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From Carbohydrates to Carbocycles: Radical Routes *via* Tellurium Derivatives

Derek H. R. Barton,[a] José Camara,[b] Xiaoqin Cheng,[a] Stephane D. Géro,[b] Joseph Cs. Jaszberenyi*[a,c] and Beatrice Quiclet-Sire*[b]

[a]Department of Chemistry, Texas A&M University, College Station, Texas 77843

[b]Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France.

[c]Research Group for Antibiotics of the Hungarian Academy of Sciences, Lajos Kossuth University, H-4010 Debrecen, Hungary.

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Abstract: D-Ribose was transformed to its protected tosylate **15**, followed by a Wittig-reaction to give **16** as a 3:1 mixture of the corresponding **Z** and **E** isomers. This mixture was then transformed to the anisyltelluride **17** and the latter cyclized in a radical exchange reaction to a mixture of the carbocycles **18a** and **18b** (in a 17:2 ratio). The major product **18a** was then transformed to various chiral cyclopentane derivatives including the cyclopentenone-derivative **23**. Various other carbohydrate-based approaches have also been explored.

The synthesis of various chiral carbocyclic derivatives from carbohydrates (the 'chiral pool')[1] has been a synthetic challenge for some time in organic chemistry. The idea behind the use of radical chemistry to achieve this goal is related to the mildness of radical reactions and their compatibility with various functional groups sensitive to ionic processes[2]. It is also known that a given ε-unsaturated carbon radical (5-hexenyl radical) will cyclize with preference for the formation of a cyclopentylmethyl radical[3]. This means that a suitably substituted precursor of a 5-hexenyl radical could lead to chiral carbocycles. This idea has indeed been utilized by Wilcox for the cyclization of a halide-generated radical[4]. However, the method employs the classic Bu_3SnH/AIBN reagent pair that has the obvious drawbacks associated with the use of tin reagents.

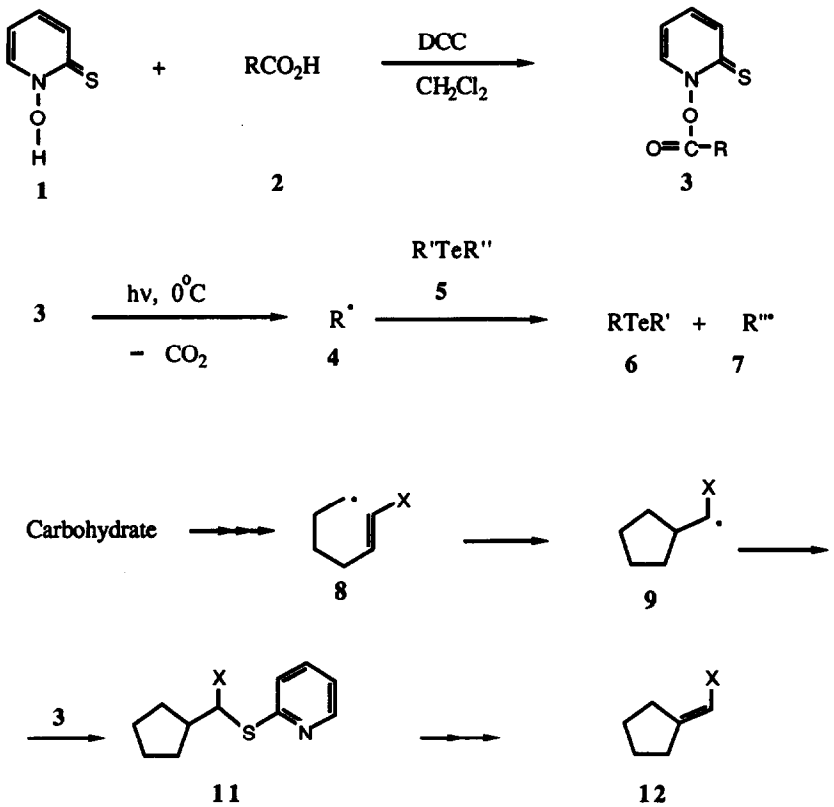
Various pseudo-sugar derivatives have been synthesized employing this methodology. The term pseudo-sugar is used to describe naturally occurring or synthetic compounds in which the ring oxygen (furanoses or pyranoses) has been replaced by a methylene group. These compounds often exert their biological properties by mimicking their parent oxygenated counterparts. They exhibit resistance to enzymes responsible for their catabolism and inactivation[5].

Since the pioneering and enlightened work of H. O. L. Fischer[6] on cyclitols, many carbocyclic analogues of furanosides, pyranosides and nucleosides have been prepared[7]. In contributions more closely related to our own research programs, several groups have described methodologies generating carbocycles from carbohydrate derived precursors. For example, Kiely and Fletcher[8] cyclized D-xylo-hexo-5-ulose into inositols by

nonenzymatic biomimetic means. Ferrier's elegant rearrangement[9] was frequently used for the preparation of cyclohexanoid derivatives.

We have shown earlier that O-acyl derivatives of N-hydroxy-2-thiopyridone are an excellent source of disciplined carbon radicals[10]. Later it was also demonstrated, that nitrogen-centered[11] and various oxygen-centered[12] radicals can also be generated from these precursors. These O-acyl N-hydroxy-2-thiopyridone derivatives form radicals easily upon photolysis with visible light. We have also shown that these reactions have quantum yields in the region of Φ = 10-30 indicating their potential in Organic Synthesis[13]. Indeed, there are several successful synthetic applications of this methodology[14]. We conceived that a carbon radical, generated by this method could generate by radical exchange more complex carbon radicals. We showed the feasibility of this idea using organic tellurides as exchangers of carbon radicals.[15,16] We have summarized the background information related to this synthetic plan in Scheme I.

Scheme I



Thus, a given acid **2** is transformed to the corresponding O-acyl N-hydroxy-2-thiopyridone derivative **3** and photolysed to provide the first radical **4**. This is preferably a reactive primary radical, like Me·. This radical reacts with the radical exchanger tellurium compound **5**, formed in this case from a suitably substituted

carbohydrate. Anisyl tellurides of carbohydrates are easily prepared and were recently used for the synthesis of showdomycin[16], cyclonucleosides[17] and for the preparation of simple six-membered carbocycles[18]. The exchange process ideally provides the new telluride **6** and the carbohydrate radical **7**. The latter, in turn, undergoes the '5-hexenyl radical' cyclisation (**8** to **9**) process as shown in Scheme I. This adduct radical then reacts with the O-acyl N-hydroxy-2-thiopyridone derivative **3**, producing another primary radical as well as the endproduct of the radical reaction **11**, thereby carrying the radical chain. There are various possibilities for the transformation of **11** depending on the nature of the activating group X, used to make the double bond electron-deficient in **8**. Oxidation/elimination results in the formation of products of type-**12**. This olefin can be transformed into various cyclopentanone and cyclopentenone derivatives.

