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Vinyl Sulfone- and Vinyl Sulfoxide-Modified Tetrahydrofurans: A Preliminary Account of the Enantiomeric Synthesis of and Diastereoselectivity of Addition to New Classes of Michael Acceptors

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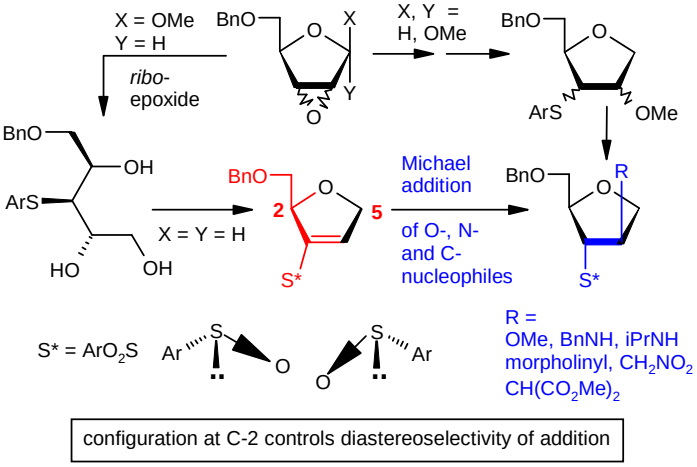


Abstract

Enantiomerically pure 2-hydroxymethylene substituted -2,5-dihydro-3-(arylsulfonyl)- and 2-hydroxymethylene substituted-2,5-dihydro-3-(arylsulfinyl)-furans have been prepared from easily accessible carbohydrate derivatives for the first time. The strategy for accessing both these sulfones and sufoxides is more efficient than the methods reported so far for the synthesis of this type of compounds. Hydroxymethylene group is sufficient to impose diastereoselectivity on the addition of a wide range of nucleophiles to vinyl sulfone-modified tetrahydrofurans. The benzyl protected hydroxymethylene group also suppresses the influence of chirally pure sulfoxides as two diastereomeric vinyl sulfoxide-modified tetrahydrofurans afforded the Michael adducts with same configurations at C-2 and C-3; this has been established by oxidizing the adducts which were found to be identical to the products obtained by adding the same nucleophiles to the corresponding vinyl sulfones. These highly reactive Michael acceptors may be considered as a new addition to the arsenals of synthetic chemists interested in the functionalization of tetrahydrofurans.

Key-words: Vinyl sulfone, Vinyl sulfoxide, Tetrahydrofuran, Michael addition; Modified tetrahydrofuran, Chiral auxiliary

Introduction

α,β-unsaturated -sulfones[1] and -sulfoxides[2] are versatile reagents and useful building blocks in synthetic chemistry because they have the potential to undergo Michael addition of carbon and various heteroatom nucleophiles as well as cycloaddition reactions.[3,4] 2,5-Dihydro-3-(alkyl/arylsulfonyl) furans **1a-e** (Figure 1) represent the basic skeleton of a special class of

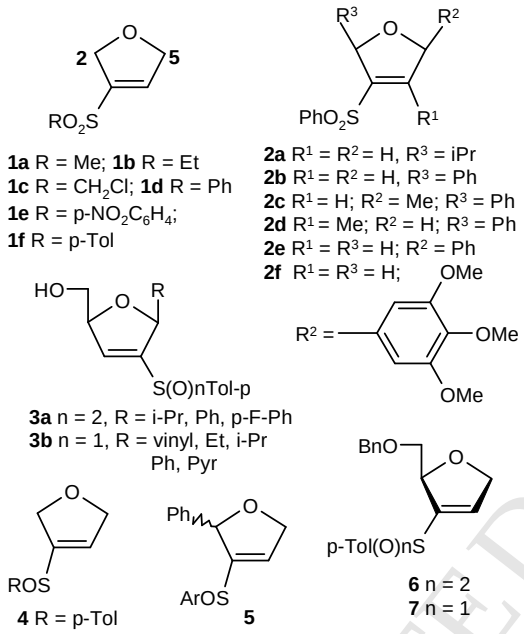


Figure 1. Selected examples of vinyl sulfone- and vinyl sufoxide-modified tetrahydrofurans.

cyclic Michael acceptors with high potential as synthetic intermediates.[5]. 2,5-Dihydro-3-(phenylsulfonyl)-furan was used further as a dienophile for the regioselective Diels-Alder reactions; the desired cyclic vinyl sulfone **1d** was obtained by irradiating the 2,5-dihydrofuran and phenylselenenyl benzenesulfonate followed by oxidation.[6] Pyrroles derived from **1f** was utilized in the synthesis of porphyrins.[7] A group of substituted 2,5-dihydrofurans **2a-d** was synthesized by the acid treatment of the corresponding enediols, obtained through multi-step synthetic routes.[8] 2-Substituted 4-benzenesulfonyl-2,5-dihydrofuran **2e** was synthesized from propargyl ethers through a complex reaction sequence

of alkynyl(phenyl)iodonium salts which also afforded 2,5-dihydrofuran **2f,** an intermediate required for lignan synthesis.[9] The sulfonyl diene monoepoxides were converted to the corresponding sulfonyl dihydrofurans **3a** under acid catalyzed conditions.[10]

