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Exploratory Experiments with Aryl Telluride Carbohydrates. Synthesis of Carbocycles using Intramolecular Radical Cyclization

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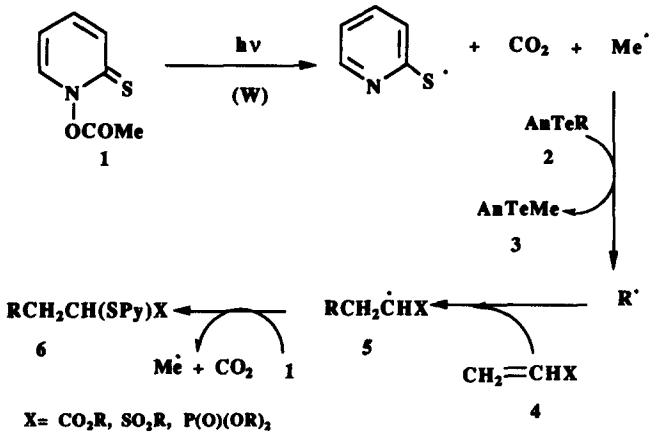
Abstract *- The preparation of cyclohexanoids and cyclopentanoids, potential precursors of biologically interesting molecules is described. The key step of the synthesis is an exo cyclization of 5-hexenyl or 6-heptenyl radicals. The radical, generated by radical exchange from carbohydrate anisyl tellurides (D-galactose or D-arabinose) cyclized into polyhydroxylated cyclohexane or cyclopentane derivatives.*

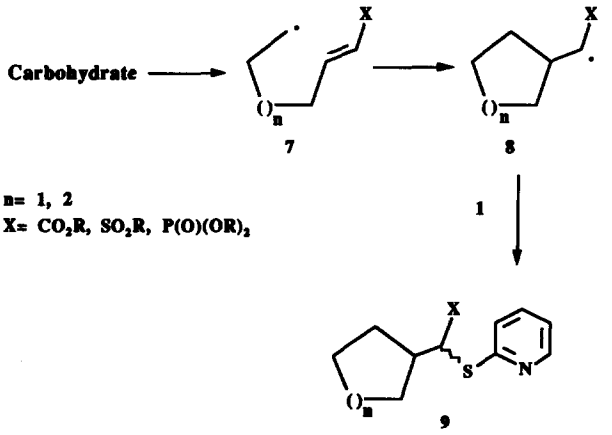
The cyclohexanoids and cyclopentanoids are often present in biologically important natural products. These important systems lend themselves to chemical modification. In this field, most of the carbocycles derived from carbohydrates have been synthesised using ionic processes[1]. The use of radical chemistry[2] is also an efficient way to prepare carbocycles from carbohydrates[3]. Such a methodology is characterized by its mild reaction conditions and is compatible with various functional groups present in carbohydrates. It was first reported by Wilcox *et al*[2]. They realized the 5-hexenyl radical cyclization of halide carbohydrates in the presence of the Bu_3SnH/AINB reagent to obtain chiral carbocycles. However, tin residues are toxic and difficult to remove. These limitations led Barton *et al* [4] to invent a new source of alkyl radicals by radical exchange. They have shown that the acetyl derivative of *N*-hydroxy-2-thiopyridone **1** is a convenient source of methyl radicals which will react with the anisyl telluride derivative **2** to afford anisylmethyl telluride **3** and the desired radical **R** (Scheme 1). The latter with trap **4** then affords radical **5** which is disciplined by reaction with the thiocarbonyl group of **1** to give **6** with reformation of the methyl radical. This methodology is well suited to carbohydrate chemistry because the carbon radical is generated from a hydroxyl group via the anisyl telluride derivative readily accessible by S_N2 displacement on a primary or secondary mesylate or tosylate. This radical exchange was used recently in a short synthesis of showdomycin[4]. Using an internal olefin as a radical trap, simple six-

membered carbocycles[5], cyclonucleosides[6], cyclopentane and cyclopentenone[7] derivatives have been recently prepared.



Scheme 1

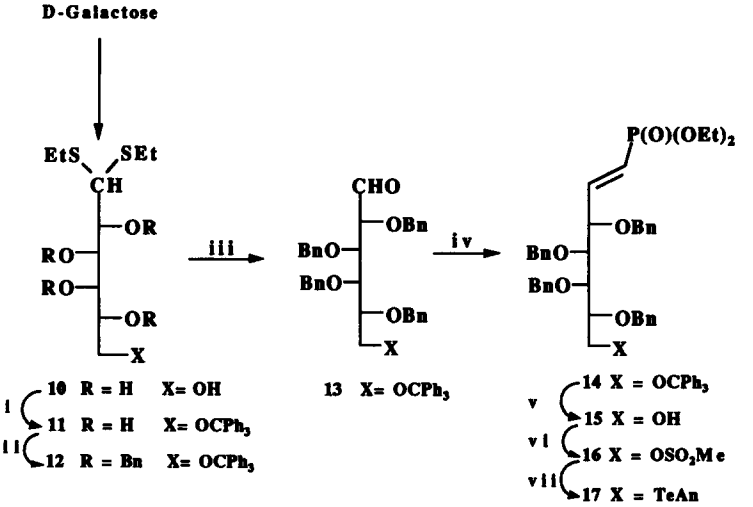
We decided to use the radical exchange process to generate a carbohydrate radical **7** which undergoes the 5 or 6-exo-radical cyclization to produce 5 or 6 membered carbocycles. The primary radical **8** thus obtained reacts with the N-acetoxy-2-thiopyridone **1** to give the thiopyridyl product **9**. We know that the replacement of a phosphate group in a biologically active molecule by a phosphonic acid often gives rise to interesting biological effects[8]. The adopted strategy allows us to obtain in one step carbocycles, substituted with a methylene phosphonate. This functionalization can be extended to other groups according to the nature of the activating group X (carboxylate, sulfonate, phosphonate). The chirality of the carbocyclic molecule depends on the nature of the starting carbohydrate (Scheme 2).



Scheme 2

We applied this radical cyclization to the preparation of metabolically more stable analogues of inositol phosphates. It has been demonstrated[9] that the 5-methylene phosphonate analogue of D-myo-inositol 1,4,5-trisphosphate is a long lived agonist of calcium mobilization. Starting from D-galactose, we anticipated obtaining a precursor of phosphonate analogue of D-*myo*-Inositol-1,4,5-Trisphosphate (Ins-IP_3) with D-*chiro* configuration.

