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# Palladium-Catalysed Cyclisation of Chiral Carbohydrate-Derived Geminal Diacetates

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*Dedicated to the memory of Professor Sir Derek Barton*

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***Abstract***: The Pd(0) and Pd(II)-catalysed cyclisation/functionalisation reactions of acyclic carbohydrate-derived 1,1-diacetoxy-2,7-diene and 1,1-diacetoxy-2-en-7-yne compounds proceeded in a stereospecific fashion to furnish chiral, multi-functionalised furanoid and cyclopentanoid products. The products contained valuable enolacetate moieties, which can be further elaborated to enable the facile entry to an array of substituted five membered ring compounds.

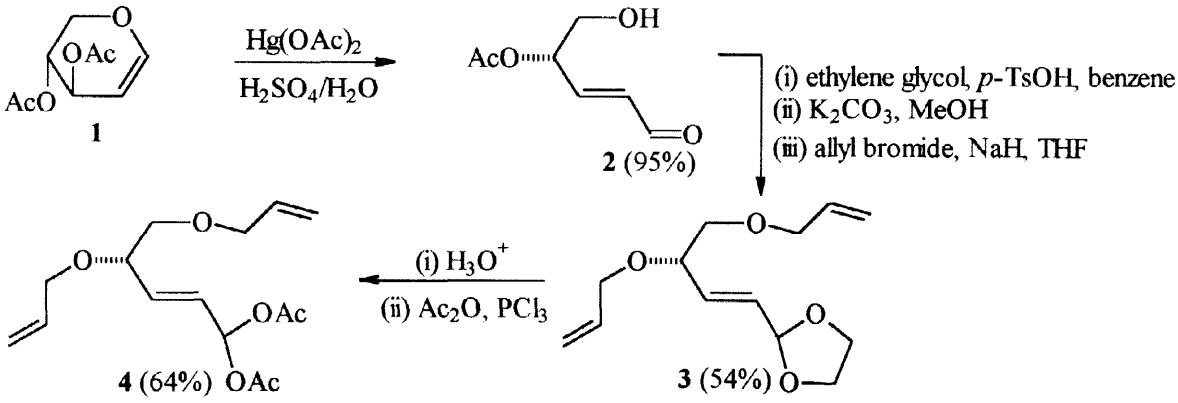

## Introduction

The intramolecular insertion of alkene and alkyne groups into allylpalladium species of acetoxy-2,7-diene and acetoxy-2-en-7-yne derivatives has evolved into a synthetically powerful means of producing a variety of five (and six-) membered carbo- and heterocyclic systems.[1] In an attempt to introduce additional differentiated functionality into the cyclised products, we previously explored the feasibility of employing geminal diacetate starting materials for these palladium-catalysed 'metallo-ene' cyclisation reactions.[2]

The work presented here[3] is intended to illustrate the application of this methodology to carbohydrate-derived geminal diacetate starting materials for the construction of chiral, multi-functionalised furanoid and cyclopentanoid compounds. Such compounds, endowed with rich stereochemical complexity, are important structural units in a wide variety of naturally occurring substances.[4]

## Preparation of Carbohydrate-Derived Allylic Geminal Diacetate Substrates

The preparation of the pentose-derived allylic geminal diacetate **4** commenced by conversion of D-xylal[5] (**1**) into the α,β-unsaturated aldehyde **2** upon treatment of **1** with mercuric acetate in dilute sulphuric acid at room temperature for 10 minutes, according to the method developed by Perlin and co-workers.[6] The sensitive

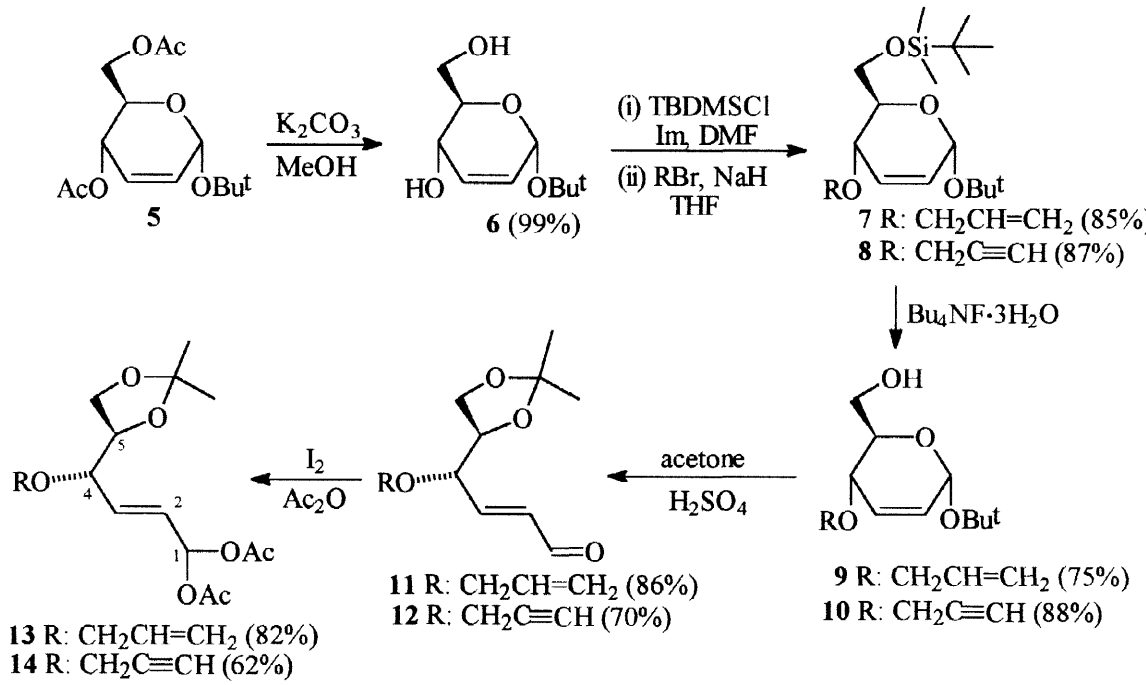



**Scheme 1**

0040-4020/99/$ - see front matter 
*PII:* S0040-4020(98)01155-7

α,β-unsaturated aldehyde moiety was protected as the corresponding dioxolane by heating a solution of **2** and a catalytic amount of *p*-TsOH in ethylene glycol and benzene under reflux, using a Dean-Stark apparatus to assist in the azeotropic removal of water formed during the course of the reaction. Base-assisted solvolysis of the acetate, followed by di-allylation of the resulting diol under standard conditions provided **3**. Acid-catalysed hydrolysis of the acetal moiety, followed by reaction of the aldehyde with acetic anhydride and $PCl_3$ at ambient temperature furnished the geminal diacetate **4** in good yield.