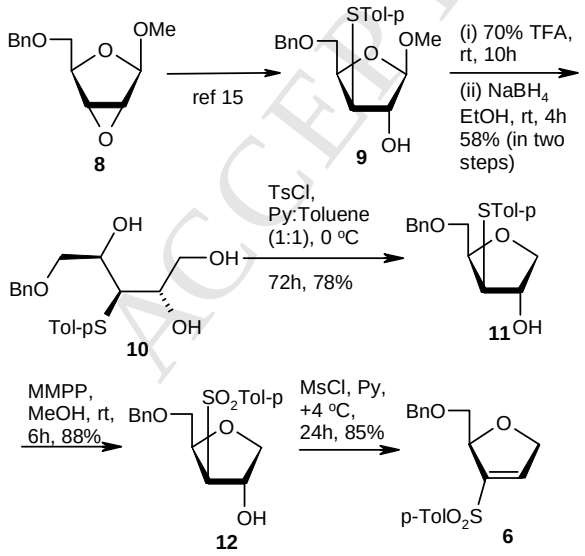
Realizing the importance of this class of compounds, attempts have also been made to synthesize the 2,5-dihydro-3-(alkyl-/arylsulfinyl)furans because in addition to the participation of these Michael acceptors in the reactions mentioned above, α,β-unsaturated sulfoxides have the potential to act as efficient chiral auxiliaries in asymmetric synthesis. Although the applications of acyclic varieties are well known,[3,4] the ability of the cyclic vinyl sulfoxides to differentiate between the diastereotopic faces of a proximal or even remote reaction center is rarely documented. Nucleophilic epoxidation of hydroxyl sulfinyl dienes produced the sulfinyl tetrahydrofurans **3b** in poor yields.[11] α-(Diethoxyphosphoryl)vinyl *p*-tolyl sulfoxides on reactions with the sodium salt of α-hydroxyacetaldehyde, generated 3-*p*-toluenesulfinyl-2,5-dihydrofuran **4**.[12] A complex multi-step route was devised to synthesize 2,5-dihydron arylsulfinyl furan from (*S*)-*o*-(N,N-dimethylamino)phenyl methyl sulfoxide; the reaction afforded a mixture of (2*R*,S*R*)-and (2*S*,S*R*)- of **5** in the ratio of 6:94.[13]

Results and Discussion

The utilization of Michael acceptors like **1-5** (Figure 1) in synthetic chemistry would inevitably depend on the availability of suitable preparative methods for easy access to these compounds. It appears from the published reports mentioned above, that the strategies for accessing substituted 3-(alkyl/aryl)-sulfonyl or -sulfinyl-2,5-dihydrofurans reported so far are cumbersome and low yielding.[5-13] We and others have reported earlier that one of the easiest ways of incorporating vinyl sulfone[14] or vinyl sulfoxide[2e] group in a furan (or pyran) ring is to take advantage of easy S_N2-type displacement of appropriately selected leaving group or

epoxide ring opening on carbohydrates by sulfur nucleophiles. Oxidation of sulfur followed by displacement of a leaving group at the β-position would produce the vinyl sulfone or vinyl sulfoxide moiety. We report herein the synthesis and reaction patterns of enantiopure vinyl sulfone- and vinyl sulfoxide-modified tetrahydrofurans **6** and **7** (Figure 1).