At first, we performed an efficient synthesis of the unsaturated anisyl telluride **17** from D-galactose (Scheme 3). The known D-galactose dithioacetal[10] **10** was selectively tritylated to give **11** (84%) (Scheme 3). Benzylation of the secondary hydroxyl groups in **11** furnished the tetra-*O*-benzyl derivative **12**. Dethioacetalization[11] of **12** in the presence of mercury (II) chloride and calcium carbonate gave the adehyde **13** (80%). This latter underwent a Wittig-Horner reaction using tetraethylmethylenediphosphonate and HMDS in THF to afford the *E* olefin phosphonate **14** (95%). Deprotection of the trityl group with p-toluenesulfonic acid in ethyl acetate-methanol furnished the primary alcohol **15** (77%). Mesylation of **15** with mesyl chloride and 4-dimethylaminopyridine in dichloromethane gave the compound **16** which was used for the next step without purification. The S_N2 substitution of the mesylate **16** with anisyl telluride anion[12] was effected in THF at 40°C to furnish the telluride **17** (60% from 15).

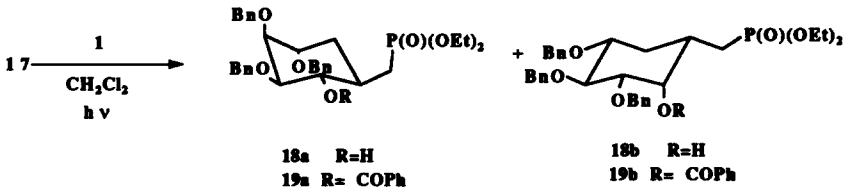


i: Ph_3CCl, DMAP, C_5H_5N; ii: NaH, DMF, BnBr; iii: $Hg(OAc)_2$, $CaCO_3$, MeCN; iv: $(EtO)_2P(O)CH_2P(O)(OEt)_2$, HMDS, THF; v: PTSA, AcOEt-MeOH; vi: $MeSO_2Cl$, DMAP, CH_2Cl_2; vii: $(AnTe)_2$, $NaBH_4$, EtOH-THF.

Scheme 3

The radical cyclization was realized in a degassed mixture of cyclohexane-dichloromethane under argon by photolysis of **17** with a halogen lamp (Xenophot 100 Watts) in the presence of an excess of *N*-acetoxy-2-thiopyridone (Scheme 4). The mixture of carbocyclic compounds was treated with p-toluenesulfonic acid in ethanol-chloroform to afford the alcohols (45%) as a mixture of isomers **18a** and **18b** in a ratio 42:58

respectively and the benzoates **19a** and **19b** (20%) in a ratio 46:54 respectively. The ratio of isomers was determined by HPLC and confirmed by ^{31}P NMR spectroscopy.

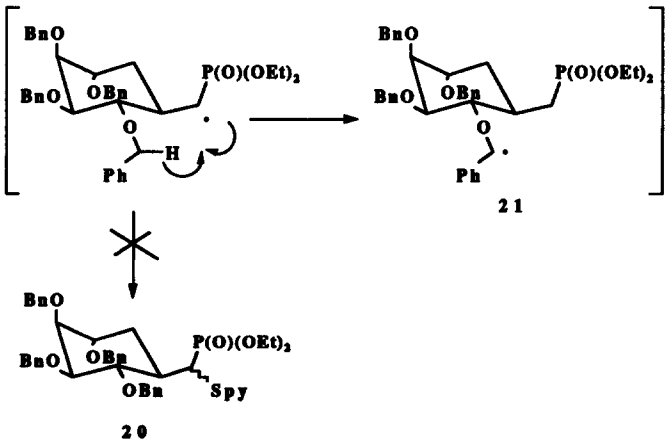


18a R=H
19a R= COPh

18b R=H
19b R= COPh

Scheme 4

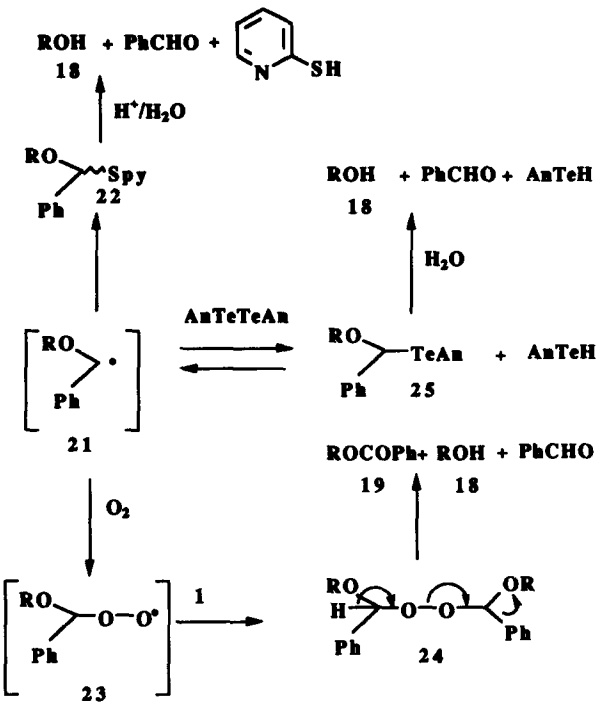
To explain the formation of the alcohols **18a** and **18b** and the benzoates **19a**, **19b**, a 6-exo-cyclization followed by 1,5 hydrogen atom transfer[13] process is proposed. Indeed, the radical cyclization does not produce the expected thiopyridyl derivative **20** (Scheme 5). The radical resulting from the 6-exo-cyclization underdergoes an 1,5 hydrogen atom transfer with formation of a six membered transition state giving the stabilized radical **21**. This benzylic radical is then trapped by the thiopyridyl of the Barton ester to produce the thioacetal **22** which is hydrolyzed into the alcohols **18** under acidic conditions (Scheme 6). The same benzylic radical **21** can be trapped by traces of oxygen to give the intermediate peroxide radical **23**. This latter reacts with the stabilized radical **21** to give the peroxide **24** which is cleaved into alcohols **18** and benzoates **19**. In the absence of Barton ester, the intramolecular radical cyclization gave a mixture of alcohols **18** (37%) and benzoates **19** (26%) with 30% of unreacted starting material. In this case, the capture of the benzylic radical by dianisylditelluride formed in the reaction affords the telluride **25** which is hydrolyzed into alcohols **18**.