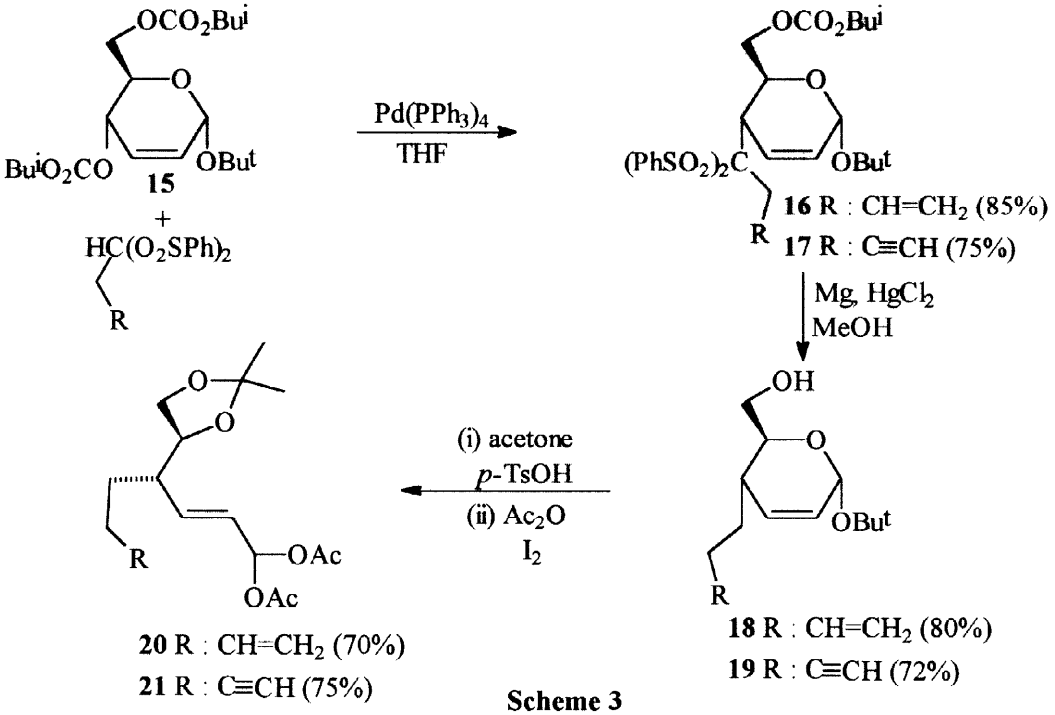
A synthetically more attractive protocol was employed for the synthesis of the corresponding hexose-derived allylic geminal diacetate starting materials in which protection and deprotection of the generated aldehyde moiety was circumvented. To this end (Scheme 2), the pseudoglucal **5**, obtained by the Ferrier-rearrangement reaction[7] of commercially available tri-*O*-acetyl-D-glucal with *tert*-butanol,[8] was subjected to base-assisted solvolysis to form the corresponding diol **6**, which was selectively protected at the primary position to give the corresponding *tert*-butyldimethylsilyl ether. Subsequent allylation or propargylation of the remaining hydroxyl group furnished **7** or **8** in respective yields of 85 and 87%, whereafter fluoride-mediated deprotection of the silyl group provided the primary alcohols **9** and **10** in excellent yields.




**Scheme 2**

The crucial transformation into the α,β-unsaturated aldehydes **11** and **12** was accomplished by treatment of **9** and **10** in anhydrous acetone with catalytic amounts of *p*-TsOH or concentrated $H_2SO_4$ at temperatures ranging from 10-25 °C. Having thus efficiently prepared the α,β-unsaturated aldehydes **11** and **12**, the stage was set for final acetylation of these compounds in acetic anhydride at room temperature using iodine as mild Lewis acid catalyst[9] to form **13** and **14** in respective yields of 82 and 62% yield.

Mindful of the importance of five-membered carbocyclic systems as substructures in many natural products, the *C*-1' analogues of **13** and **14** were synthesised (Scheme 3). The alkene and alkyne side-chains were incorporated at C-4 of the pseudoglucal **15** via Pd(0)-catalysed nucleophilic allylic substitution reactions to give **16** and **17**, respectively.[8]



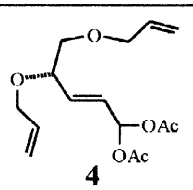
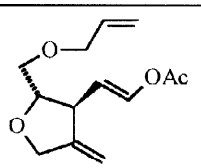
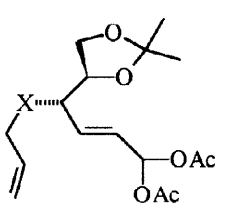
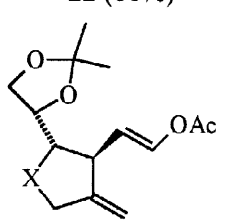

**Scheme 3**

The simultaneous reductive cleavage of the phenylsulphonyl and removal of the isobutoxycarbonyl groups was achieved by heating the sulphones and magnesium turnings (5 mol equiv.) in methanol under reflux in the presence of $HgCl_2$ (0.02 mol equiv.) for 20 minutes.[10] Thereafter, the primary alcohols **18** and **19** were converted into the corresponding open-chain diacetates **20** and **21**, respectively, in the manner previously described.

**Palladium-Catalysed 'Metallo-Ene' Cyclisation**

In the presence of $Pd(PPh_3)_4$, solutions of **4**, **13** and **20** in acetic acid at 75-80 °C were transformed into the enantiopure *trans* enolacetates **22**, **23** and **24**, respectively (Table 1). The stereochemistry of the compounds was assigned on the basis of nOe measurements.

**Table 1 $Pd(PPh_3)_4$-catalysed 'metallo-ene' cyclisation reactions**

| Entry | Starting material | Product (Yield) |
|---|---|---|
| 1 |  **4** |  **22** (88%) |
| 2 |  **13** X = O |  **23** X = O (84%) |
| 3 | **20** X = $CH_2$ | **24** X = $CH_2$ (80%) |

The results indicate that the absolute stereochemistry of the products is dictated by the stereochemistry at C-4 of the substrates. The invariable 2,3-*trans* stereochemistry of the products suggests that cyclisation proceeds through a lower energy conformation with the enolacetyl and the non-participating C-4 substituent in an *anti* orientation.[12]

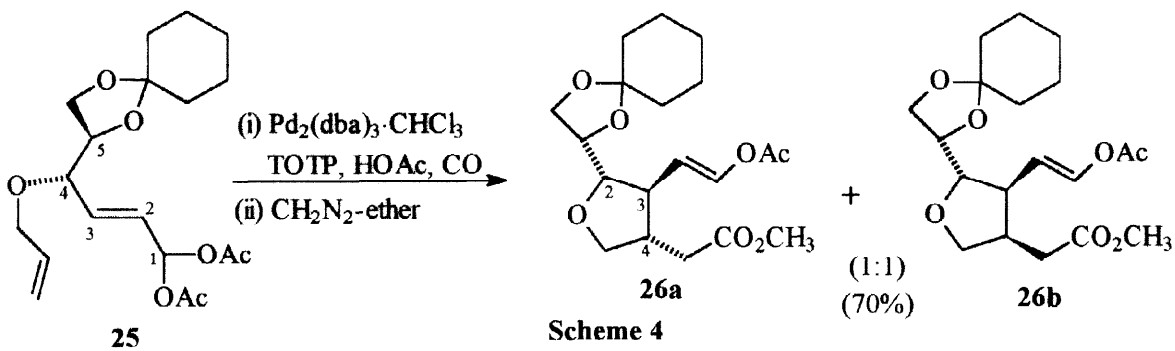
A comparitive study to determine the influence of different Pd(0) catalysts both on the 'metallo-ene' cyclisation rate of **13** and the product yields was subsequently undertaken. The findings (Table 2) were largely in agreement with those previously obtained for the achiral geminal diacetates.[2] The most favourable results were obtained by using a combination of $Pd_2(dba)_3$·$CHCl_3$/tri-*o*-tolylphosphine. The use of palladium acetate and tributylphosphine, and $Pd_2(dba)_3$·$CHCl_3$/tri-2-furylphosphine, however, failed to catalyse any detectable 'metallo-ene' cyclisation, as did the presence of the bidentate ligand[11] 1,3-bis(diphenylphosphino)propane.