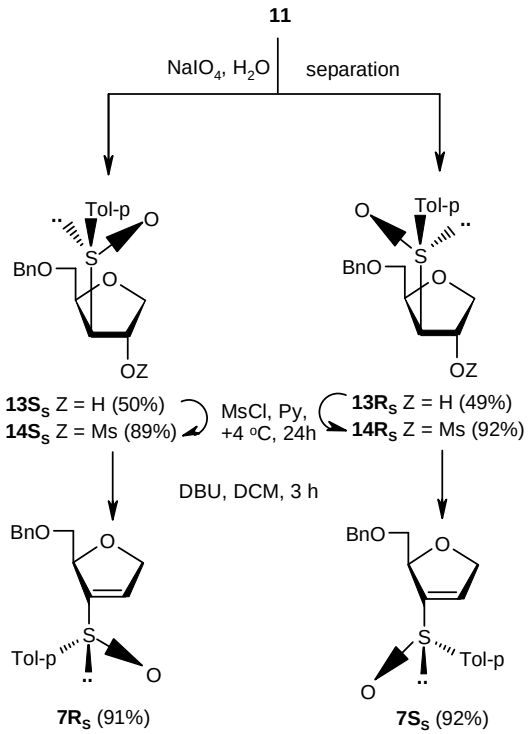
In order to have a pre-decided asymmetric centre at C-2 and also for accessing compound **6** (Figure 1) in relatively large amount, we selected the known *ribo*-epoxide as the starting material. Thus the *ribo*-epoxide **8** was treated with *p*-thiocresol in the presence of 1,1,3,3-tetramethylguanidine (TMG) to generate the corresponding sulfide **9**.[15] Compound **9** was consecutively treated with trifluoroacetic acid (TFA) and sodium borohydride ($NaBH_4$) to afford acyclic compound **10**. Selective tosylation of **10** gave the desired cyclic compound **11** having a furan moiety. Compound **11** was oxidized with magnesium monoperoxyphthalate hexahydrate (MMPP) to the corresponding sulfone **12**. The hydroxyl group of **12** was mesylated and subsequent elimination of the mesyl group produced the desired vinyl sulfone **6** (Scheme 1). The appearance of the characteristic vinylic proton at δ 6.92 in ^{1}H NMR and



Scheme 1. Synthesis of vinyl sulfone-modified tetrahydrofurans.

the corresponding carbon at δ 140.5 in ^{13}C NMR spectra of compound **6** indicated the formation of the vinyl sulfone moiety. The carbon peaks at δ 70.9, 73.1 and 74.5 ppm indicated the presence of three CH_2 groups and there were four tertiary carbons at δ 136.4, 138.0, 141.5 and 144.9 ppm in the ^{13}C NMR of compound **6**. All these in combination with HRMS data supported the proposed structure **6**.

To synthesize the corresponding vinyl sulfoxides, compound **11** was oxidized under controlled conditions[16a] by sodium metaperiodate ($NaIO_4$) and water-methanol mixture at room temperature for 5h to give a mixture of diastereomeric sulfoxides which were easily separated to afford **13S$_S$** and **13R$_S$** roughly in 1:1 ratio. We reported earlier[16a] that the partial oxidation of pyranoside ring by $NaIO_4$ produced only one sulfoxide, enantiomeric at sulfur atom; in this case oxygen atoms of IO_4^- attack the sulfides perpendicularly to the plane of C-S-C atoms and the S$^{\cdots}$O$^{\cdots}$I atoms are in a linear arrangement in the very early transition state.[16b] However, in case of furanosides such a positioning of the aryl sulfide group was not possible due to the pseudo-axial and pseudo- equatorial nature of bonds in a five membered ring and therefore enantiomers with respect to the sulfur atom were produced in almost equal ratio.[16a] It appears that even in the absence of the anomeric methoxy group, similar pattern of enantioselectivity with respect to sulfur is manifested in the oxidation of **11**. The isomeric sulfoxides **13S$_S$** and **13R$_S$** thus obtained, were reacted with mesyl chloride in pyridine at +4 ^{o}C for 24h to produce the corresponding mesylated compounds **14S$_S$** and **14R$_S$** respectively. Compounds **14S$_S$** and **14R$_S$** were then treated with DBU in DCM at room temperature for 3h to generate the corresponding vinyl sulfoxides **7R$_S$** and **7S$_S$** respectively (Scheme 2). The structure of compound **7R$_S$** was confirmed by X-ray crystallography which indirectly helped us to establish the structure of **7S$_S$**. The absolute configuration at the sulfur of vinyl sulfoxides **7R$_S$** and **7S$_S$** could also be confirmed by comparing the NMR data with those

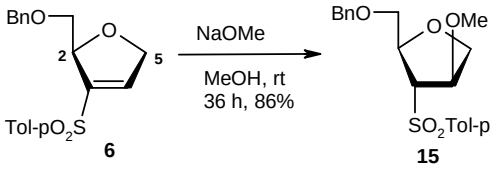


Scheme 2. Synthesis of vinyl sulfoxide-modified tetrahydrofurans

reported for 2-aryl-3-sulfinyl-2,5-dihydrofurans.[13] In the reported data, the vinylic proton was used as a tool for assigning the stereochemistry of sulfur atom because of the highly deshielding effect induced by the sulfinyl oxygen on the vinylic hydrogen.[13] The vinylic proton of compound **7R$_S$** appeared at δ 6.68 in its ^{1}H NMR spectrum whereas that for the compound **7S$_S$** was at δ 6.56. Thus the chemical shift values showed that the vinylic proton of **7R$_S$** was much more deshielded than that in **7S$_S$**. According to the reported data,[13] the higher chemical shift value of vinylic proton is possible if sulfur oxygen was oriented towards the vinylic proton. So from the above discussion it was clear that in compound **7S$_S$** the sulfur oxygen was oriented opposite to the vinylic proton.