21

20

Scheme 5

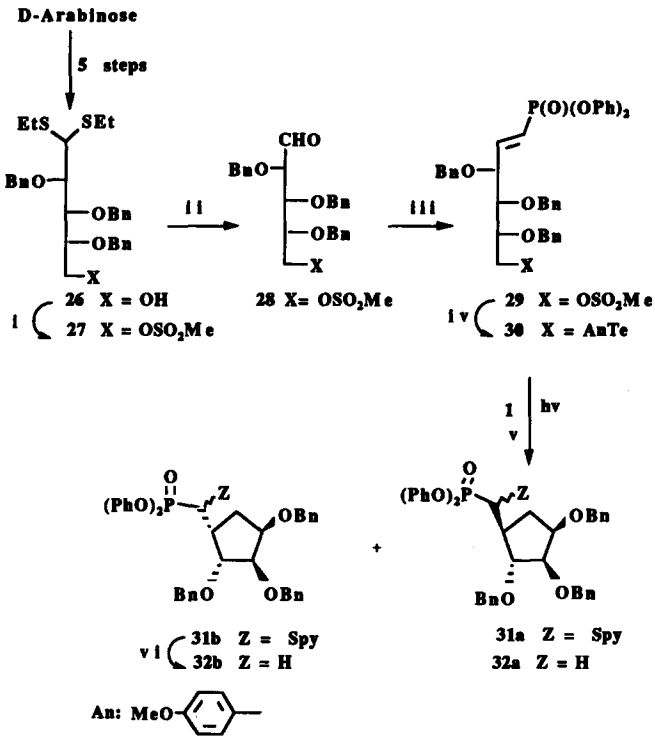


Scheme 6

This radical exchange process can also be applied to prepare cylopentanoid systems containing a phosphonate group. These compounds can be considered as precursors of carbocyclic analogues of sugars and nucleosides[14]. D-arabinose was transformed into the known[11] alcohol **26** (Scheme 7). This latter was mesylated in the usual way to give the crystalline mesylate **27** (91%). Dethioacetalization of **27** in the presence of mercury (II) chloride gave the crystalline aldehyde **28** (90%). The formation of the *E* olefin **29** was effected using a Wittig-Horner reaction in the presence of diphenyl[(triphenylphosphoranylidene) methyl]phosphonate[15] (60%). Treatment of **29** with anisyl telluride anion[12] afforded the crystalline telluride **30** (84%). This compound, when treated with methyl radicals generated by photolysis of N-acetoxy-2-thiopyridone, gave the expected carbocycles **31a** and **31b** as a mixture of 4 isomers (92%). Reduction of the thiopyridyl derivatives **31** using tri-*n*-butyltin and AIBN in reflux toluene furnished the phosphonates **32** (60%) as a mixture of two isomers. It was not possible to separate by chromatography the two diastereomers **32a** and **32b** but their ratio of 60:40 was determined NMR spectroscopy. Likewise as the cyclohexane derivatives **18**, we observed a low stereocontrol in this cyclization. This phenomenon was reported by Wilcox *et al*[3a] in the cyclization of *E* olefins.

In conclusion, the results presented in this paper clearly demonstrate that the radicals generated from anisyl telluride carbohydrates (D-galactose or D-arabinose) produce 6 or 5 membered metabolically more stable

carbocycles. These data should provide the impetus for further exploration of this radical chemistry from the readily accessible and cheap sugars.



i: $MeSO_2Cl$, DMAP, CH_2Cl_2; ii: $Hg(OAc)_2$, $CaCO_3$,iii: MeCN; $Ph_3P{=}CHP(O)(OPh)_2$, PhMe; iv: $(AnTe)_2$, $NaBH_4$, EtOH-THF; v: 1, hv, CH_2Cl_2. vi: Bu_3SnH, AINB, toluene.

Scheme 7

Experimental section

Column chromatography was carried out on silica gel 60 (0.040 - 0.063 μm). TLC analyses were performed on thin layer analytical plates 60F254 (Merck). Unless stated otherwise ^1H and ^{13}C and ^{31}P NMR spectra were recorded on Bruker WP200 SY (200 MHz) or at AC 250 (250 MHz). Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Coupling constants *J* are in Hz. Most spectra were taken in $CDCl_3$. In other cases the solvent is specified. Melting points were taken on a Reicher apparatus and are uncorrected. Routine mass spectra were recorded on an AEI MS50, AEI MS9 and Kratos MS80 (for FAB spectra). Elementary analyses were carried out in the Institut de Chimie des Substances Naturelles.

6-O-Trityl-D-galactose-diethyl dithioacetal 11

To a stirred solution of *D*-galactose diethyl dithioacetal **10** (46 g, 160 mmol.) in pyridine (500 ml), triphenylmethyl chloride (58.3 g, 1.3 eq.) and 4-dimethylaminopyridine (3.9 g, 0.2 eq.) were added. The reaction mixture was stirred at 70°C for a period of 4 h and was diluted with ethyl acetate (200 ml), washed with

water and then with a saturated sodium chloride solution. The organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-heptane, 3:7 and triethylamine 1%) to yield compound **11** (71 g, 84%). Anal.Calcd. for $C_{29}H_{36}O_5S_2$, C(65.88); H(6.86); S(12.13); Found. C(66.08); H(6.82); S(12.15). MS (FAB, NaCl, m/z): 551 $(M+Na)^+$, $[\alpha]_D^{20}$ = +45 (c=0.65, $CHCl_3$). ^{13}C NMR (50MHz, $CDCl_3$) δppm .143.5 (Cq Ph); 128.6, 128, 127.2 (Ph); 87.2 ($OCPh_3$); 72.5, 70.3, 70.0, 69,2 (*C*HOH); 66.4 (CH_2OCPh_3); 55.8 (*C*H); 25.5, 23.6 (2 CH_2CH_3); 14.6, 14.4 (2 CH_2CH_3).