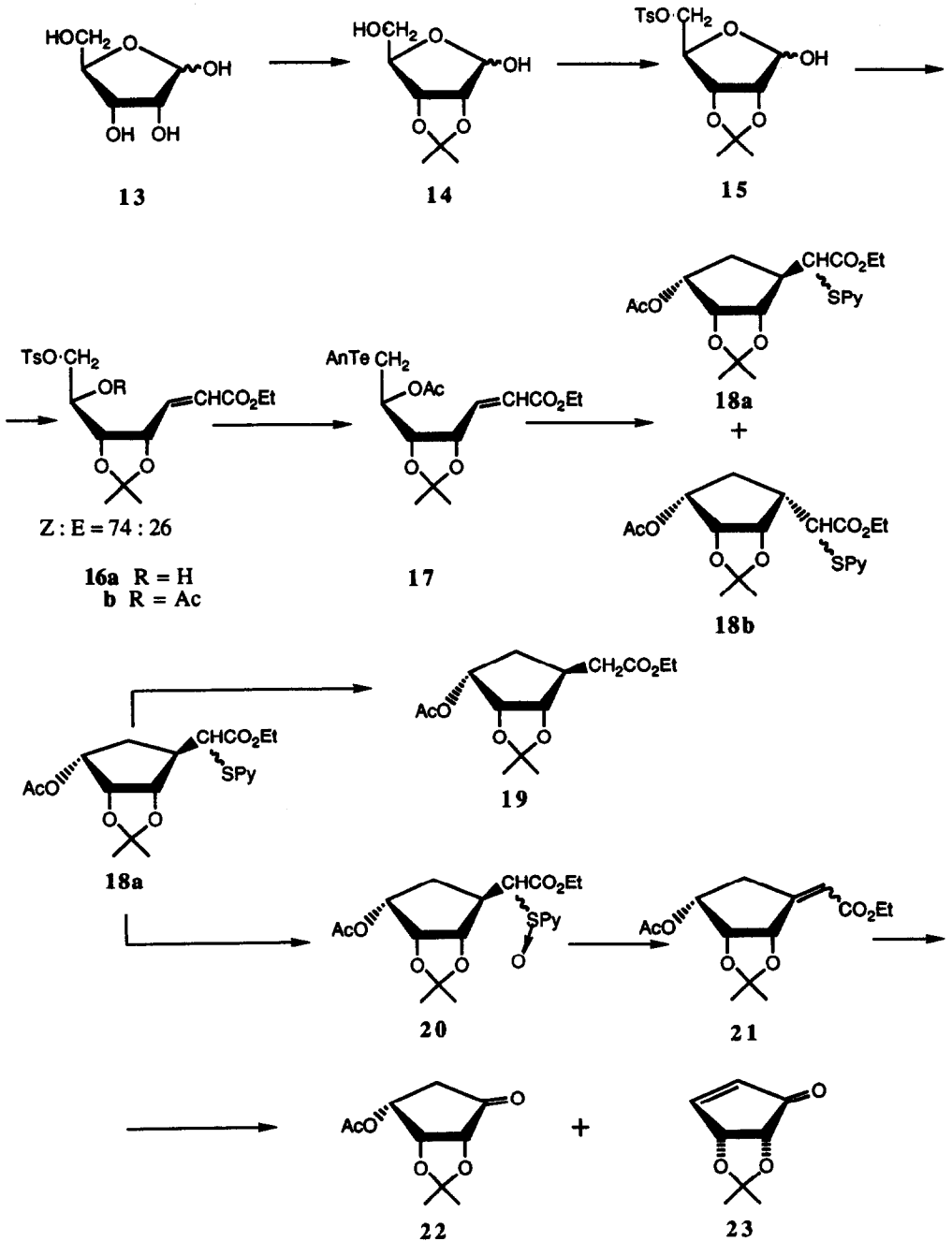
Thus, Scheme II, D-ribose **13** was transformed via **14** to the known 2,3-di-O-isopropylidene tosylate **15**, followed by a Wittig-reaction to furnish the olefin **16a** as a 74:26 mixture of the Z:E isomers. This compound was then acetylated to **16b** and transformed to the p-anisyltelluride derivative **17**. This compound, when treated with methyl radicals generated from O-acetyl N-hydroxy-2-thiopyridone did indeed undergo formation and cyclization of the carbohydrate radical as expected, giving rise to a mixture of the carbocycles **18a** (76%) and **18b** (9%).

The stereochemical preference for **18a** was predicted from our earlier studies,[10,16] where a dimethylketal function exerted a strong steric effect in directing the formation of a new center of chirality. In the case of **18a** the effect is reinforced by the acetate function being also on the same side of the five-membered ring as the dimethylketal function. This compound can then be transformed to the cyclopentylacetic acid derivative **19** (88%) or to the acrylate **21** (88%, Z:E = 38:62) *via* the sulfoxide **20** (95%). Ozonolysis of the acrylate **21** at -78°C, followed by treatment with Me_2S resulted in the formation of the cyclopentanone derivative **22** (14%) and of the cyclopentenone **23** (71%). It is clear that the cyclopentenone **23** was not formed during ozonolysis, but resulted from a β-elimination process during the work-up.

This finding demonstrates an efficient transformation of carbohydrates to cyclopentenone and cyclopentane derivatives utilizing the phenomena of photolytic radical generation, radical exchange using tellurium compounds and intramolecular trapping of carbon radicals. The chirality and functional groups of the carbocyclic product are determined by the starting carbohydrate molecule.

We have assumed that the required anisyl tellurides could be obtained either by opening an epoxide function or by displacing a tosylate group by the anisyl telluride anion.[19] Starting from D-ribonolactone **24** the known ketal[20] **25** and thence the derived iodide[20] **26** were prepared[21] (Scheme III). Reductive elimination afforded the known acid[22] **27**. This acid was converted to its N-hydroxy-2-thiopyridone derivative which on photolysis in the presence of phenyl vinyl sulfone gave the adduct **29** *via* radical **28**. Without purification the thiopyridyl group was oxidised to the mixed sulfoxides (75%) which on thermal elimination gave vinyl sulfone **30**.