**Table 2**. Transformation of **13** → **23**

| Entry | Catalyst | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | 3.5 | 84 |
| 2 | $Pd_2(dba)_3$·$CHCl_3$/tri-*o*-tolylphosphine | 0.1 | 96 |
| 3 | $Pd(OAc)_2$/triisopropylphosphite | 8 | 86 |
| 4 | $Pd(OAc)_2$/tributylphosphine | 8 | - |
| 5 | $Pd_2(dba)_3$·$CHCl_3$/1,3-bis(diphenylphosphino)propane | 10 | - |
| 6 | $Pd_2(dba)_3$·$CHCl_3$/tri-2-furylphosphine | 10 | - |

**Palladium-Catalysed 'Metallo-Ene' Cyclisation/Carbonylation**

The palladium-catalysed 'metallo-ene' cyclisation/carbonylation of 1,1-diacetoxy-2,7-dienes in the presence of carbon monoxide results in the formation of a second new stereocentre. We therefore probed the topological influence of the substituent at C-4 of **25** (prepared in a manner similar to **13**, but substituting cyclohexanone for acetone in the acetalisation step) over the developing second new stereocentre in the palladium-catalysed 'metallo-ene' cyclisation/carbonylation of the diacetate. In the event, a chromatographically inseparable mixture of diastereoisomers **26a** and **26b** (*ca.* 1:1 by $^1$H-NMR) was formed when **25** was stirred in acetic acid under an atmosphere of carbon monoxide at 47 °C for 24 hours in the presence of a $Pd_2(dba)_3$·$CHCl_3$/tri-*o*-tolylphosphine (TOTP) catalyst, followed by treatment with an excess of diazomethane-ether (Scheme 4). It appeared that the large substituent at C-4 of the substrate was presumably too far removed from the second prochiral centre to exert any noticeable stereocontrol on the formation of the second new stereocentre. This is in accordance with analogous results by Oppolzer's group[12] who conducted a systematic study on the asymmetric induction exerted by pre-existing on developing stereogenic centres in Pd(0)- and Ni(0)-catalysed 'metallo-ene' cyclisation and cyclisation/carbonylation reactions.

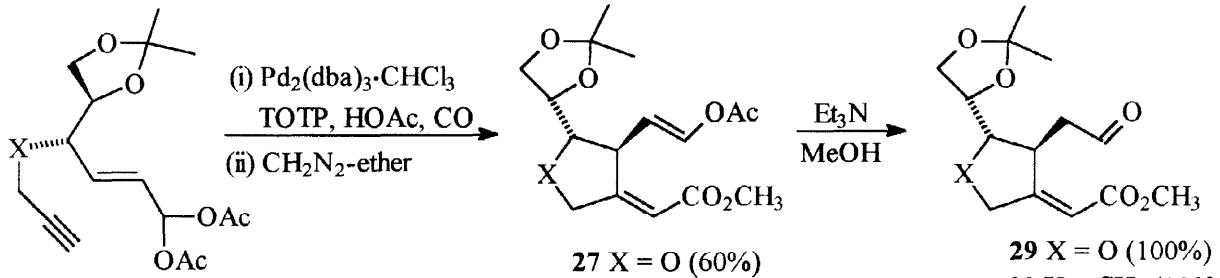



**25** **26a** **26b**

**Scheme 4**

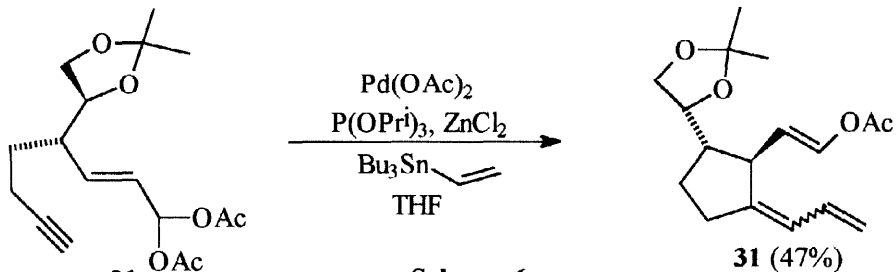
Although somewhat disappointing, the lack of enantioselectivity at C-4 creates the opportunity of endeavouring for greater enantioselectivity by utilizing chiral Pd(0) complexes.[13] In this regard, recent work has been directed at the development of an asymmetric version of the 'metallo-ene' reaction.[14] This approach, however, still remains to be elaborated and refined.

Subsequent work focussed on the palladium-catalysed cyclisation/carbonylation of chiral enynyl diacetates that would generate unsaturated products containing only one new stereocentre. The decision was reinforced by numerous reports in the literature on the catalytic hydrogenation of achiral and chiral olefins with exceptional stereoselectivity, through the action of enantiomerically pure rhodium complexes.[15] When the enynyl geminal diacetates **14** and **21** were subjected to $Pd_2(dba)_3{\cdot}CHCl_3$/tri-*o*-tolylphosphine-catalysed 'metallo-ene' cyclisation/carbonylation reaction conditions, followed by diazomethane methylation, the methyl carboxylate derivatives **27** and **28** were obtained upon chromatographic isolation (Scheme 5). Complete conversion of the enolacetates into the aldehydes **29** and **30** was effected by treatment of **27** and **28** with methanol/triethylamine at ambient temperature for 10 minutes.




**Scheme 5**

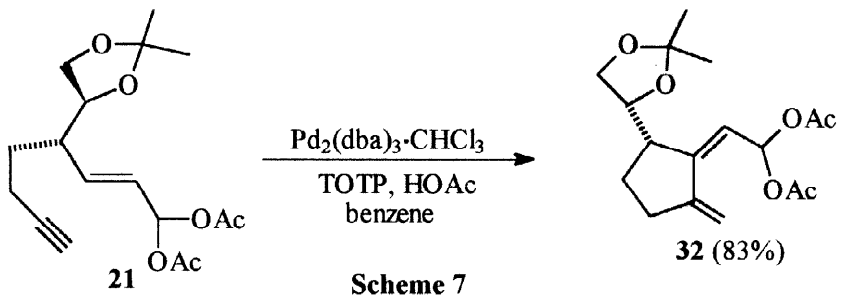
The intermediate vinylpalladium species formed during the 'metallo-ene' cyclisation of acetoxyenynes can be intercepted by trapping agents other than carbon monoxide.[16] 'Metallo-ene' cyclisation/vinylstannane coupling[17] of **21** with vinyltributyltin in THF in the presence of $Pd(OAc)_2$/triisopropylphosphite and $ZnCl_2$ provided the triene **31**, as a chromatographically inseparable mixture of (*E*)- and (*Z*)-isomers (Scheme 6).