2,3,4,5-Tetra-O-benzyl-6-O-trityl-D-galactose-diethyl dithioacetal **12**

A solution of tetrol **11** (40 g, 5.75 mmoles) in *N,N*-dimethylformamide (130 ml) was added dropwise at 0°C to a stirred suspension of sodium hydride (50% in oil) (19 g, 6.4 eq.) in *N,N*-dimethylformamide (20 ml). After stirring 30 min. at room temperature benzyl bromide (57.7 ml, 6.4 eq.) was added dropwise. After 3 h at room temperature, ethanol was added and the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$), filtered, evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-hexane, 5:95 and trietylamine 1%) to afford **12** (132 g, 95%). Anal. Calcd. for $C_{57}H_{60}O_5S_2$ C(76.99); H(6.80); S(7.21); Found. C(77.03); H(7.04); S(6.93). MS (FAB, NaCl, m/z): 911 $(M+Na)^+$, $[\alpha]_D^{20}$ = +4.8 (c=0.58, $CHCl_3$). ^1H RMN (250MHz) δppm 7.5-7.1 (m, 35H, Ph); 4.8-4.5 (m, 8H, 4 OCH_2Ph); 4.2 (dd, 1H, *CH*OBn, J= 7Hz, J = 5Hz); 3.98 (m, 2H, 2*CH*OBn); 3.9 (m, 2H); 3.6, 3.4 (2dd, 2H, CH_2OCPh_3, J= 10Hz, J= 4Hz, J= 6Hz); 2.7, 2.4 (2q, 4H, 2 CH_2CH_3); 1.2, 1.0 (2t, 6H, 2 CH_2CH_3). ^{13}C NMR (50MHz) δppm 144.1, 139.0, 138.8 (Cq Ph); 128.8, 128.2, 128.1, 127.8, 127.5, 127.2 (Ph); 87.1 ($OCPh_3$); 83.1, 81.2, 79.5 (*C*HOBn); 75.0, 74.7, 73.4 (CH_2Ph); 64.4 (CH_2OCPh_3); 54.6 (*C*H); 25.2, 24.9 (2 CH_2CH_3); 14.5, 14.4 (2 CH_2CH_3).

2,3,4,5-Tetra-O-benzyl-6-O-trityl-D-aldehydo-galactose **13**

To a solution of **12** (16 g, 18.41 mmol.) in 88 ml acetonitrile-water (10:1) was added calcium carbonate (7.3 g, 4 eq.) and mercuric (II) chloride (20 g, 4 eq.). The mixture was stirred at room temperature for 3 h. The solution was filtered through a celite pad and the filtrate was evaporated to dryness. The residue was dissolved in ether and the solution was washed with potassium iodide solution (30%), sodium thiosulfate solution (30%) and saturated sodium chloride solution. The organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-heptane, 3:7 and triethylamine 1%) to yield aldehyde **13** (9.3 g, 70%). IR (ν_{max}, neat) 1735 cm^{-1}. ^1H RMN (250MHz) δppm 9.7 (s, 1H, C*H*O); 7.5-7.0 (m, 35H, Ph); 4.7-3.9 (m, 11H, 4 OCH_2Ph, 4 *CH*OBn); 3.4, 3.1 (dd, 2H, CH_2OCPh_3, J= 10Hz, J =4Hz). ^{13}C NMR (62.5 MHz) δppm 200 (*C*HO); 143.1, 137.9, 137.1 (Cq Ph); 127.9, 127.7, 127.6, 127.4, 127.1, 126.8, 126.5, 126.3 (Ph); 86.4 ($OCPh_3$); 81.8-78.4 (*C*HOBn); 73.7, 72.3, 72.2, 71.4 (OCH_2Ph); 62.4 (CH_2OCPh_3).

(2R,3S,4S,5R)-2,3,4,5-Tetra-O-benzyl-6-O-trityl-1-diethylphosphonyl-hepten-1-pentol **14**

To a solution of tetraethymethylenediphosphonate (7.6 ml, 1.5 eq.) in dry tetrahydrofuran (30 ml) was added dropwise under argon, a solution of lithium bis(trimethylsilyl)amide 1M in tetrahydrofuran-cyclohexane (30 ml, 1.5 eq.). The mixture was stirred for 15 min. at room temperature and a solution of aldehyde **13** (16.3 g, 20.8 mmol.) in dry tetrahydrofuran (100 ml) was added. The reaction mixture was stirred for 3 h at room temperature and poured into ice-water. After extraction with methylene chloride, the organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-hexane, 3:7 and triethylamine 1%) to yield **14** as an yellow oil (15 g, 95%). Anal. Calcd. for $C_{58}H_{61}O_8P$ C(75.96); H(6.70); P(3.38); Found. C(75.69); H(6.87); P(3.04). MS (FAB, NaCl, m/z): 939 $(M+Na)^+$, $[\alpha]_D^{20}$ = +2.2 (c=0.85, $CHCl_3$). ^1H RMN (200MHz) δppm 7.7-7.1 (m, 35H, Ph); 6.75 (ddd, 1H, *CH*=CHP, J_{CH-P} = 22Hz, J = 17Hz, J = 5Hz); 5.8 (dd, 1H, CH=*CH*P, J_{CH-P} = 22Hz, J= 17Hz); 4.7-4.2 (m, 8H, 4 OCH_2Ph); 4.1 (t, 1H, *CH*OBn, J= 5Hz); 4.05-3.9 (m, 5H, 2 OCH_2CH_3, *CH*OBn); 3.8 (ttd, 1H, *CH*OBn, J= 5Hz); 3.7 (t, *CH*OBn, J= 5Hz); 3.4 (dd, 1H, *CH*OCPh$_3$, J= 5Hz, J= 10Hz); 3.2 (dd, 1H, *CH*OCPh$_3$, J= 5Hz, J = 10Hz); 1.3-1.1 (2t, 6H, 2 OCH_2CH_3). ^{13}C NMR (50 MHz) δppm 150.2 (*C*H=CHP); 143.9, 138.8 (Cq Ph); 128.7, 128.2, 127.9, 127.4 (Ph); 119 (CH=*C*HP, J_{C-P} = 185 Hz); 87.1 ($OCPh_3$); 81.4, 79.9, 79.7, 79.5

(*C*HOBn); 74.5, 73.2, 72.8, 71.4 (4 O*C*H_2Ph); 63.5 (*C*H_2OCPh$_3$); 61.7, 61.6 (2 O*C*H_2CH$_3$); 16.4, 16.3 (2 OCH$_2$*C*H$_3$).