Scheme II


HOCH2
OH
OH OH
13
HOCH2
OH
14
TsO·CH2
OH
15
TsO·CH2
OR
CHCO2Et
Z : E = 74 : 26
16a R = H
b R = Ac
AnTe CH2
OAc
CHCO2Et
17
AcO
CHCO2Et
SPy
18a
+
AcO
CHCO2Et
SPy
18b
AcO
CHCO2Et
SPy
18a
AcO
CH2CO2Et
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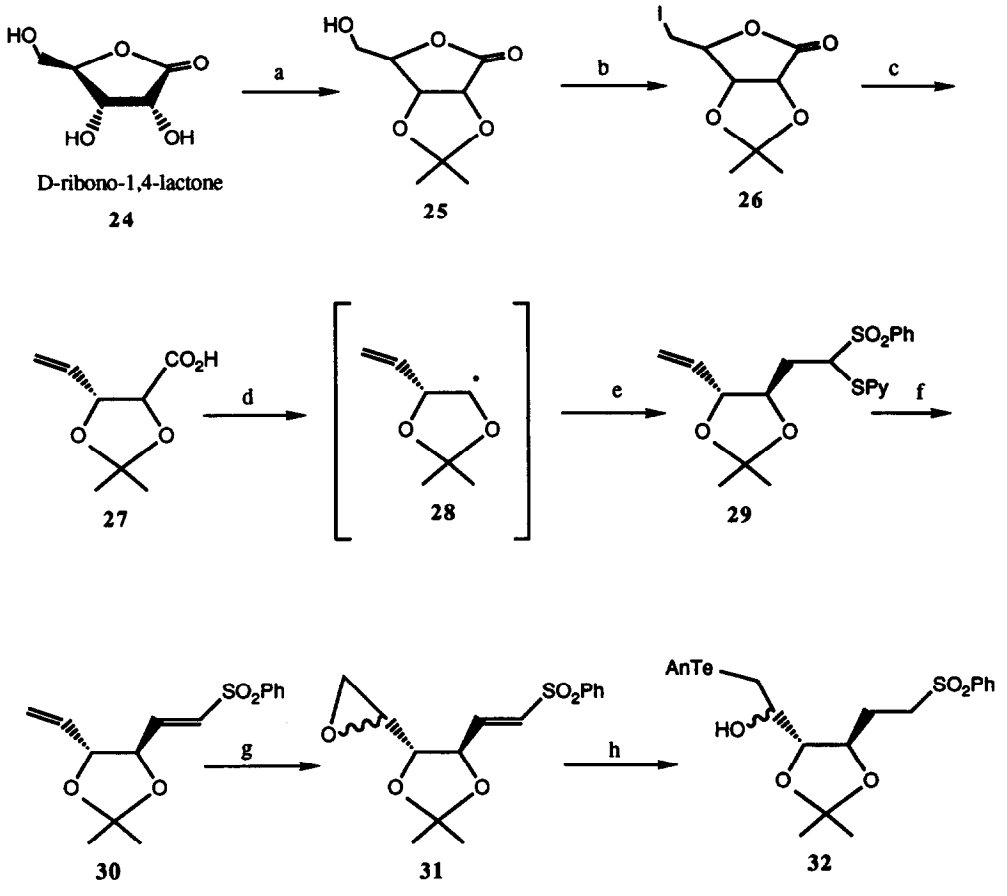
23

Scheme III



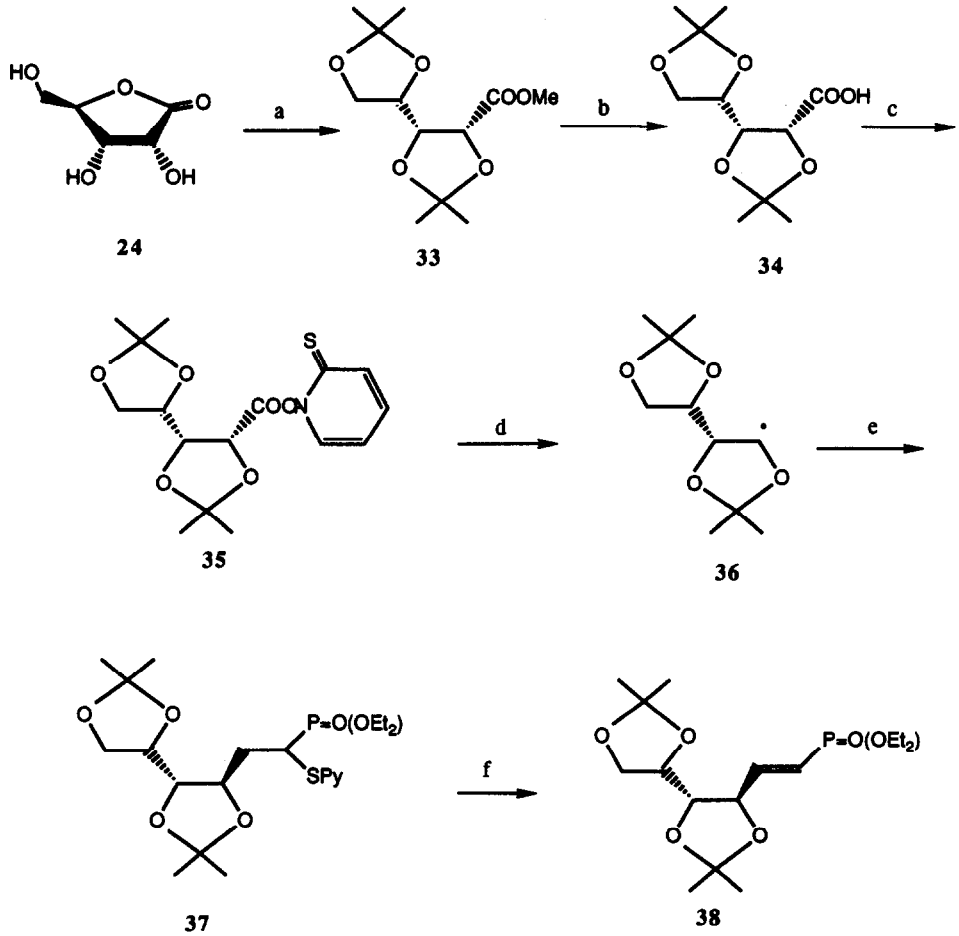
a: $Me_2C(OMe)_2$, Me_2CO, MeOH, PTSA; b: PPh_3, imidazole, iodine; c: Cu-Zn, $Me_2C{=}O$, reflux;
d: 1) $Me_2ChCH_2OC{=}OCl$, N-Me-morpholine, N-hydroxy-2-thiopyridone sodium salt; 2) h ν, CH_2Cl_2;
e: $PhSO_2CH{=}CH_2$; f: 1) MCPBA, 0°C, $CHCl_3$, 2) toluene, reflux; g: MCPBA, 50°C, $CHCl_3$;
h: An_2Te_2, EtOH, THF, sodium borohydride.

Stereochemical complications in the epoxide **31** and in **32** made us decide to examine an alternative approach and, because phosphonate groups are more interesting biologically, we chose to work with a vinylphosphonate (Scheme IV). D-ribonolactone **24** was converted to the diketal ester **33** in one step (82%).[23] Alkaline hydrolysis gave the acid **34** which was converted to the radical **36** in the usual way (*via* **35**).[24] This

radical **36** was trapped by diethyl vinylphosphonate[25] to give the adduct **37**. Peracid oxidation and elimination then gave vinylphosphonate **38**.

The radical chemistry produces stereoselectively the trans addition product. Such compounds cannot be cyclized to five-membered rings by radical cyclisation. In principle this could be done by changing the ring ketal function to (say) acetate protection. However, changing protecting groups is not an elegant solution to the problem. The sequence described in the first section from D-ribose (Scheme II) of the paper is more convenient.

Scheme IV



24 33 34 35 36 37 38

a: $Me_2C(OMe)_2$, Me_2CO, MeOH, p-toluenesulfonic acid; b: NaOH/H_2O; c: $Me_2CHCH_2OC{=}OCl$, N-Me-morpholine, N-hydroxy-2-thiopyridone sodium salt; d: h ν, CH_2Cl_2; e: $CH_2{=}CHP{=}O(OEt)_2$; f: 1) MCPBA, 0°C, $CHCl_3$,2) toluene, reflux;

Experimental Section

General Procedures and Starting Materials.

