0.92 (d, ^3J = 7.2 Hz, 3H, CH$_3$), 1.10–1.41 and 1.50–1.95 (m, 12H, Cyclohexyl and H7), 2.24 (br. dd, $^3J_{5,5'}$ = 8.4 Hz, $^3J_{6,5'}$ = 8.8 Hz, $^3J_{6,5}$ = 4.0 Hz, 2H, H5 and H5′), 2.88 (dd, $^3J_{3,2}$ = 9.6 Hz, $^3J_{Cy,2}$ = 2.0 Hz, 1H, H2), 3.46 (ddd, $^3J_{5',6}$ = 8.8 Hz, $^3J_{7,6}$ = 4.8 Hz, $^3J_{5,6}$ = 3.6 Hz, 1H, H6), 3.60 (dd, $^3J_{8,8'}$ = 10.9 Hz, $^3J_{7,8'}$= 4.3 Hz, 1H, H8′), 3.66 (dd, $^3J_{8',8}$ = 10.7 Hz, $^3J_{7,8}$ = 7.0 Hz, 1H, H8), 3.96 (d, $^3J_{2,3}$ = 9.6 Hz, 1H, H3), 4.86 (s, 1H, =CH$_2$), 5.02 (s, 1H, =CH$_2$). ^{13}C-NMR (101 MHz, CDCl$_3$): δ = 11.8 (CH$_3$), 25.8, 26.6, 26.7, 27.1, 31.1, 36.8 (6xCH$_2$, 5xCy and C5), 38.4, 38.9 (2xCH, Cy and C7), 66.6 (CH$_2$, C8), 70.0, 82.0, 87.1 (3xCH, C2, C3, C6), 105.8 (CH$_2$, C=$\underline{C}$H$_2$), 148.2 (Cq, C4). GC-MS: t$_R$ = 5.56 min, *m/z* = 254 [M]$^+$. Hrms(FAB) *m/z* calc. for C$_{15}$H$_{26}$O$_3$ 254.1882, found 254.1857 [M]$^+$.

Supporting Information Available. ^{1}H and ^{13}C NMR spectra for compounds **11**, **17–20** and **25–26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The cyclohexyl substituent at C2 and the hydroxyl substituent at C3 are in equatorial position as shown by the coupling constant between H2 and H3, ($^3J_{2,3} = 9.4$ Hz) which is typical for an axial/axial orientation of the corresponding protons at C2 and C3 (typically $^3J_{ax,ax} = 8$–10 Hz). The proton H6 is coupled to one of the protons at C5 with a small coupling constant ($^3J_{6,5} = 2.1$ Hz), which can be either an axial/equatorial or an equatorial/equatorial interaction, and to the other with a large coupling constant ($^3J_{6,5'} = 12.5$ Hz) typical for an axial/axial interaction (whereas typically $^3J_{ax/eq} = {}^3J_{eq/eq} = 2$–3 Hz). This large coupling constant shows that H5′ is H$_{Re}$, trans to H6, and that H6 is in axial position. Such a finding is well-known for tetrahydropyrans and glucosides and has previously been employed to correctly assign the relative stereochemistry of 4-*exo*-methylene tetrahydropyrans present for example in Zampanolide (see J-I Tanaka, T. Higa, *Tetrahedron Lett.* **1996**, *37*, 5535–5538) and in Dactylolide (see Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.*, **2001**, 775–778).

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