(2R,3S,4S,5R))-2,3,4,5-Tetra-O-benzyl-1-diethylhosphonyl-hepten-1-pentol **15**

To a stirred solution of **14** (20.3 g, 22.16 mmol.) in 130 ml of ethyl acetate-methanol (1:1), *p*-toluenesulfonic acid (6.3 g, 1.5 eq.) was added at 0°C. The mixture was stirred for 4 h at room temperature and poured into saturated sodium hydrogen carbonate solution. After extraction with methylene chloride, the organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-hexane, 6:4) to yield **15** as an oil (11.5 g, 77%). Anal.Calcd. for $C_{39}H_{47}O_8P$ C(69.42); H(7.02); P(4.59); Found C(69.28); H(7.03); P(4.53). MS (FAB, m/z): 675 $(MH)^+$, $[\alpha]_D^{20}$ = +7.6 (c=1, $CHCl_3$). ^{1}H RMN (250MHz) δppm 7.4-7,2 (m, 20H, Ph); 6.9 (ddd, 1H, *CH*=CHP, J_{CH-P}= 22Hz, J = 17Hz, J = 5Hz); 6.1 (dd, 1H, CH=*CH*P, J_{CH-P} = 21Hz, J= 17Hz); 4.8-4.3 (m, 8H, 4 O*C*H_2Ph); 4.1-3.9 (2q, 4H, 2 O*C*H_2CH$_3$); 3.9-3.8 (m, 4H, 4 *C*HOBn); 3.75 (s, 2H, *C*H_2OH); 2.5 (s, 1H, OH); 1.3-1.1 (2t, 6H, 2 OCH$_2$*C*H$_3$). ^{13}C NMR (50 MHz) δppm 149.8 (*C*H=CHP); 138.3, 138.2, 138.0, 137.8 (Cq Ph); 128,5, 128.3, 127.8, 127.4 (Ph); 119.4 (CH=*C*HP, J_{C-P} = 149 Hz); 81.9-79.0 (*C*HOBn); 74.8, 73.6, 72.4, 72.0 (4 O*C*H_2Ph); 61.8, 61.7 (2 O*C*H_2CH$_3$); 61.2 (*C*H$_2$OH); 16.5, 16.4 (OCH$_2$*C*H$_3$).

(2R,3S,4S,5R))-2,3,4,5-Tetra-O-benzyl-6-O-methanesulfonyl-1-diethylphosphonyl-hepten-1-pentol **16**

To a solution of the alcohol **15** (3 g, 4.44 mmol) in dichloromethane (11 ml), 4-dimethylaminopyridine (0.813 g, 1.5 eq.) and mesylchloride (0.446 ml, 1.3 eq.) were added at 0°C. The mixture was stirred for 1 h at 0°C and 2 h at room temperature. The reaction mixture was diluted with methylene chloride and the solution was washed with a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution. The organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue containing **16** was used for the next step without further purification. ^{1}H RMN (250MHz) δppm 7.4-7,2 (m, 20H, Ph); 6.9 (ddd, 1H, *CH*=CHP, J_{CH-P}= 22Hz, J= 17Hz, J= 5Hz); 6.1 (dd, 1H, CH=*CH*P, J_{CH-P} = 22Hz, J = 17Hz); 4.8-4.3 (m, 8H, 4 O*C*H_2Ph); 4.1-3.9 (2q, 4H, 2 O*C*H_2CH$_3$); 4.4, 3.8 (m, 6H, *CH*OBn, *C*H_2SO$_2$); 2.8 (s, 3H, SO$_2$*C*H_3); 1.3-1.1 (2t, 6H, 2 OCH$_2$*C*H_3). ^{13}C NMR (50MHz) δppm 149.5 (*C*H=CHP); 137.8, 128.5, 127.9, 121.3 (Ph); 119.4 (CH=*C*HP, J_{C-P} = 149Hz); 81.9, 79.5 (*C*HOBn); 74.8, 73.6, 71.9, 70.6 (4 O*C*H_2Ph); 61.9, (O*C*H_2CH$_3$), (*C*H_2SO$_2$); 37.1 (SO2*C*H_3); 16.5 (OCH$_2$*C*H_3).

(2R,3S,4S,5R))6-Anisyl-telluro-2,3,4,5-tetra-O-benzyl-6-desoxy-1-diethylphosphonyl-hepten-1-tetrol **17**

To a stirred mixture of $NaBH_4$ (0.753 g, 3 eq) in degassed ethanol (20 ml) in a three necked flask at 0°C under argon was added dropwise a solution of An_2Te_2 (3.11 g, 1.5 eq.) in degassed tetrahydrofuran (30 ml). The red solution became colourless and the *O*-mesyl derivative **16** (5 g, 6.64 mmol) in dry and degassed tetrahydrofuran (30 ml) was added slowly. The reaction mixture was stirred at 40°C for 2 h and then water (30 ml) was added. The solvent was evaporated to dryness. After extraction with methylene chloride, the organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-heptane, 4.5:5.5) to yield **17** as an oil (4 g, 69% from 5). Anal.Calcd. for $C_{46}H_{53}O_8PTe$ C(61.91); H(5.99); P(3.47); Found: C(62.02); H(5.97); P(3.58). MS (FAB, LiCl, m/z): 899 $(M+Li)^+$, $[\alpha]_D^{20}$ = +4.2 (c=1.18, $CHCl_3$). ^{1}H RMN (250 MHz) δppm 7.6, 6.6 (d, 2H, Ph, J= 8Hz); 7.4-7.1 (m, 20H, Ph); 6.9 (ddd, 1H, *CH*=CHP, J_{CH-P} = 22.5 Hz, J= 17Hz, J = 5Hz); 6.1 (dd, 1H, CH=*CH*P, J_{CH-P} = 21Hz, J= 17 Hz, J= 1.5 Hz); 4.8-4.35 (m, 8H, 4 O*C*H_2Ph); 4.35-4.3 (m, 1H, *CH*OBn); 4.15 (dd, 1H, *CH*OBn, J= 3 Hz, J= 7 Hz); 4.0 (m, 4H, 2 O*C*H_2CH$_3$); 3.9 (m, 1H, *CH*OBn); 3.8 (dd, 1H, *CH*OBn, J= 7 Hz, J= 3Hz); 3.75 (s, 3H, O*C*H_3); 3.2 (dd, 1H, *CH*TeAn, J= 12 Hz, J= 5 Hz); 2.9 (dd, 1H, *CH*TeAn, J= 12 Hz, J= 7.5 Hz); 1.35-1.1 (2t, 6H, 2 OCH$_2$*C*H_3). ^{13}C NMR (62.5MHz) δppm 150.3 (*C*H=CHP); 141.2, 138.2, 115.3, 114.9, 128.5, 128.4, 128.3, 127.8, 127.6 (Ph); 119.3 (CH=*C*HP, J_{C-P} = 187.5 Hz); 81.0, 80.0, 79.8, 79.0 (*C*HOBn); 74.2, 73.8 (O*C*H_2Ph); 61.8, 61.8 (2 O*C*H_2CH$_3$); 55.2 (O*C*H$_3$); 16.5, 16.4 (2 OCH$_2$*C*H$_3$), 10.8 (*C*H$_2$TeAn).