Melting points were determined with a Kofler hot-stage melting point apparatus or on a Reicher apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 spectrophotometer. UV spectra were recorded on a Beckman DU-7 spectrometer. Specific rotations were determined on a Jasco DIP-360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were determined for solutions in deuteriochloroform (unless specified otherwise) with TMS internal reference on Varian Gemini 200, Varian XL 200E or Varian XL 400 spectrometer and a Bruker WP200 SY (200 MHz) instrument. Gas chromatography (glc) measurements were performed on a Chrompack Packard Model 439 gas chromatograph on 30 m capillary columns. GC-MS data were obtained on a Hewlett-Packard 5890 GC-MS system. Mass spectra were obtained on a VG Analytical 70S high resolution double focusing magnetic sector mass spectrometer with attached VG 11/250J data system in the EI or FAB mode. FAB spectra were obtained neat or in glycerol matrix. Routine mass spectra were recorded on an AEI MS50, AEI MS9 and Kratos MS80 (for FAB spectra). TLC analysis was performed on thin layer analytical plates $60F_{254}$ (Merck). Column chromatography was carried out on silica gel 60 (0.040 - 0.063 mm). Microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia or at the Institut de Chimie des Substances Naturelles. Solvents were used either as purchased or dried and purified by standard methodology. N-hydroxy-2-thiopyridone was isolated from its sodium salt (Omadine^{R}). A 40% solution of the sodium salt of N-hydroxy-2-thiopyridone was a kind gift of the Olin Corporation, Cheshire, CT. Other reference compounds and starting materials were purchased from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin.

All water and air sensitive reactions were performed under an argon atmosphere in oven-dried glassware.

Tetrahydrofuran (THF, Fisher Scientific) and benzene (Fisher Scientific) were distilled from sodium benzophenone ketyl under nitrogen immediately before use. Methylene chloride (CH_2Cl_2, J. T. Baker or Mallinckrodt) was distilled from CaH_2 under nitrogen immediately before use. Absolute ethanol (Aaper Alcohol and Chemical Co., 200 proof) was degassed with argon and sealed with a septum prior to use. Pyridine (Fisher Scientific) and triethylamine (Aldrich) were distilled from KOH prior to use, and stored over 4 Å molecular sieves. Dry dimethoxyethane (DME) and absolute methanol were dried over 4 Å molecular sieves.

Chromatographic solvent systems are indicated in the text. The visualizing agent solution used for determining the presence of organotellurides was a palladium spray, consisting of 5% $PdCl_2$ in diluted HCl solution. Upon treatment with this solution, organotellurides will become colored from bright yellow to dark orange.

2,3-O-isopropylidene-D-ribofuranose 14.

This compound was prepared by the published procedure from D-ribose.[26] Thus 12 g D-ribose **13** was transformed to 12.03 g (78% after purification on a silica column using ethyl acetate : hexanes = 1:1 as eluent, lit.

59%) of **14**, obtained as a colorless oil. IR ν_{max} (neat) 3451, 2980, 2112, 1671, 1041 cm^{-1}; ^1H NMR 1.22 (s, 3H, Me), 1.38 (s, 3H, Me), 3.6 (m, 2H, H-5), 4.27 (t, 1H, J = 3, H-4), 4.37 (t, 1H, J = 6, OH), 4.46 (d, 1H, J= 6, H-3), 4.69 (d, 1H, J = 6, H-2), 5.29 (d, 1H, J = 6, H-1), 5.73 (d, 1H, J = 6, OH); ^{13}C NMR 24.5, 26.2, 63.3, 81.5, 86.5, 87.4, 102.5, 112.0; MS 175 (M^+-15).

2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribofuranose 15.[27,28]

The title compound **15** was prepared from **14**. Thus, 4.70 g (0.025 mol) of **14** was dissolved in 30 mL of pyridine at 0 °C, and then 7.0 g (0.037 mol) of TsCl was added in portions. The reaction mixture was stirred for 10 hours at 0 °C. 100 mL of ethyl acetate was then added and the solution was washed with a 10% H_2SO_4 solution several times until it was neutral, which was then extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated to get a white crystalline solid. Recrystallization from methylene chloride/ethyl ether/hexanes afforded colorless needles (6.19 g, 72%): mp 95 - 96 °C; IR ν_{max} (neat) 3482, 2986, 2944, 1595, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.26 (s, 3H, i-prop), 1.42 (s, 3H, i-prop), 2.43 (s, 3H, OCH_3), 3.10 (s, 1H, OH), 3.97 - 4.16 (m, 2H, 2H-5), 4.22 (m, 1H, H-4), 4.54 - 4.72 (m, 2H, H-2 and H-3), 5.26 (d, 1H, *J* = 4.0 Hz, H-1), 7.34 (dd, 2H, *J* = 7.6 Hz, ArH), 7.75 (d, 2H, *J* = 7.6 Hz, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 22.13, 25.12, 25.32, 26.53, 26.83, 70.45, 71.13 (C-5), 78.76, 79.55, 81.57, 81.97, 84.40, 86.15, 98.16, 103.6, 113.2 (*C* Me_2), 128.3, 130.4, 130.5, 143.0.

Wittig reaction of 15. Synthesis of Olefin 16a.

The tosylate **15** (4.0 g, 11.6 mmol) was dissolved in dry dimethoxyethane (30 ml, dried over molecular sieves), placed under argon in a round bottom flask and reacted with the phosphorane $Ph_3P{=}CHCO_2Et$ (8.0 g, 23 mmol) at room temperature for 24 hours. Then the reaction mixture was concentrated in vacuum and the product was purified on silica gel (EtOAc/hexanes = 1:1) to give a colorless oil (4.76 g, 99%) as a 74:26 mixture of Z (**16a**) and E (**16a**). IR ν_{max} (neat) 3471, 2987, 1709, 1640, 1596, 1063 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) for the mixture: 1.24 (s, 3H), 1.36 (s, 3H), 2.38 (s, 3H), 3.16-3.27 (dd, 1H, J_1 = 4.0, J_2 = 5.5), 3.6-3.8 (m, 1H), 4.02 (m, 2H), 4.12 (q, 2H, J = 5.5) 4.18 (m, 1H), 4.79 (m, 1H), 5.51 (dd, J_1 = 7.8, J_2 = 6.5), 5.88-6.21 (m), 6.97 (ddd, J_1 = 15.5, J_2 = 4.8, J_3 = 1.8), 7.29 (d, 2H, J = 8), 7.73 (d, 2H, J = 8); ^{13}C NMR ($CDCl_3$, δ, ppm) 14.52, 14.61, 22.03, 25.65, 28.07, 60.80, 61.50, 68.98, 72.29, 74.91, 78.57, 110.0, 123.1, 128.4, 130.2, 130.3, 145.2, 145.3, 167.0.

Synthesis and Radical Chemistry of Telluride 17.