**Scheme 6**

**Palladium(II)-Catalysed Cyclisation of Enynyl Geminal Diacetates**

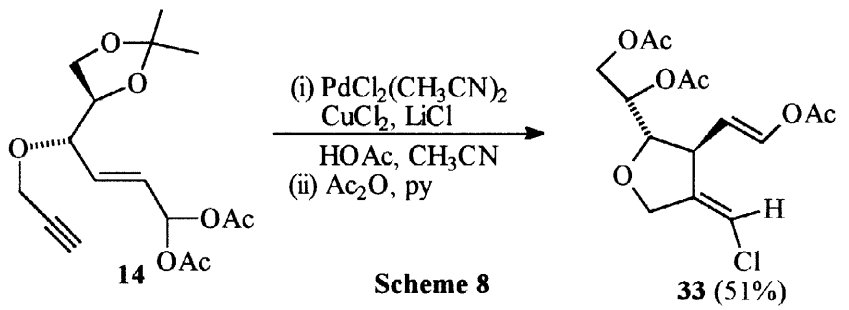
The highly atom economical[18] Trost-type cycloisomerisation[19] of a solution of **21** in acetic acid and benzene under refux provided the 1,3-diene **32** in an isolated yield of 83% (Scheme 7).




**Scheme 7**

In contrast to the 'metallo-ene' protocol, these cycloisomerisation transformations are initiated by addition of an *in situ* generated hydridopalladium species to the triple bond,[19] followed by intramolecular carbopalladation and termination by *syn* β-hydride elimination.

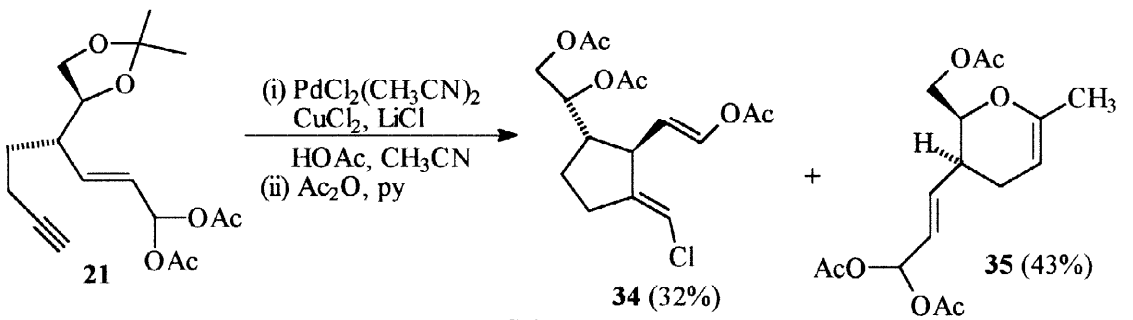
The smooth *trans* chloropalladation, carbopalladation and *anti* palladium acetate elimination sequence[20] of **14** to provide **33** was accomplished by exposure of the enyne to Wacker-like conditions, i.e. $PdCl_2(CH_3CN)_2$, $CuCl_2$ and an excess of LiCl in acetic acid/acetonitrile for 20 minutes, followed by acetylation of the diol under standard conditions (Scheme 8).




**Scheme 8**

Under these conditions, the isopropylidene protecting group, having served its purpose during the preparation of the acyclic geminal diacetate, underwent solvolytic cleavage. Again, stereochemical assignment was established by nOe measurements. The exclusive formation of the (*E*)-isomer of **33** is in accordance with observations by Bäckvall and co-workers,[21] who observed that an increased amount of product arose from *trans* chloropalladation at a higher chloride concentration.

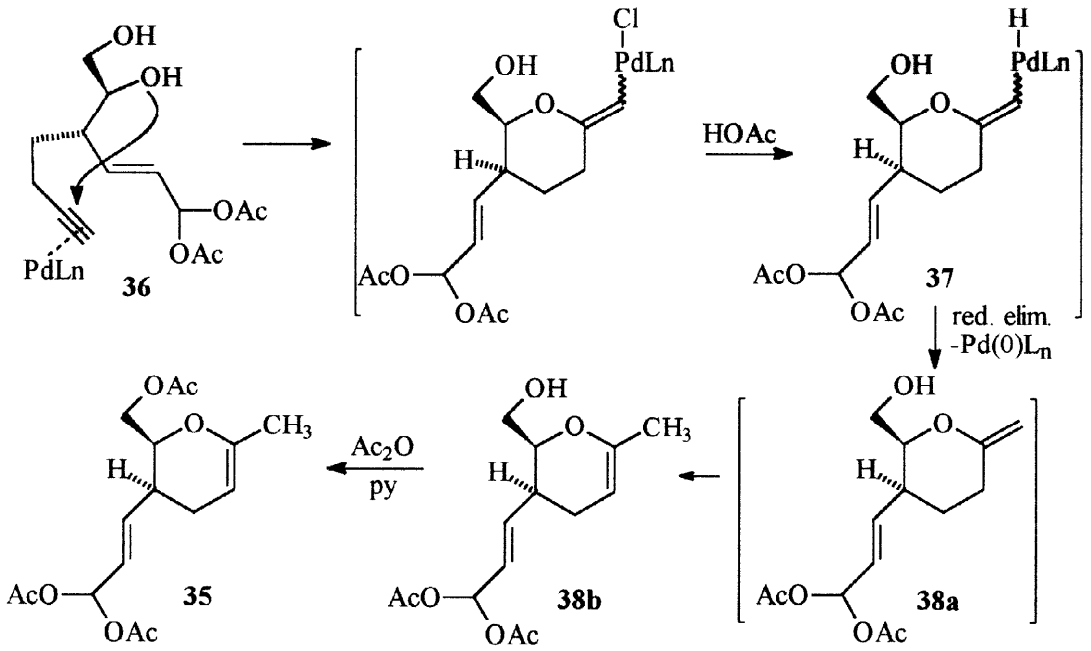
The expected chloro compound **34** and the dihydropyran **35** were formed by stirring a solution of **21** in acetic acid/acetonitrile under Wacker-like conditions in the presence of LiCl (Scheme 9).




**Scheme 9**

The dihydropyran product **35** most likely resulted from the intramolecular oxypalladation reaction[22] of the diol **36** that was produced by the acid-catalysed solvolysis of the isopropylidene group of **21** (Scheme 10). Subsequent reductive elimination of a putative palladium hydride intermediary species **37** furnished **38** which contained an exocyclic methylene moiety that isomerized to form the more stable **35**. The preferred formation of