(2R,3S,4S,5R)-3,4,5-Tri-O-benzyl-6-deoxy-1-C-diethylphosphonylmethyl-(R,S)-2,3,4,5-cyclohexanetetrol 18a, 18b (2R,3S,4S,5R)-2-O-Benzoyl-3,4,5-tri-O-benzyl-6-deoxy-1-C-diethylphosphonylmethyl-2,3,4,5-cyclohexanetetrol 19a, 19b

To a solution of **17** (0.2 g, 0.22 mmol.) in dry and degassed cyclohexane (1 ml) was irradiated with a halogen lamp (Xenophot , 100 W) and a solution *N*-acetoxy-2-thiopyridone (0.223, 6eq.) in dry and degassed dichloromethane was added dropwise for 2 h. The solvent was evaporated under reduced pressure and the residue was taken up in a mixture of ethanol-chloroforme (1:1). To this mixture, *p*-toluenesulfonic acid (0.142 g, 3.4 eq.) was added. After 12 h at room temperature, the solution was neutralized with Amberlite IRA 68. The solution was filtered and evaporated to dryness. The residue was purified on a silica gel column (gradient elution ethyl acetate-heptane, 2:8, 4:6) to yield the hydroxyl compounds **18a** and **18b** as an oil (0.056 g, 45%) in a ratio 4:6 and the benzoate derivatives **19a** and**19b** in a ratio 4.5:5.5 (0.027g, 20%). The ratio of isomers was determined by HPLC and confirmed by ^{31}P NMR.

Compound 18a

Anal. Calcd. for $C_{32}H_{41}O_7P$ C(67.59); H(7.26); P(5.44); Found C(67.37); H(7.12); P(5.31). MS (CI, m/z) 569 $(MH)^+$. $[\alpha]_D^{20}$ = -5.8 (c=0.94, CH_2Cl_2). ^1H RMN (200MHz) δppm 7.4-7.2 (m, 15H, Ph) ; 4.7-4.3 (m, 6H, 3 OCH_2Ph); 4.1 (2q, 4H, 2 OCH_2CH_3); 3.85 (m, 1H, *CH*OBn, J= 3 Hz); 3.7 (q, 1H, *CH*OBn, J= 3 Hz); 3.65 (t, 1H, *CH*OH, J= 5Hz); 3.62 (m, 1H, *CH*OBn); 2.42 (dtd, 1H, *CH*P, J_{CH-P} = 19 Hz, J= 15 Hz, J= 3 Hz); 2.32 (dt, 1H, CH_2, J= 3 Hz, J= 14 Hz); 2.15 (m, 1H, *CH*); 1.7-1.48 (m, 2H, CH_2, *CH*P); 1.32, 1.29 (2t, 6H, 2 OCH_2CH_3, J = 7 Hz). ^{13}C RMN (50MHz) δppm 138.4 (Cq, Ph); 128.4, 128.0, 127.8 (Ph); 81.7 , 74.9, 74.2 (*C*HOBn); 73 (*C*HOH); 72.7, 72.1, 70.5 (OCH_2Ph); 61.6 (OCH_2CH_3); 32.5 (*C*H); 29.4 (CH_2); 27.8 (CH_2P, J_{C-P} = 150 Hz); 16.5 (OCH_2CH_3).

Compound 18b

Anal. Calcd. for $C_{32}H_{41}O_7P$ C(67.59); H(7.26); P(5.44); Found C(67.84); H(7.38); P(5.25). $[\alpha]_D^{20}$ = -38 (c=1.21, CH_2Cl_2). ^1H RMN (200 MHz) δppm 7.5-7.1 (m, 15H, Ph); 4.9-4.5 (m, 6H, 3 OCH_2Ph); 4.12 (t, 1H, *CH*OH, J= 5 Hz); 4.05 (2q, 4H, 2 OCH_2CH_3); 3.89 (t, 1H, *CH*OBn, J= 3 Hz); 3.88 (dtd, 1H, *CH*OBn, J= 9 Hz, J= 4 Hz); 3.7 (m, 1H, *CH*OBn); 3.8 (dd, 1H, *CH*OBn, J= 3 Hz, J= 9 Hz); 2.3 (m, 1H, *CH*); 2.0-1.8 (m, 2H, CH_2P); 1.8-1.6 (m, 2H, CH_2); 1.3 (2t, 6H, 2 OCH_2CH_3). ^{13}C RMN (50 MHz) δppm 139 (Cq, Ph); 128.3-127.3 (Ph); 80.7, 78.6, 77.6 (*C*HOBn); 73.0, 72.4 (OCH_2Ph); 69.4 (*C*HOH); 61.9, 61.8 (OCH_2CH_3); 32.6 (CH_2); 30.9 (*C*H); 27.5 (CH_2P, J_{C-P} = 138 Hz); 16.5 (OCH_2CH_3).