The tosylate **16a** (R = H) (4.137 g, 10 mmol) was dissolved in dry pyridine (4.0 ml) and treated with acetic anhydride (4.5 ml) at 50°C for 30 min. Then the reaction mixture was concentrated in vacuum and the

acetylated product **16b** (R = Ac) was isolated on a silica column as a colorless oil (4.417 g, 97%).[29] A 74 : 26 mixture of *Z* and *E* isomers was obtained from 4.137 g (10 mmol) of **16a**: IR ν_{max} (neat) 2985, 2939, 1745, 1717, 1650, 1596, 1449, 1413, 1368, 1307, 1218, 1189, 1176, 1095, 1060, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.24 (t, 3H, OCH_2CH_3), 1.25 (s, 3H, i-prop), 1.32 (s, 3H, i-prop), 1.84 (s, 3H, OAc), 2.38 (s, 3H, OCH_3), 4.10 (m, 4H, 2H-5 and OCH_2Me), 4.47 (t, 1H, J = 6.6 Hz, H-3), 4.80 (m, 1H, H-4), 5.62 (dt, 1H, J_1 = 6.8 Hz, J_2 = 1.3 Hz, H-2), 5.81 (dm, 1H, J = 11.5 Hz, $=CHCO_2Et$), 6.05 (m, 1H, H-1), 7.28 (d, 2H, H = 8.1 Hz, ArH), 7.71 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 14.60, 20.98, 21.21, 22.03, 25.29, 25.64, 27.77, 28.02, 60.98, 61.07, 68.41, 68.96, 69.46, 74.82, 75.53, 76.19, 109.8, 110.1, 123.1, 128.4, 130.2, 133.4, 140.2, 143.7, 145.2, 165.5, 166.0, 170.0; MS (EI) *m/z* 380, 344, 271.

General Procedure *A* for the Conversion of Tosylates to Tellurides.[16]

In a dry three-neck round bottom flask, 27 mg (0.71 mmol) of $NaBH_4$ was dissolved in 3 mL of absolute ethanol with stirring under an argon atmosphere, and the solution was warmed to 50 °C. Then 226 mg (0.48 mmol) of An_2Te_2 solution in 5 mL of THF and the solution of the corresponding tosylate (0.533 mmol) in 5 mL of THF were transferred into the flask dropwise. The reaction mixture was heated for an hour at 50 °C, concentrated, and purified on a silica gel column (4 : 1 hexanes : ethyl acetate to 2 : 1 hexanes : ethyl acetate).

General Procedure *B* for the Conversion of Tosylates to Tellurides.[16]

In a dry three-neck round bottom flask, 27 mg (0.71 mmol) of $NaBH_4$ was dissolved into 3 mL of absolute ethanol with stirring under an argon atmosphere. Then 226 mg (0.48 mmole) of An_2Te_2 solution in 5 mL of THF and 0.533 mmol of the corresponding tosylate (a solution in 5 mL of THF) were transferred into the flask dropwise. The reaction mixture was stirred for 10 hours at 0 °C, concentrated, and purified on a silica gel column (4 : 1 hexanes : ethyl acetate to 2 : 1 hexanes : ethyl acetate).

Tellurides 17a and 17b.

The title compounds were synthesized from **16b** by general procedure *A*.[16] **17a** was obtained as a light yellow oil (*Z* isomer, 61%): $[\alpha]^{25}_D$ = -11.3° (c = 5.9, $CHCl_3$); IR ν_{max} (neat) 2985, 2938, 1736, 1716, 1643, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.28 (t, 3H, J = 7.0 Hz, $OCH2CH_3$), 1.34 (s, 3H, i-prop), 1.45 (s, 3H, i-prop), 1.84 (s, 3H, OAc), 2.92 (dd, 1H, J_1 = 4.5 Hz, J_2 = 13.5 Hz, H-7), 3.13 (dd, 1H, J_1 = 4.5 Hz, J_2 = 13.5 Hz, H-7), 3.77 (s, 3H, OCH_3), 4.17 (q, 2H, J = 7.3 Hz, CH_2CH_3), 4.19 (dt, 1H, H-5), 4.93 (m, 1H, H-6), 5.69 (m, 2H, $=CHCO_2Et$ and H-4), 6.10 (ddd, 1H, J_1 = 1.0 Hz, J_2 = 7.5 Hz, J_3 = 11.3 Hz, $CH=CHCO_2Et$), 6.73 (d, 2H, J = 8.8 Hz, ArH), 7.64 (d, 2H, J = 8.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 14.6, 26.0, 27.8, 32.7, 39.9, 61.1, 81.3, 83.7, 84.6, 84.8, 114.9, 120.0, 120.2, 121.6, 122.8, 136.4, 137.8,

149.8, 150.0, 159.4; MS (EI) *m/z* (rel intensity) 520 (M^+, 23.2), 522 (M^++2, 24.7). **17b**, also a light yellow oil, was obtained at the same time (*E* isomer, 15%): IR ν_{max} (neat) 2984, 2956, 2935, 1721, 1714, 1662, 1585, 1486, 1371, 1281, 1242, 1176, 1065, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.22 (t, 3H, OCH_2CH_3), 1.29 (s, 3H, i-prop), 1.48 (s, 3H, i-prop), 1.72 (s, 3H, OAc), 2.58 (dd, 1H, J_1 = 5.7 Hz, J_2 = 4.0 Hz, H-4), 3.01 (ddd, 1H, J_1 = 1.5 Hz, J_2 = 8.5 Hz, J_3 = 12.5 Hz, H-7), 3.34 (dd, 1H, J_1 = 4.6 Hz, J_2 = 12.5 Hz, H-7), 3.70 (s, 3H, $PhOCH_3$), 4.42 (m, 2H, CH_2Me), 4.67 (m, 1H, H-5), 4.79 (m, 1H, H-6), 6.06 (d, 1H, *J* = 11.6 Hz, $=CHCO_2Et$), 6.77 (dd, 1H, J_1 = 5.0 Hz, J_2 = 15.5 Hz, H-3), 6.70 (d, 2H, *J* = 8.8 Hz, ArH), 7.66 (d, 2H, *J* = 8.8 Hz, ArH).

General Procedure *A* for the Photolysis of a Pyridine-2-thione Derivative with a Diorgano Monotelluride.[30]

Monotelluride (0.8 mmol, 1 equiv) was dissolved in 5 mL of dry methylene chloride in a flask equipped with a stir bar under an argon atmosphere. The flask was set in an ice bath (0 °C), and then *N*-hydroxy-2-thiopyridone ethanoate (0.25 equiv) was added. The solution was irradiated with a 150 W tungsten lamp placed at a distance of 24 cm from the reaction flask. 0.25 equivalent of Barton ester was added in every 10 minutes with stirring and photolyzing. The total of 2.7 equivalents of Barton ester was added during the procedure. The solution was then stirred for about 4 hours at 0 °C, concentrated, and separated on a silica column using 6 : 1 = hexanes : ethyl acetate as eluent.

General Procedure *B* for the Photolysis of a Pyridine-2-thione Derivative with a Diorgano Monotelluride.[30]

Monotelluride (0.8 mmol, 1 equiv) was dissolved in 5 mL of dry methylene chloride in a flask equipped with a stir bar under an argon atmosphere. The flask was set in an ice bath (0 °C), and then *N*-hydroxy-2-thiopyridone cyclohexanoate (0.25 equiv) was added. The solution was irradiated with a 150 W tungsten lamp placed at a distance of 24 cm from the reaction flask. 0.25 equivalent of Barton ester was added in every 10 minutes with stirring and photolyzing. The total of 2.7 equivalents of Barton ester was added during the procedure. The solution was then stirred for about 6 hours at 0 °C, concentrated, and separated on a silica column using 6 : 1 = hexanes : ethyl acetate as eluent.