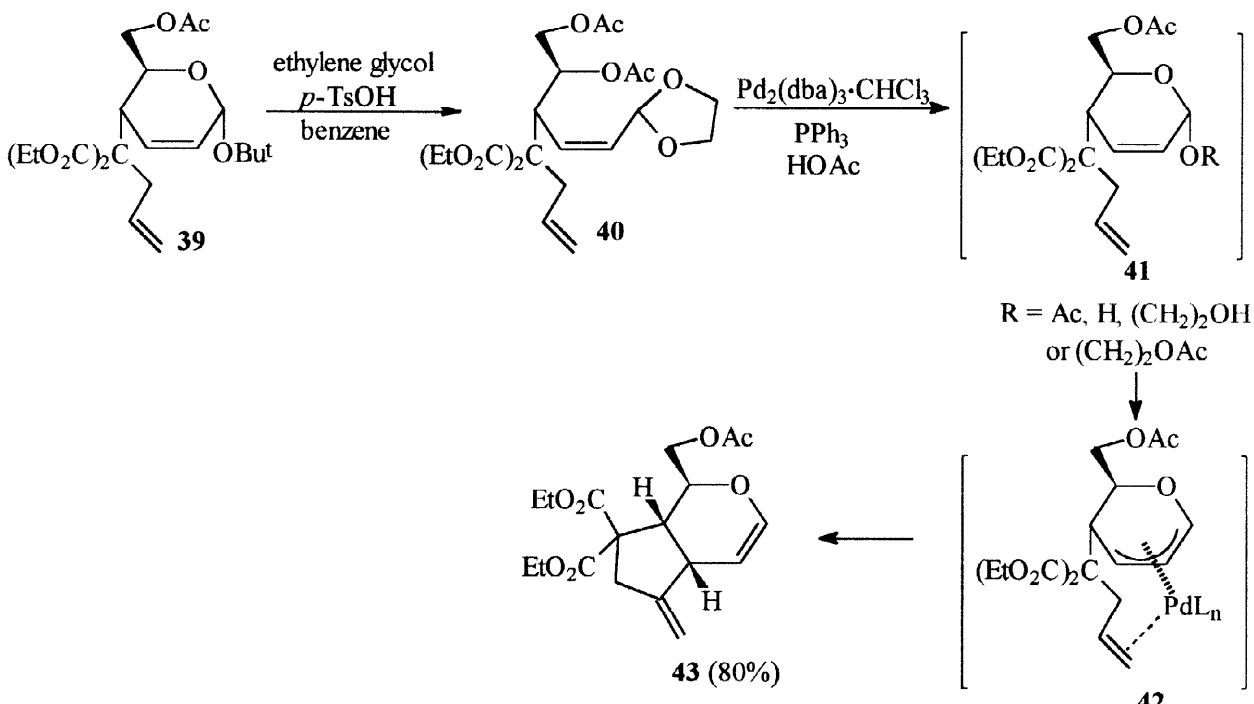
**34** over **35** can most likely be ensured by replacing the acid labile isopropylidene moiety by more robust protecting groups.




**Scheme 10**

**'Metallo-Ene' Cyclisation of α,β-Unsaturated Acetal Derivatives**

At this stage of the study we were curious to probe the reactivity of α,β-unsaturated acetals under these Pd(0)-catalysed 'metallo-ene' conditions, i.e. to examine whether these compounds would sustain oxidative addition by Pd(0) and subsequently form the corresponding π-allylpalladium complexes.




**Scheme 11**

Stirring a solution of **40** (prepared by heating a solution of **39** and *p*-TsOH (cat.) in ethylene glycol and benzene under reflux) and $Pd_2(dba)_3$·$CHCl_3$/$PPh_3$ in acetic acid at 70 °C for 5 hours indeed resulted in 'metallo-ene' cyclisation, but the outcome was somewhat surprising '!' (Scheme 11).

The exact mechanism of the transformation was not established, but in the progression of **40** to **43** under the mild 'metallo-ene' reaction conditions recyclisation of the starting material presumably occurred to form an intermediate pseudoglucal derivative **41**. Oxidative addition of the Pd(0) catalyst to the pseudoglucal **41** would give rise to an intermediate $\eta^3$-allylpalladium species **42** which should undergo alkene insertion and subsequent β-hydride elimination to form **43** (80% yield). This diene **43** was previously synthesised by the 'metallo-ene' cyclisation of a pseudoglucal derivative.[8]

In summary, the work described here amply demonstrates that carbohydrates can be readily converted into allylic geminal diacetates that undergo various palladium-catalysed transformations to form chiral, multi-functionalised furanoid and cyclopentanoid products. These compounds can be further elaborated to enable facile entry to an array of natural product synthons.

## Experimental

All reactions were carried out under a nitrogen atmosphere in flamed-out glass apparatus. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (unless otherwise stated) on a Varian VXR 200 (200 MHz) or a Varian Gemini 2000 (300 MHz) spectrometer. Mass spectra, as well as accurate mass determinations, were recorded on a Finnigan-MAT 8200 mass spectrometer (70 eV; electron impact). Optical rotations were obtained on a Jasco DIP-370 digital polarimeter (a 1 $cm^3$ cell was used; concentration *c* refers to g/100ml in $CHCl_3$). Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh); eluents are given in v/v ratios. All reactions were monitored by thin layer chromatography using glass supported Merck silica gel 60 $F_{254}$ plates with a 0.25 mm silica layer. Detection was done by observation under a UV lamp (254 nm) and by heating the plate over an open flame after it had been sprayed with a dilute chromic acid solution.

*(2E,4S,5S)-4-Allyloxy-5,6-isopropylidenedioxyhex-2-enal (11)*

A mixture of **9** (600 mg, 2.476 mmol), anhydrous $CuSO_4$ (500 mg) and concentrated $H_2SO_4$ (25 µl, 0.250 mmol) in acetone (10 ml) was stirred at rt for 18 h. The reaction mixture was diluted ($CH_2Cl_2$), washed consecutively with saturated aq. $NaHCO_3$ solution and water, dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash chromatography (EtOAc:hexane; 1:3) furnished **11** (484 mg, 86%) as a pale yellow syrup. $[\alpha]_D^{24}$ -5.8° (*c* 1.0); NMR: $\delta_H$ 1.32 (s, 3H), 1.41 (s, 3H), 3.88-4.16 (m, 6H), 5.20 (dddd, 1H, *J* 10.3, 1.3, 1.3, 1.3 Hz), 5.25 (dddd, 1H, *J* 17.3, 1.6, 1.6, 1.6 Hz), 5.85 (dddd, 1H, *J* 17.3, 10.3, 6.1, 5.4 Hz), 6.31 (ddd, 1H, *J* 15.9, 7.8, 1.2 Hz), 6.79 (dd, 1H, *J* 15.9, 7.8, 1.2 Hz), 6.79 (dd, 1H, *J* 15.9, 5.2 Hz), 9.60 (d, 1H, *J* 7.8 Hz); $\delta_C$ 25.1, 26.6, 66.9, 71.1, 77.2, 79.0, 109.9, 117.9, 133.6, 133.7, 153.4, 193.0; *m/z*: 226 ($M^+$, 7%), 101 (62%), 43 (100%); HRMS calcd for $C_{12}H_{18}O_4$: 226.1205 ($M^+$), found 226.1200.

*General procedure for the preparation of the geminal diacetates*

A dark brown solution of the α,β-unsaturated aldehyde and iodine (0.03 mol equiv) or $PCl_3$ (0.01 mol equiv) in acetic anhydride was stirred at rt overnight. The solution was diluted ($CH_2Cl_2$), washed consecutively with sat. aq. $Na_2S_2O_3$ solution and water, dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash chromatography (EtOAc:hexane; 1:5) provided the diacetate as a colourless syrup.