Compound 19a

Anal. Calcd. for $C_{39}H_{45}O_8P$ C(69.63); H(6.74); P(4.60); Found C(69.69); H(6.82); P(4.54). IR (ν_{max}, neat) 1731 cm^{-1}. $[\alpha]_D^{20}$ = -3.2 (c=0.5, CH_2Cl_2). ^1H RMN (200 MHz) δppm 8.07 (d, 2H, PhCO, J = 8 Hz); 7.6-7.0 (m, 20H, Ph); 5.45 (t, 1H, *CH*OCOPh, J= 10 Hz); 4.9-4.3 (m, 6H, 3 OCH_2Ph); 4.05 (2q, 4H, 2 OCH_2CH_3); 3.85 (m, 2H, *CH*OBn, J= 10 Hz, J= 6 Hz); 3.7 (dd, 1H,*CH*OBn, J= 6 Hz, J= 3 Hz); 2.5 (m, 1H, CH_2); 2.4 (m, 1H, *CH*); 2.0 (ddd, 1H, *CH*P, J= 1.5 Hz, J= 15 Hz, J_{CH-P} = 21 Hz); 1.8-1.6 (m, 2H, CH_2, *CH*P); 1.25 (2t, 6H, 2 OCH_2CH_3). ^{13}C RMN (50 MHz) δppm 160.7 (*C*O); 132.9-127.6 (Ph); 79.3 (*C*HOCOPh); 76, 75.6, 74.6 (*C*HOBn); 73.3, 72.5, 70.7 (3 OCH_2Ph); 61.5 (2 OCH_2CH_3); 31.6 (*C*H); 29.7 (CH_2P); 26.5 (CH_2); 16.5 (OCH_2CH_3).

Compound 19b

Anal. Calcd. for $C_{39}H_{45}O_8P$ C(69.63); H(6.74); P(4.60); Found C(69.74); H(6.94); P(4.70). IR (ν_{max}, neat) 1731 cm^{-1}. $[\alpha]_D^{20}$ = +3.4 (c=0.38, CH_2Cl_2). ^1H RMN (200 MHz) δppm 7.95 (d, 2H, PhCO, J = 8Hz); 7.6-7.0 (m, 20H, Ph); 5.32 (t, 1H, *CH*OCOPh, J= 3 Hz); 4.85-4.25 (m, 6H, 3 OCH_2Ph); 4.15-3.9 (m, 6H, *CH*OBn, 2 OCH_2CH_3); 3.6 (dd, 1H, *CH*OBn, J= 3 Hz, J= 10 Hz); 2.65 (m, 1H, *CH*); 2.3 (tdd, 1H, CH_2, J= 13.5 Hz, J= 4.5 Hz); 2-1.75 (m, 2H, CH_2P); 1.75-1.55 (m, 1H, CH_2); 1.25 (2t, 6H, 2 OCH_2CH_3). ^{13}C RMN (50 MHz) δppm 138.3-127.6 (Ph); 80.5 (*C*HOCOPh); 77.0, 75.3 (*C*HOBn); 73.2, 73.0, 72.8 (OCH_2Ph); 61.8, 61.6 (2 OCH_2CH_3); 33.3 (*CH*); 29.3 (CH_2); 26.0 (CH_2P); 16.5 (2 OCH_2CH_3).

2,3,4-Tri-O-benzyl-5-O-methanesulfonyl-D-arabinose diethyl dithioacetal 27

To a solution of *2,3,4-Tri-O-benzyl-D-arabinose diethyl dithioacetal* **26** (4 g, 7.6 mmol) in dichloromethane (20 ml), 4-dimethylaminopyridine (1.39 g, 1.5 eq.) and mesylchloride (0.765 ml, 1.3 eq.) were added at 0°C. The mixture was stirred for 1 h at 0°C and 2 h at room temperature. The reaction mixture was diluted with methylene chloride and the solution was washed with a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution. The organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was cristallized from ether-pentane to afford **27** (4.2 g, 91%). Mp 42-43°C. Anal. Calcd. for $C_{31}H_{40}O_7S_3$ C(61.56); H(6.66); S(15.90); Found C(61.55); H(6.77); S(16.18). MS (FAB, LiCl, m/z) 611 $(M+Li)^+$; 509 $(MH-MsOH)^+$. $[\alpha]_D^{20}$ = +13 (c=1.3, CH_2Cl_2). ^1H RMN (200MHz) δppm 1.2 (t, 6H, SCH_2CH_3); 2,7 (m, 4H, SCH_2CH_3); 3.9 (m, 2H, CH_2OSO_2); 4.05 (d, 1H, *CH*, J= 5 Hz); 4.25 (t, 1H, *CH*OBn, J= 5 Hz); 4.36 (dd, 1H, *CH*OBn, J= 10 Hz); 4.5-4.9 (m, 7H, $3CH_2Ph$, *CH*OBn); 7.35 (sl, 15H, Ph). ^{13}C RMN (50 MHz) δppm 14.5 (SCH_2CH_3); 25.2; 25.6 (SCH_2CH_3); 37.4 (CH_3SO_2); 53.6 (*CH*); 69.1, 72.2, 75 (CH_2Ph, CH_2OSO_2); 78.2, 79.4, 82.6 (*CH*OBn); 127.8, 127.9, 128.3, 138 (Ph).

(2R, 3R, 4R)-2,3,4 -Tri-O-benzyl-5-O-methanesulfonyl-aldehydo-arabinose 28

To a solution of **27** (4.5 g, 7.45 mmol.) in 50 ml acetonitrile-water (10:1) was added calcium carbonate (2.97 g, 4 eq.) and mercuric (II) chloride (8 g, 4 eq.). The mixture was stirred at room temperature for 2 h. The solution was filtered through a celite pad. The filtrate was evaporated to dryness. The residue was dissolved in ether and the solution was washed with potasium iodide (30%), sodium thiosulfate (30%) and saturated sodium chloride solutions. The organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was cristallized from dichloromethane-ether-pentane to yield aldehyde **28** (3.35 g, 90%). Mp 58-59°C. Anal. Calcd. for $C_{27}H_{30}O_7S_3$ C(65.04); H(6.06); S(6.43); Found C(64.65); H(6.15); S(6.38).IR (ν_{max}, nujol) 1742 cm^{-1}. $[\alpha]_D^{20}$ = -18 (c=1, CH_2Cl_2). ^1H RMN (200MHz) δppm 9.66 (s, 1H, *CH*O); 7.33 (sl, 15H, Ph); 4.75-4.26 (CH_2Ph, *CH*, $2CH$OBn); 4.0-3.8 (m, 2H, CH_2OSO_2); 2.83 (s, 3H, CH_3SO_2). ^{13}C RMN (50MHz) δppm 37.3 (CH_3SO_2); 67.7 (CH_2OSO_2); 72.3, 73.2, 74 (CH_2Ph); 76.3, 77.9, 83.2 (*CH*OBn); 127.9, 128.2, 128.3, 128.4, 138 (Ph); 201.8 (*CH*O).