Carbocycles 18a and 18b

The title compounds were synthesized from **17** according to the method of Barton,[31] "general procedure *A* for the photolysis of a pyridine-2-thione derivative with a diorgano monotelluride". **18a** was obtained as a light yellow oil (*trans*, 76.2%): $[\alpha]^{25}_D$ = +53.3° ($CHCl_3$); IR ν_{max} (neat) 2990, 2933, 1751, 1586, 1487, 1374, 1281, 1245, 1224, 1176, 1082, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.21 (t, 3H, *J* = 7.5 Hz, OCH_2CH_3), 1.44 (s, 3H, i-prop), 1.78 - 1.95 (broad, 1H, H-5), 2.04 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.10 - 2.28 (m, 1H, H-5), 2.58 -2.80 (m, 1H, H-4), 4.16 (dq, 2H, *J* = 7.0 Hz, OCH_2Me), 4.50 - 4.75 (m, 3H, H-2, H-3 and H-4), 5.09 (m, 1H, CHSPy), 6.98 (m, 1H, ArH), 7.18 (dd, 1H, ArH), 7.50 (m, 1H, ArH), 8.36 (m,

1H, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 14.53, 21.41, 25.10, 26.76, 30.12, 30.06, 32.18, 44.40, 44.83, 47.80, 48.02, 62.00, 62.06, 73.58, 73.61, 79.04, 79.29, 83.23, 112.4, 112.5, 120.7, 122.7, 122.8, 136.7, 149.8, 157.0, 171.9, 172.0; MS (EI) *m/z* (rel intensity) 395 (M^+, 8.9), 380 (M^+-CH_3, 37.0); HRMS (EI) Calcd for $C_{19}H_{25}NO_6S$ 395.470, Found 395.138. **18b**, a light yellow oil, was also obtained in the same reaction (*cis*, 9.7%): $[\alpha]^{25}_D$ = -33.85° ($CHCl_3$); IR ν_{max} (neat) 2982, 2939, 1736, 1576, 1450, 1414, 1369, 1299, 1242, 1208, 1164, 1121, 1095, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.24 (m, 6H, i-prop and OCH_2CH_3), 1.44 (s, 3H, i-prop), 1.93 (m, 1H, H-5), 2.02 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.20 (m, 1H, H-5), 4.08 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 4.15 (m, 1H, H-4), 4.49 (d, 1H, *J* = 10.5 Hz, CHSPy), 4.66 (m, 3H, H-1, H-2 and H-3), 6.96 (m, 1H, ArH), 7.18 (d, 1H, ArH), 7.50 (m, 1H, ArH), 8.36 (m, 1H, ArH), 8.36 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 14.59, 21.34, 24.69, 26.10, 30.61, 40.26, 46.93, 60.85, 73.69, 77.89, 79.26, 111.5, 120.5, 123.1, 136.5, 149.7, 150.0, 157.8, 171.2, 172.4.

Compound 19.[4]

This compound was obtained from **18a**. 125 mg (0.32 mmol) of **18a** was dissolved in 5 mL of dry benzene under an argon atmosphere. 372 mg (1.28 mmol) of Bu_3SnH and 5 mg (0.038 mmol) of 2, 2'-Azobis (2-methyl propinonitrile) (AIBN) were then added into the flask with stirring. The solution was boiled for 24 h, concentrated and purified on silica (eluent = 2 :1 hexanes : ethyl acetate). **19** is a colorless oil (81.5 mg, 87%): $[\alpha]^{25}_D$ = +59.8° ($CHCl_3$); IR ν_{max} (neat) 2982, 1740, 1731, 1448, 1371, 1241, 1208, 1165, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.24 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 1.26 (s, 3H, i-prop), 1.44 (s, 3H, i-prop), 1.60 - 1.80 (m, 1H, H-5), 1.90 -2.20 (m, 1H, H-5), 2.06 (s, 3H, OAc), 2.25 (q, 2H, *J* = 7.0 Hz, *CH*SPy), 2.48 (m, 1H, H-4), 4.11 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 4.34 (t, 1H, *J* = 5.0 Hz, H-3), 4.64 (q, *J* = 5.8 Hz, H-2), 4.88 (m, 1H, H-1); ^{13}C NMR ($CDCl_3$, δ, ppm) 14.17, 20.91, 24.49, 26.13, 32.53 (C-6, lit. 33.36), 36.82 (C-4, lit. 37.00), 37.66 (C-5, lit. 37.84), 60.61, 73.05, 78.03, 83.97 (C-1, lit. 84.21), 111.7, 170.7, 171.7.

Compound 21 was obtained from 18a *via* 20.

The starting **18a** (123 mg, 0.31 mmol) was dissolved in 3 mL of methylene chloride in a flask equipped with stir bar. The solution of 70 mg (ca. 80% purity, 0.32 mmole) of m-chloroperoxybenzoic acid (MCPBA) in 1 mL of chloroform was added dropwise at 0 °C. The reaction mixture was warmed up to room temperature and stirred for one more hour. About 15 mL of ethyl acetate was added. The solution was washed with a solution of $NaHCO_3$ and extracted with ethyl acetate (4 x 50 mL). The organic layers were combined, dried, concentrated and isolated on silica gel (eluent = 2 : 1 hexanes : ethyl acetate). A white solid (121.5 mg, 95%) was obtained as a mixture of four isomers: IR ν_{max} (neat) 2984, 2940 1729, 1575, 1450, 1424, 1371, 1241, 1159, 1055 cm^{-1}; ^1H NMR showed broad peaks for the four isomers. ^{13}C NMR gave multiple peaks for the four isomers. The solution of 689 mg (1.68 mmole) of **20** in 5 mL of dry benzene was kept boiling for 10 hours, concentrated,

purified on silica gel. Colorless oil **21** (421 mg, 88%) as a mixture of $Z : E = 38 : 62$. For (*E*): $[\alpha]^{25}_D$ = +127.4° ($CHCl_3$); IR ν_{max} (neat) 2983, 2935, 1720, 1666, 1428, 1371, 1210, 1161, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.15 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 1.23 (s, 3H, i-prop), 1.33 (s, 3H, i-prop), 2.00 (s, 3H, OAc), 3.38 (ddd, 1H, J_1 = 17.5 Hz, J_2 = 7.0 Hz, J_3 = 1.5 Hz, H-5), 4.05 (q, 2H, *J* = 7.0 Hz, OCH_2Me), 4.61 (t, 1H, *J* = 4.6 Hz, H-3), 4.72 (d, 1H, *J* = 5.0 Hz, H-2), 4.79 (m, 1H, H-4), 5.89 (m, 1H, $=CHCO_2Et$); ^{13}C NMR ($CDCl_3$, δ, ppm) 14.61, 21.22, 25.25, 27.05, 33.19, 60.56, 72.11, 77.74, 81.84, 113.1, 120.2, 156.6, 166.2, 170.8. For (*Z*): ^1H NMR ($CDCl_3$, δ, ppm) 1.07 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 1.19 (s, 3H, i-prop), 1.29 (s, 3H, i-prop), 1.92 (s, 3H, OAc), 2.48 (dd, J_1 = 15.0 Hz, J_2 = 7.0 Hz, H-5), 2.74 (m, 1H, H-5), 3.98 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 4.59 (m, 2H, H-3 and H-4), 5.39 (d, 1H, *J* = 5 Hz, H-2), 5.74 (m, 1H, $=CHCO_2Et$).