*(2E,4R)-4,5-Diallyloxypent-2-ene-1,1-diacetate (4)* NMR: $\delta_H$ 3.48 (dd, 1H, *J* 12.5, 4.9 Hz), 3.49 (dd, 1H, *J* 12.5, 6.1 Hz), 3.85-4.14 (m, 5H), 5.09-5.33 (m, 4H), 5.72-6.00 (m, 4H), 5.63 (d, 1H, *J* 4.9 Hz); $\delta_C$ 20.8, 70.2, 72.3, 72.4, 77.4, 88.6, 117.0, 117.0, 125.9, 134.1, 134.5, 134.6, 168.5; *m/z*: 298 ($M^+$, 3%), 238 (18%); HRMS calcd for $C_{15}H_{22}O_6$: 298.1416 ($M^+$), found 298.1410.

*(1'S,2E,4S)-4-Isopropylidenedioxyethyloct-2,7-dienyl-1,1-diacetate (20)* $[\alpha]_D^{23}$ +29.0° (*c* 1.0); NMR: $\delta_H$ 1.31 (s, 3H), 1.35 (s, 3H), 1.35-1.76 (m, 2H), 2.06 (s, 6H), 1.83-2.29 (m, 3H), 3.57 (dd, 1H, *J* 7.3, 7.3 Hz), 3.95 (dd, 1H, *J* 7.0, 7.0 Hz), 4.03 (m, 1H), 4.94 (dm, 1H, *J* 10.1 Hz), 4.96 (dm, 1H, *J* 17.3 Hz), 5.55 (dd, 1H, *J* 15.8, 6.0 Hz), 5.73 (m, 1H), 5.86 (dd, 1H, *J* 15.8, 9.1 Hz), 7.10 (d, 1H, *J* 6.1 Hz); $\delta_C$ 20.8, 25.4, 26.3, 30.0, 31.1, 44.4, 67.1, 77.8, 89.3, 109.0, 115.0, 126.1, 136.5, 138.0, 168.6; *m/z*: 326 ($M^+$, 1%), 209 (12%), 166 (40%).

*(1'S,2E,4S)-4-Isopropylidenedioxyethyloct-2-en-7-ynyl-1,1-diacetate (21)* $[\alpha]_D^{23}$ +58.5° (*c* 1.0); NMR: $\delta_H$ 1.31 (s, 3H), 1.35 (s, 3H), 1.52-1.73 (m, 2H), 1.93 (t, 1H, *J* 2.6 Hz), 2.06 (2s, 2x3H), 2.07 (m, 1H), 2.19 (m, 1H), 2.35 (m, 1H), 3.58 (dd, 1H, *J* 8.1, 7.5 Hz), 3.96 (dd, 1H, *J* 8.1, 6.4 Hz), 4.06 (ddd, 1H, *J* 7.5, 6.4, 4.6 Hz), 5.62 (ddd, 1H, *J* 15.6, 6.0, 0.6 Hz), 5.84 (ddd, 1H, *J* 15.6, 9.3, 0.9 Hz), 7.08 (dd, 1H, *J* 6.0, 0.9 Hz); $\delta_C$ 16.0, 20.7, 25.3, 26.1, 29.5, 43.5, 67.0, 69.0, 77.5, 83.5, 109.1, 126.8, 135.4, 168.7; *m/z*: 324 ($M^+$, 37%), 309 (58%), 265 (22%), 207 (33%); HRMS calcd for $C_{17}H_{24}O_6$: 324.1573 ($M^+$), found 324.1565.

*(2E,4S,5S)-4-Allyloxy-5,6-cyclohexylidenedioxyhex-2-enyl-1,1-diacetate (25)* $[\alpha]_D^{26}$ -15.2° (*c* 2.0); NMR: $\delta_H$ 1.37-1.58 (m, 10H), 2.07 (2s, 6H), 3.76-4.10 (m, 6H), 5.15 (dddd, 1H, *J* 10.2, 1.7, 1.7, 1.6 Hz), 5.23 (dddd, 1H, *J* 17.1, 1.6, 1.5, 1.5 Hz), 5.78 (ddd, 1H, *J* 15.9, 5.7, 1.2 Hz), 5.86 (ddm, *J* 17.1, 10.2 Hz), 5.97 (ddd, 1H, *J* 15.9, 6.0 Hz, 0.9 Hz), 6.43 (dd, 1H, *J* 5.7, 0.9 Hz); $\delta_C$ 20.7, 23.7, 23.8, 25.0, 34.8, 36.2, 66.1, 70.4, 77.0, 78.9, 88.5, 110.2, 117.4, 126.6, 133.9, 134.3, 168.7; *m/z*: 368 ($M^+$, 13%), 325 (18%), 311 (5%), 250 (9%); HRMS calcd for $C_{19}H_{28}O_7$: 368.1835 ($M^+$), found 368.1827.

***General procedure for the 'metallo-ene' cyclisation of geminal diacetates***

A soln. of the geminal diacetate and a suitable palladium(0) catalyst (0.1 mol equiv.) were stirred in acetic acid at 78-80 °C. The solvent was evaporated *in vacuo* and the residue subjected to flash chromatography (EtOAc:hexane; 1:5) to provide the cyclised product as a colourless syrup.

*(2R,3R)-2-Allyloxymethyl-3-[2-acetoxy-(E)-vinyl]-4-methylidenetetrahydrofuran (22)* NMR: $\delta_H$ 2.12 (s, 3H), 3.04 (br t, 1H, *J* 9.1 Hz), 3.48 (dd, 1H, *J* 10.6, 5.8 Hz), 3.62 (dd, 1H, *J* 10.7, 2.3 Hz), 3.62-3.80 (m, 1H), 4.02 (d, 1H, *J* 5.6 Hz), 4.04 (d, 1H, *J* 5.8 Hz), 4.33 (ddd, 1H, *J* 13.4, 2.2, 2.2 Hz), 4.53 (d, 1H, *J* 13.4 Hz), 4.89 (dd, 1H, *J* 4.8, 2.6 Hz), 4.97 (dd, 1H, *J* 4.6, 2.2 Hz), 5.21 (dd, 1H, *J* 12.5, 9.6 Hz), 5.10-5.35 (m, 2H), 5.90 (dddd, 1H, *J* 16.1, 11.1, 5.6, 5.6 Hz), 7.17 (d, 1H, *J* 12.5 Hz); $\delta_C$ 20.6, 44.9, 70.2, 71.2, 72.5, 83.4, 105.7, 112.0, 117.2, 134.5, 138.1, 150.4, 167.83; HRMS calcd for $C_{13}H_{18}O_4$: 238.1205 ($M^+$), found 138.1206.

*(1'E,1'R,2S,3S)-3-(2-Acetoxy-(E)-vinyl)-2-isopropylidenedioxyethyl-4-methylidenetetrahydrofuran (23)*

(See Table 2 for reaction times and product yields). NMR: $\delta_H$ 1.33 (s, 3H), 1.40 (s, 3H), 2.11 (s, 3H), 3.14 (m, 1H), 3.67 (dd, 1H, *J* 7.9, *J* 5.3 Hz), 3.91 (dd, 1H, *J* 8.2, 6.0 Hz), 4.02 (dd, 1H, *J* 8.2, 6.4 Hz), 4.16 (dddd, 1H, *J* 6.4, 6.0, 5.3 Hz), 4.33 (ddd, 1H, *J* 13.4, 2.2, 2.2 Hz), 4.46 (dm, 1H, *J* 13.4 Hz), 4.94 (dddd, 1H, *J* 2.2, 2.2, 2.2 Hz), 5.00 (dddd, 1H, *J* 2.2. 2.2, 2.2 Hz), 5.28 (dd, 1H, *J* 12.5, 9.3 Hz), 7.20 (d, 1H, *J* 12.5 Hz); $\delta_C$ 20.5, 25.1,

26.5, 45.3, 65.9, 71.0, 76.7, 84.2, 106.2, 109.5, 113.0, 137.5, 150.0, 167.8; *m/z*: 268 ($M^+$, 1%), 101 (45%); HRMS calcd for $C_{14}H_{20}O_5$: 268.1311 ($M^+$), found 268.1309.