(2R, 3R, 4R)-2,3,4-Tri-O-benzyloxy-5-O-methanesulfonyl-1-diphenylphosphonyl-hexen-1-tetrol 29

To a stirred solution of aldehyde **28** (2,3 g, 4,61 mmoles) in dry toluene (30 ml) diphenyl[(triphenylphosphoranylidene)methyl]phosphonate 3.5 g, 1.5 eq.) was added under argon. The reaction mixture was heated under reflux for 3 h and the solvent was evaporated under reduced presssure. The residue was purified on a silica gel column (ethyl acetate-heptane, 1:1) to yield the crystalline **29** (1.965 g, 60%). Mp 45-46°C (from dichloromethane-ether-pentane). Anal. Calcd. for $C_{40}H_{41}O_9PS$ C(65.92); H(5.67); P(4.25); S(4.39); Found C(66.08); H(5.63); P(4.01); S(4.38). MS (FAB, m/z) 611 (MH^+). $[\alpha]_D^{20}$ = -5 (c=0.93, CH_2Cl_2). ^{13}C RMN (50MHz) δppm 37.3 (CH_3SO_2); 68.5 (CH_2OSO_2); 71.8, 72.5, 74.8 (CH_2Ph); 76.8, 78.6, 79.5 (*CH*OBn); 115.5, 116.5, 120.5, 120.6, 125.4, 128.0, 128.1, 128.3, 128.5, 129.9, 152.8, 152.9 [Ph, *CH*=*CH*-P(O)(OPh)$_2$].

(2R, 3R, 4R)-5-Anisyltelluro-2,3,4-tri-O-benzyloxy-5-O-methanesulfonyl-1-diphenylphosphonyl-hexen-1-triol 30

To a stirred mixture of $NaBH_4$ (0.478 g, 3 eq) in degassed ethanol (15 ml) in a three necked flask at 0°C under argon was added dropwise a solution of An_2Te_2 (2.94 g, 1.5 eq.) in degassed tetrahydrofuran (40 ml). The red solution became colourless and the *O*-mesyl derivative **29** (3.05 g, 4.19 mmol) in dry and degassed tetrahydrofuran (40 ml) was added slowly. The reaction mixture was stirred at 40°C for 2 h and then water (30 ml) was added. The solvent was evaporated to dryness. After extraction with methylene chloride the organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-heptane, 3:7) to yield the crystalline **30** (3.05 g, 84%). Anal. Calcd. for $C_{46}H_{45}NO_7PTe$ C(63.62); H(5.22); P(3.56); Found C(63.84); H(5.46); P(3.86). MS (FAB, NaCl m/z): 870 $(MH)^+$, $[\alpha]_D^{20}$ = +41. (c=1, $CHCl_3$).Mp 79°C (dichloromethane-pentane) ^1H RMN (250MHz) δppm 7.6 (d, 2H, Ph); 7.2 (m, 26H, Ph, *CH*=CHP); 6.66 (d, 2H, Ph); 6.26 (dd, 1H, CH=*CH*P, J= 17 Hz, J_{CH-P}= 22 Hz); 4.56-4.16 (2m, 8H, $3CH_2Ph$, *CH*OBn); 3.83 (m, 1H); 3.75 (s, 3H, PhOCH_3); 3.25 (ddd, 2H,CH_2TeAn). ^{13}C NMR (50

MHz) δppm 10.0 (CH_2TeAn); 52.8 (PhOCH_3); 69.5, 69.8, 72.6 (CH_2Ph); 77.1, 77.7, 81.2 (CHOBn); 114.0, 114.5, 118.5, 119.5, 124.1, 126.6, 126.8, 127.0, 127.5, 128.7, 136.7, 152.4 [Ph, CH=CH-P(O)(O*Ph*)$_2$].

(2S,3R,4R)-1,2,3-tri-O-benzyl-1-C-(R,S)-diphenylphosphonyl-(2'-thiopyridyl)-methyl-cyclopentanetriol-2,3,4 ***31a , 31b***

A solution of **30** (1.67 g, 1.926 mmol.) in dry and degassed dichloromethane (12 ml) and *N*-acetoxy-2-thiopyridone (1.3 g, 4eq.) was irradiated under argon with halogen lamps (2x150 W) for 1 h 30 at a temperature between 20°C and 40°C. The solvent was evaporated under reduced pressure and the residue purified on a silica gel column (ethyl acetate-heptane, 3.7) to yield the cyclic compound **31** as an oil (1.31 g, 92%). MS (FAB, m/z): 744 $(MH)^+$; 633 $(MH\text{-}Spy)^+$; 112 $(Spy+H)^+$. ^{1}H RMN (250MHz) δppm 8.5-7.0 (m, 29H, Ph, Py); 4.6-4.35 (m, 6H, CH2Ph); 4.3-2.8 (m, 4H); 2.5-2.0 (2H). ^{31}P NMR δppm 16.9, 15.9.

(2S,3R,4R)-1,2,3-tri-O-benzyl-1-C-(R,S)-diphenylphosphonylmethyl-cyclopentanetriol-2,3,4 ***32a and 32b***

A solution of **31** (0.25 g, 0.336 mmol.) was dissolved in dry toluene (2 ml) under an argon atmosphere. 0.36 ml of Bu_3SnH (1.34 mmol) and 5 mg of 2,2'-Azobisisobutyronitrile (AIBN) (0.034 mmol.) were then added. The solution was boiled, concentrated and purified on a silica gel column. The solvent was evaporated under reduced pressure and the residue purified on a silica gel column (ethyl acetate-heptane, 3.7) to yield the reduced compound **32** (60%) as inseparable isomers trans and cis in a ratio 60:40 respectively. MS (C.I, m/z): 635 $(MH)^+$. ^{13}C NMR (75 MHz) δppm 138.3, 129.8-120.6 (Ph); 87.9, 87.6 (CHOBn); 83.6, 83.0 (CHOBn); 76.7 (CHOBn); 72.4-71.3 (CH_2Ph); 35.3, 32.7 (CH); 34.7 (CH_2, J^3_{CP}= 8 Hz, isomer 32b), 33.5 (CH_2, J^3_{CP}= 4.2 Hz, isomer 32a), 31.5, 26.4 (CH_2P, J^1_{CP}= 139 Hz). ^{31}P NMR δppm 23.9, 21.9. Anal. Calcd. for $C_{39}H_{39}O_6P$ C(73.80); H(6.19); P(4.58); Found C(73.20); H(6.08); P(4.28).

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