Compound 22 and 23[32]

The title compounds were obtained from **21**.[33] 157 mg (0.55 mmol) of **21** was dissolved in 5 mL of methylene chloride in a three-neck round bottom flask equipped with a stir bar and a pipet inserted under the surface of the solution. The flask was set in an dry-ice acetone bath (-78 °C). O_3 / O_2 was passed into the solution for 40 minutes. The solution was blue while bubbling O_3 / O_2 at -78 °C and colorless when it warmed up to room temperature. Several drops of Me_2S were added to destroy the excess ozone. The solution was concentrated and separated on silica gel (eluent = 3 : 1 hexanes : ethyl acetate). A white crystalline solid **22** (17 mg, 14%) was obtained as one of the products: mp 94 °C; $[\alpha]^{25}_D$ = -78.4° ($CHCl_3$); IR ν_{max} (neat) 2994, 2947, 1740, 1420, 1374, 1220, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, δ, ppm) 1.42 (s, 3H, i-prop), 1.50 (s, 3H, i-prop), 2.13 (s, 3H, OAc), 2.84 (d, 1H, *J* = 6.8 Hz, H-5), 2.87 (d, 1H, *J* = 10.6 Hz, H-5), 4.58 (dd, 1H, J_1 = 3.7 Hz, J_2 = 2.0 Hz, H-3), 5.21 (ddd, 1H, J_1 = 2.3 Hz, J_2 = 6.6 Hz, J_3 = 10.7 Hz, H-1), 5.84 (d, 1H, *J* = 3.8 Hz, H-2); ^{13}C NMR ($CDCl_3$, δ, ppm) 21.31, 26.50, 27.74, 30.68, 65.30, 73.64, 99.55, 113.9, 166.8, 174.0. MS (EI) *m/z* 215 (M^+); HRMS (EI) Calcd for $C_{10}H_{14}O_5$ 215.218, found 215.056. Another white crystalline compound **23**[32a] (60.5 mg, 71%) was obtained in the same reaction: mp 69 °C; $[\alpha]^{25}_D$ = -51.0° ($CHCl_3$)(in the literature[32a] a rotation of -71° is recorded); IR ν_{max} (neat) 2995, 2932, 1724, 1374, 1270, 1191, 1151, 1100, 1052 cm^{-1}; UV 271, 345 nm; ^1H NMR ($CDCl_3$, δ, ppm) 1.37 (s, 6H, 2i-prop), 4.43 (d, 1H, *J* = 5.5 Hz, H-5), 5.23 (dd, 1H, J_1 = 5.5 Hz, J_2 = 2.0 Hz, H-4), 6.18 (d, 1H, *J* = 6.0 Hz, H-2), 7.57 (dd, 1H, J_1 = 6.0 Hz, J_2 = 2.0 Hz, H-3); ^{13}C NMR ($CDCl_3$) d 26.07, 27.34, 76.51, 78.53, 115.4, 134.2, 159.7, 203.0; MS (EI) *m/z* 154 (M^+); HRMS (EI) Calcd for $C_8H_{10}O_3$ 154.165, found 154.061.

2,3-*O*-isopropylidene-1,4-*D*-ribono-lactone 25.

To a suspension of *D*-ribono-1,4-lactone **24** (25 g, 167 mmol) in 2,2-dimethoxy propane (100 ml), acetone (30 ml) and methanol (7 ml) was added *p*-toluene sulphonic acid (1 g, 5.2 mmol). The reaction mixture was stirred at room temperature and neutralized with $NaHCO_3$. The solution was filtered, diluted with ethyl acetate and washed with water. The organic phase was dried over $MgSO_4$ and, after filtration evaporated under reduced pressure. The residue thus obtained was purified on a silica gel column (ethyl acetate-heptane, 2:3) to yield **33** as a white powder (19.7 g, 63 %). Mp: 134-137° (ethyl acetate-heptane).

5-Iodo-2,3-*O*-isopropylidene-*D*-ribono-1,4-lactone 26.

To a solution of compound **25** (15 g, 79.8 mmol) in dry toluene (200 ml) triphenylphosphine (62.7 g, 240 mmol) and imidazole (16.2 g, 240 mmol) were added under vigorous stirring. The mixture was then heated to 70 °C and iodine (45 g, 177 mmol) was added in small portions. After 30 min, the reaction mixture was cooled and then washed with a solution of sodium thiosulphate and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and, after filtration evaporated under reduced pressure. The residue thus obtained was purified on silica gel (ethyl acetate-heptane, 1:3) to yield **34** as a white solid (21.6 g, 91 %). Mp 89-91°C[18] (ethyl acetate-heptane).

3,4-*O*-isopropylidene-1-phenylsulfonyl-1-(2'-pyridyl)thio-5-hexen-3,4-diol (3R, 4R) 29

To the acid **27**[21] (8.0 g, 46.5 mmol) in anhydrous tetrahydrofuran (150 ml) *N*-methylmorpholine (5.3 ml, 46.4 mmol)) and isobutyl chloroformate (6.5 ml, 50.1 mmol) were added at 0°C under argon. After formation of the mixed anhydride (tlc, ethyl acetate-heptane, 1:2), the sodium salt of *N*-hydroxy-2-thiopyridone (7.9 g, 53 mmol) was added. The reaction mixture was stirred under argon at 0° for 1 h with exclusion of light (aluminium foil) to form the thiohydroxamic ester. The mixture was then filtered and the solution was evaporated with the exclusion of light. The residue was then dissolved in dichloromethane (200 ml) and the yellow solution was irradiated with a tungsten lamp (250 watts) at 0° for 2 hours in the presence of phenyl vinyl sulfone (40g, 237 mmol). After evaporation of the solvent, the residue thus obtained was purified on silica gel (ethyl acetate-heptane, 1:3) to give the coupled derivative **29**. This a mixture of two isomers was used without futher purification.

3,4-*O*-isopropylidene-1-phenylsulfonyl-1,5-hexadiene-3,4-diol (3R, 4R) 30.

To a solution of **29** (10.6 g, 28.4 mmol) in chloroform (8 ml) m-chloroperbenzoic acid (4.9 g, 28.4 mmol) was added under argon at 0°C. The mixture was stirred at 0°C for 2 h, diluted with dichloromethane and then washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. The organic phase was dried over $MgSO_4$ and, after filtration evaporated under reduced pressure to give the sulfoxide (8.3 g, 75 %). The latter was dissolved in dry toluene (150 ml) and boiled for 18 hours. The reaction mixture was then cooled, evaporated and the residue thus obtained was separated on a silica gel column (ethyl acetate-heptane, 2:3) to yield the vinylsulfone **30** as an oil (4.1 g, 65.4 %). Anal. Calcd. for $C_{15}H_{18}O_4S$ C(61.2); H(6.1); S(10.9); Found: C(60.8); H(6.3); S(11.0). MS (C.I., Isobut., m/z): 295 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ ppm: 8.1-7.5 (m, 5H, CH Ph); 6.8-6.0 (m, 5H, H-1, H-2, H-5, H-6, H-6'); 5.4 (m, 1H, H-4); 4.2 (m, 1H, H-3); 1.45 (s, 3H, CH_3 of Me_2); 1.35 (s, 3H, CH_3 of Me_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm: 140.6-127.6 (CH Ph, C-1, C-2, C-5); 120.2 (C6); 110.2 (CMe_2); 81.7-78.6 (C3, C4); 26.8-26.5 (CH_3 of Me_2).