***General prcedure for the Pd(0)-catalysed 'metallo-ene' cyclisation/carbonylation of geminal diacetates***
Carbon monoxide was gently bubbled through a soln. of the diacetate, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 mol equiv.) and TOTP (0.3 mol equiv.) in acetic acid at 47 °C for 24 h. The solvent was evaporated *in vacuo* and the residue treated with $CH_2N_2$-ether at 0 °C until TLC indicated the complete consumption of the polar carboxylic acid. Flash chromatography (EtOAc:hexane; 1:3- 1:5) furnished the methyl carboxylate compound.
*(1'R,2S,3R,4S)-3-(2-Acetoxy-(E)-vinyl)-2-cyclohexylidenedioxyethyl-4-(methoxycarbonylmethyl)tetrahydrofuran (**26a**) and (1'R,2S,3R,4R)-3-(2-Acetoxy-(E)-vinyl)-2-cyclohexylidenedioxyethyl-4-(methoxycarbonylmethyl)tetrahydrofuran (**26b**)* NMR: $\delta_H$ 1.53-1.61 (m, 20H), 2.09 (s, 6H), 2.18-2.95 (m, 8H), 3.44-4.17 (m, 8H), 3.63 (s, 3H), 3.64 (s, 3H), 5.27 (dd, 1H, *J* 12.6, 7.5 Hz), 5.32 (dd, 1H, *J* 12.6, 7.5 Hz), 7.14 (d, 1H, *J* 12.6 Hz), 7.16 (d, 1H, *J* 12.6 Hz); $\delta_C$ 20.5, 23.7, 23.8, 23.8, 25.0, 32.8, 34.6, 35.5, 36.2, 36.3, 38.9, 42.5, 42.8, 47.0, 51.7, 65.9, 66.3, 72.2, 72.9, 83.7, 84.7, 110.0, 110.1, 111.9, 113.7, 137.0, 137.3, 167.8, 172.5, 172.7; *m/z*: 356 ($M^+$, 10%).

*(1'R,2S,3S)-3-(2-Acetoxy-(E)-vinyl)-2-isopropylidenedioxyethyl-4-(methoxycarbonyl)methylideneterahydrofuran (**27**)* $[\alpha]_D^{27}$ +188.7° (*c* 0.9); NMR: $\delta_H$ 1.29 (s, 3H), 1.37 (s, 3H), 2.08 (s, 3H), 3.71 (s, 3H), 3.84 (dd, 1H, *J* 7.8, 4.2 Hz), 3.87-4.05 (m, 3H), 4.20 (m, 1H), 4.44 (dd, 1H, *J* 15.0, 2.0 Hz), 4.53 (ddd, 1H, *J* 15.0, 2.0 Hz), 5.49 (dd, 1H, *J* 12.6, 8.4 Hz), 5.80 (ddd, 1H, *J* 2.0, 2.0, 2.0 Hz), 7.28 (dd, 1H, *J* 12.6, 1.2 Hz); $\delta_C$ 20.6, 25.0, 26.4, 42.6, 51.3, 66.6, 71.4, 76.1, 86.3, 109.8, 112.1, 113.2, 137.4, 161.2, 165.6, 167.8; *m/z*: 326 ($M^+$, 1%), 325 ($M^+$-1, 18%), 282 (4%); HRMS calcd for $C_{16}H_{22}O_7$: 326.1366 ($M^+$), found 326.1400.

*(1'S,2R,3S)-2-(2-Acetoxy-(E)-vinyl)-3-isopropylidenedioxyethyl-3-(methoxycarbonylmethylidene)cyclopentane (**28**)* $[\alpha]_D^{24}$ -59.7° (*c* 1.3); NMR: $\delta_H$ 1.29 (s, 3H), 1.37 (s, 3H), 1.90 (m, 1H), 2.06 (s, 3H), 2.11 (m, 1H), 2.42-2.60 (m, 2H), 2.66-3.67 (m, 1H), 3.67 (s, 3H), 3.87-4.00 (m, 2H), 4.05 (m, 1H), 5.49 (dd, 1H, *J* 12.6 , 7.2 Hz), 5.82 (ddd, 1H, *J* 1.8, 1.8, 1.8 Hz), 7.11 (dd, 1H, *J* 12.6, 1.5 Hz); $\delta_C$ 20.6, 25.4, 25.6, 26.6, 33.9, 43.0, 49.2, 50.9, 67.7, 78.0, 109.1, 113.8, 116.0, 136.0, 166.1, 166.7, 168.8; *m/z*: 324 ($M^+$, 48%), 309 (18%), 266 (43%), 235 (12%), 207 (22%), 193 (40%); HRMS calcd for $C_{17}H_{24}O_6$: 324.1573 ($M^+$), found 324.1570.

*(1'S,2R,3S,4E/Z)-2-(2-Acetoxy-(E)-vinyl)-1-(prop-2-enylidene)-3-(isopropylidenedioxyethyl)cyclopentane (**31**)*
To a solution of **31** (120 mg, 0.370 mmol), $Pd(OAc)_2$ (8 mg, 0.037 mmol) and triisopropylphosphite (55 µl, 0.222 mmol) in THF (3 ml) were added $ZnCl_2$ (dried *in vacuo* at 130 °C for 16 h, 101 mg, 0.741 mmol) and vinyltributyltin (216 µl, 0.741 mmol). The mixture was heated under reflux for 15 min., diluted with ether, washed successively with sat. aq. KF soln. and water, dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash chromatography (EtOAc:hexane; 1:8) gave the inseparable (*ca.* 2:1 by $^1$H-NMR) enantiomeric mixture **36** (52 mg, 47%) as a colourless oil. NMR: $\delta_H$ 1.30, 1.31 (2s, 6H), 1.27, 1.39 (2s, 6H), 2.08 (s, 3H), 2.12 (2, 3H), 1.82-2.54 (m, 10H), 3.32-4.15 (m, 8H), 4.92-5.12 (m, 4H), 5.24 (dd, 1H, *J* 12.3, 9.3 Hz), 5.46 (dd, 1H, *J* 12.3, 7.2 Hz), 5.77-6.03 (m, 2H), 6.33-6.51 (m, 2H), 6.96-7.09 (m, 2H); $\delta_C$ 20.6, 25.3, 25.4, 26.4, 26.7, 28.0, 32.7, 33.4, 42.4, 46.5, 48.3, 49.9, 50.3, 66.5, 67.8, 77.7, 78.3, 108.8, 109.0, 115.4, 115.6, 117.3, 117.4, 123.7, 124.2, 133.7, 133.9, 136.0, 136.4, 146.2, 168.1; *m/z*: 292 ($M^+$, 2%).