Methyl 2,3:4,5-di-*O*-isopropylidene-2,3,4,5-tetrahydroxy-pentanoate (2R, 3R, 4R) 33.

To **24** (10 g, 67.5 mmol) in 2,2-dimetoxypropane (50 ml), acetone (10 ml) and methanol (2 ml) *p*-toluenesulfonic acid (0.5 g, 2.6 mmol) was added. The solution was stirred at room temperature for 48 h, neutralized with $NaHCO_3$ and filtered. The mixture was then diluted with ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-heptane, 1:2) to yield **33** as an oil (14.5 g, 82%). Anal. Calcd. for $C_{12}H_{20}O_6$. C(55.40); H(7.70); Found: C(55.23); H(7.52). MS (CI, m/z): 261 $[MH]^+$, 203 $[MH\text{-}Me_2CO]^+$. IR: ν_{max} ($CHCl_3$): 1764 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ (ppm): 4.7 (d, 1H, H-2, $J_{2,3}$= 6 Hz); 4.2 (t, 1H, H-3, $J_{3,4}$= 6Hz); 4.0 (m, 2H, H-4, H-5); 3.9 (m, 1H, H-5'); 3.7 (s, 3H, COO*Me*); 1.6-1.2 (m, 12H, C*Me*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 168.7 (CO); 110.6-109.4 (*C*Me$_2$); 76.3 (C-3); 75.7 (C-2); 73.6 (C-4); 66.9 (C-5); 51.5 (*COO*Me); 26.9, 25.0 (C*Me*$_2$).

2,3:4,5-di-*O*-isopropylidene-2,3,4,5-tetrahydroxy-pentanoic acid (2R, 3R, 4R) 34.

To the ester **33** (30.6 g, 117.7 mmol) in H_2O (300 ml) was added NaOH (26.6 g, 665 mmol). The reaction mixture was then stirred at room temperature for 12 h, diluted with ethyl acetate (400 ml) and acidified at 0°C with citric acid (280 g). The organic layer was washed with water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue corresponding to the acid **34** (24.1 g, 83%) was used for the next step without futher purification. IR (ν_{max}, $CHCl_3$): 1752 (CO). MS (CI, m/z): 247 $[MH]^+$, 189 $[MH\text{-}Me_2CO]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ (ppm): 10.5 (br s, 1H, COO*H*); 4.8 (d, 1H, H-2, $J_{2,3}$= 6 Hz); 4.4-4.0 (m, 4H, H-3, H-4, H-5, H-5'); 1.7-1.2 (m, 12H, C*Me*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 173.5 (CO); 111.3, 110.1 (*C*Me$_2$); 76.4 (C-3); 75.7 (C-2); 73.8 (C-4); 66.9 (C-5); 27.0-25.3 (C*Me*$_2$).

Diethyl 1-(2'-piridyl)thio-3,4:5,6-di-*O*-isopropylidene-3,4,5,6-tetrahydroxy-1-hexanephosphonate (2R, 3R, 4R) 37.

To the acid **34** (5.8 g, 23.6 mmol) in anhydrous tetrahydrofuran (100 ml) *N*-methylmorpholine (2.61 ml, 23.7 mmol) and isobutyl chloroformate (3.1 ml, 23.9 mmol) were added. After stirring at 0° under argon, until all of the acid reacted (t.l.c., ethyl acetate-heptane: 1:2) the sodium salt of *N*-hydroxy-2-thiopyridone (3.52 g, 23.6 mmol) was added. The reaction mixture was stirred under argon at 0° with exclusion of light (aluminium foil) to form the O-acyl thiohydroxamic acid **35**. The mixture was then filtered and the solvent evaporated with the exclusion of light. The residue was then dissolved in dichloromethane (120 ml) and diethyl vinylphosphonate (14.5 ml, 94.3 mmol) was added. The red solution was then irradiated with a tungsten lamp (250 watts) at 10°C for 4 h. The solvent and the excess of diethyl vinylphosphonate were removed under reduced pressure. The residue thus obtained was purified on a silica gel column. Elution with ethyl acetate-heptane 6:4 gave **45** as an oil (6.7 g, 60%) which was a mixture of two isomers. MS (C.I., Isobut., m/z): 476 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ (ppm): 8.6-7.0 (m, 4H, SPy); 6.4-6.0 (m, 1H, H-1); 4.9 (m, 1H, H-4); 4.4-3.8 (m, 7H, H-5, H-6, H-6', 2*CH*$_2$CH$_3$); 3.6 (m, 1H, H-3); 2.3 (m, 2H, H-2, H-2'); 1.6-1.1 (m, 18H, C*Me*$_2$, CH$_2$*CH*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 148.8-119.7 (Spy), 109.2-108.7 (*C*Me$_2$); 81.4-80.7 (C-4); 77.7 (C-3); 76.5 (C-5);

67.2 (C-6); 62.6, 61.5 (CH_2CH_3); 36.6-32.9 (C-1); 34.8-33.8 (C-2); 27.0, 25.0 (CMe_2); 16.0 (CH_3CH_2). ^{31}P NMR (81 MHz, $CDCl_3$): δ (ppm) (H_3PO_4): 23.1; 22.8.

Diethyl 3,4:5,6-di-*O*-isopropylidene-3,4,5,6-tetrahydroxy-1-hexene-1-phosphonate (3R, 4R, 5R) 38.

To a solution of **37** (5.9 g, 12.4 mmol) in dichloromethane (75 ml) was added under argon, at 0°C, a solution of *m*-chloroperbenzoic acid (2.54 g, 14.7 mmol) in dichloromethane (20 ml). After 2h the mixture was diluted with dichloromethane, washed with saturated sodium hydrogen carbonate solution and water. The organic phase was separated, dried over $MgSO_4$ and, after filtration evaporated under reduced pressure. The residue was then dissolved in toluene (30 ml) and the solution was kept boiling for 3 h. Then the solvent was evaporated to dryness. The residue thus obtained was purified on a silica gel column. Elution with ethyl acetate-heptane 7:3 gave **38** as an oil (3.2 g, 71%). Anal. Calcd. for $C_{16}H_{29}O_7P$. C(52.75); H(7.97); O(30.77); Found: C(53.14); H(7.81); (O)30.64. MS (C.I. m/z): 365 $(MH)^+$. ^1H NMR (200 MHz, $CDCl_3$): δ (ppm): 6.9 (m, 1H, H-2, $J_{2,1}$= 20Hz, $J_{2,3}$= 4Hz); 6.1 (m, 1H, H-1); 4.5 (m, 1H, H-3, $J_{3,4}$= 8Hz); 4.4-3.9 (m, 7H, H-5, H-6, H-6', CH_2CH_3); 3.7 (m, 1H, H-4, $J_{4,5}$= 7Hz); 1.5-0.9 (m, 18H, CMe_2, CH_3CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 119.5, 115.7 (C-1, C-2); 110.3, 109.9 ($2CMe_2$); 81.3 (C-4); 80.1-79.6 (C-3); 77.1 (C-5); 67.6 (C-6); 61.8 (CH_2CH_3); 26.9, 25.2 (CMe_2); 16.3 (CH_3CH_2). ^{31}P NMR (81 MHz, $CDCl_3$): δ (ppm) (H_3PO_4): 15.1, 14.3.

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