*(1'S,2Z,3S)-2-(2,2-Diacetoxyethyl)-3-isopropylidenedioxyethyl-1-methylidenecyclopentane (32)*

A solution of **21** (60 mg, 0.186 mmol), $Pd_2(dba)_3$·$CHCl_3$ (10 mg, 9.2 x $10^{-3}$ mmol) and tri-*o*-tolylphosphine (23 mg, 0.074 mmol) in acetic acid (0.2 ml) and benzene (1.5 ml) was heated under reflux for 6 h. *In vacuo* evaporation and flash chromatography (EtOAc:hexane; 1:5) furnished **32** (324 mg, 83%) as a colourless syrup. $[\alpha]_D^{25}$ +112.7° (*c* 1.3); NMR: $\delta_H$ 1.27, 1.37 (2s, 2x3H), 1.42-1.49 (m, 1H), 1.70-1.85 (m, 1H), 2.02 (s, 3H), 2.09 (s, 3H), 2.40-2.47 (m, 2H), 3.30 (ddd, 1H, *J* 9.5, 8.1, 1.2 Hz), 3.65 (dd, 1H, *J* 8.1, 8.1 Hz), 3.88 (ddd, 1H, *J* 9.5, 8.1, 6.3 Hz, H-1'), 4.08 (dd, 1H, *J* 8.1, 6.3 Hz), 5.01 (ddd, 1H, *J* 2.2, 2.2, 2.2 Hz), 5.48 (ddd, 1H, *J* 2.2, 2.2, 2.2 Hz), 5.93 (dd, 1H, *J* 8.8, 1.2 Hz), 7.48 (d, 1H, *J* 8.8 Hz); $\delta_C$ 20.8, 25.6, 25.9, 26.3, 30.6, 45.8, 68.7, 76.6, 89.7, 107.0, 109.5, 114.9, 147.1, 147.6, 168.7, 168.8; *m/z*: 324 ($M^+$, 25%); HRMS calcd for $C_{17}H_{24}O_6$: 324.1573 ($M^+$), found 324.1567.

*(1'R,2S,3S,4E)-2-(1,2-Diacetoxyethyl)-3-(2-acetoxy-(E)-vinyl)-4-chloromethylidenetetrahydrofuran (33)*

A dark brown solution of **14** (200 mg, 0.613 mmol), $PdCl_2(CH_3CN)_2$ (16 mg, 0.061 mmol), LiCl (150 mg, 3.539 mmol) and anhydrous $CuCl_2$ (412 mg, 3.067 mmol) in acetic acid (3 ml) and acetonitrile (3 ml) was stirred at rt for 40 min. To the solution were added acetic anhydride (8 ml) and pyridine (8 ml), whereafter it was stirred at rt for 10 min. The volatile component was evaporated *in vacuo*. Flash chromatography (EtOAc:hexane; 1:5) afforded **33** (108 mg, 51%) as a colourless syrup. $[\alpha]_D^{26}$ -15.0° (*c* 1.2); NMR: $\delta_H$ 1.97, 2.03, 2.15 (3s, 3x3H), 4.06 (dd, 1H, *J* 12.3, 5.1 Hz), 4.21 (dd, 1H, *J* 8.4, 6.3 Hz), 4.41 (ddd, 1H, *J* 14.7, 2.7, 1.2 Hz), 4.36-4.45 (m, 1H), 4.48 (dd, 1H, *J* 12.3, 2.7 Hz), 4.56 (ddd, 1H, *J* 14.7, 2.7, 2.7 Hz), 4.79 (dd, 1H, *J* 10.5, 6.6 Hz), 5.02 (ddd, 1H, *J* 8.4, 6.3, 2.7 Hz), 5.91 (m, 1H), 7.13 (dd, 1H, *J* 6.6, 0.9 Hz); $\delta_C$ 20.5, 20.6, 20.7, 41.5, 62.9, 69.7, 69.9, 79.7, 108.4, 111.3, 136.1, 143.5, 167.4, 169.7, 170.7.

*(1'S,2R,3S)-2-(2-Acetoxy-(E)-vinyl)-3-(1,2-diacetoxyethyl)-1-chloromethylidenecyclopentane (34)* and *(1'E,5S,6S)-6-Acetoxymethyl-5-(3,3-diacetoxypropenyl)-2-methyl-1-oxacyclohex-2-ene (35)*

A dark brown solution of **21** (80 mg, 0.247 mmol), $PdCl_2(CH_3CN)_2$ (6 mg, 0.025 mmol), LiCl (80 mg, 1.887 mmol) and $CuCl_2$ (166 mg, 1.235 mmol) in acetic acid (2 ml) and acetonitrile (2 ml) was stirred at rt for 15 min. The solution was diluted with $Ac_2O$ (3 ml) and pyridine (3 ml) and stirred at rt for 20 min. The solution was diluted ($CH_2Cl_2$), washed consecutively with sat. aq. $NaHCO_3$ soln. and $H_2O$, dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash chromatography (EtOAc:hexane; 1:5) furnished **34** (27 mg, 32%) and **35** (35 mg, 43%) as colourless syrups.

**34**: $[\alpha]_D^{23}$ -13.8° (*c* 0.6); NMR: $\delta_H$ 1.53-1.92 (m, 3H), 1.97, 2.04, 2.13 (3s, 3x3H), 2.37-2.64 (m, 3H), 3.95 (dd, 1H, *J* 12.3, 5.4 Hz), 4.37 (dd, 1H, *J* 12.3, 2.7 Hz), 4.76 (dd, 1H, *J* 10.8, 6.6 Hz), 4.94 (ddd, 1H, *J* 9.9, 5.4, 2.7 Hz), 5.90 (m, 1H), 7.02 (d, 1H, *J* 6.6 Hz); $\delta_C$ 20.6, 20.7, 20.7, 25.7, 29.0, 41.3, 44.7, 64.1, 72.0, 110.9, 112.15, 134.8, 146.9, 167.5, 169.9, 170.8; *m/z*: 344 ($M^+$, 1%), 302 (3%), 284 (65%), 241 (57%), 225 (60%), 207 (70%), 182 (53%), 147 (48%); HRMS calcd for $C_{16}H_{21}O_6Cl$: 344.1027, found 344.1018 ($^{35}Cl$ isotope).

**35**: $[\alpha]_D^{25}$ +6.3° (*c* 1.4); NMR: $\delta_H$ 1.03 (d, 3H, *J* 6.9 Hz), 2.02, 2.04, 2.06 (3s, 3x3H), 2.00-2.17 (m, 3H), 2.02, 2.04, 2.06 (3s, 9H), 2.53 (ddd, 1H, *J* 7.2, 6.3, 3.3 Hz), 3.99 (dd, 1H, *J* 12.0, 7.2 Hz), 4.18 (dd, 1H, *J* 12.0, 3.3 Hz), 5.00 (m, 1H), 5.57 (ddd, 1H, *J* 15.9, 6.3, 0.6 Hz), 5.90 (dd, 1H, *J* 15.9, 8.4 Hz), 7.05 (d, 1H, *J* 6.3 Hz); $\delta_C$ 15.8, 20.6 , 20.7, 37.7, 63.5, 73.4, 89.1, 125.0, 137.3, 128.2, 129.0, 168.7, 170.4, 170.7; HRMS calcd for $C_{16}H_{22}O_7$: 326.1366, found 326.1360.

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