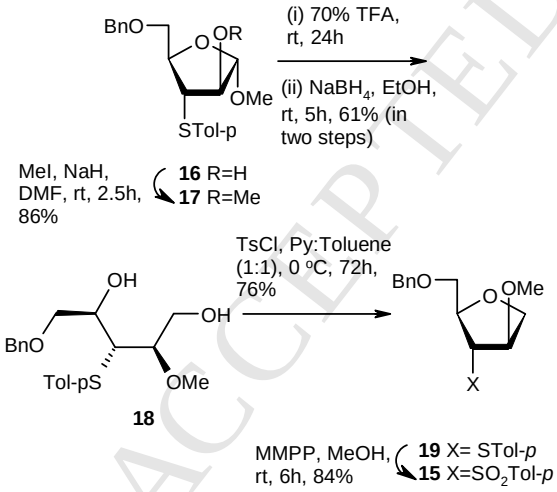
To study the diastereoselectivity of addition reaction, vinyl sulfone modified tetrahydrofuran **6** was reacted with sodium methoxide in methanol and the reaction afforded a single

diastereomer **15** (Scheme 3). Theoretically the reaction was supposed to produce four diastereomers isomeric at C-2 and C-3 but the thermodynamically most stable isomer **15** was obtained. The structure of **15** was unambiguously established via alternative synthesis. Thus,



Scheme 3 Formation of a single diastereomer from the reactions of NaOMe/MeOMe vinyl sulfone **6**.

compound **16** was methylated with methyl iodide in the presence of sodium hydride to produce **17**. Compound **17** was consecutively treated with TFA and $NaBH_4$ to generate the acyclic compound **18**. Selective tosylation of **18** produced the desired cyclic compound **19** which on oxidation with MMPP afforded the desired diastereomer **15** (Scheme 4), which was

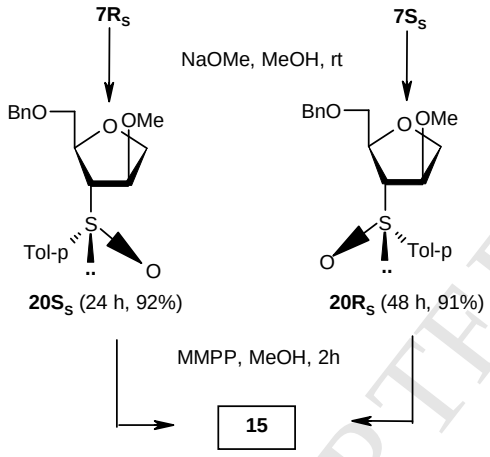


Scheme 4. Synthesis of diastereomer **15** from a thiosugar.

identical with the product obtained from **6** in scheme 3 (mixed ^{1}H NMR). Thus the methoxide ion attacked the electron deficient double bond from the β-face and the resulting carbanion at

C-3 was also protonated from the β-face of **6** (*cis*-addition) to afford the thermodynamically stable product.

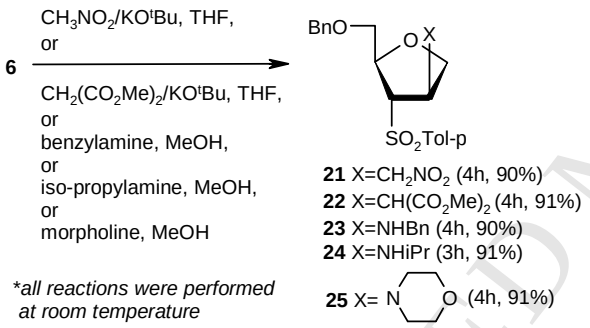
At this point, we intended to study the influence of enantiomerically pure sulfoxide groups, if any on the diastereoselectivity of addition of methoxide to vinyl sulfoxides **7R$_S$** and **7S$_S$**. Thus, **7R$_S$** was reacted with sodium methoxide in methanol at room temperature for 24h to afford a single diastereomer **20S$_S$** in excellent yield (Scheme 5). Vinyl sulfoxide **7S$_S$** was slow to react under similar reaction conditions and required 48h to afford the single diasteromer **20R$_S$** as the Michael adduct. The stereochemistry of the C-2 and C-3 centers of



Scheme 5. Matching of configurations at C-2 and C-3 of adducts obtained from Michael acceptors **7Rs** and **7S$_S$**.

the Michael addition products was confirmed by oxidizing **20S$_S$** and **20R$_S$** with MMPP in methanol at room temperature affording **15** in each case (Scheme 5). Thus, irrespective of the configurations of the sulfoxide groups, methoxide added from the β-face of the tetrahydrofuran moiety.

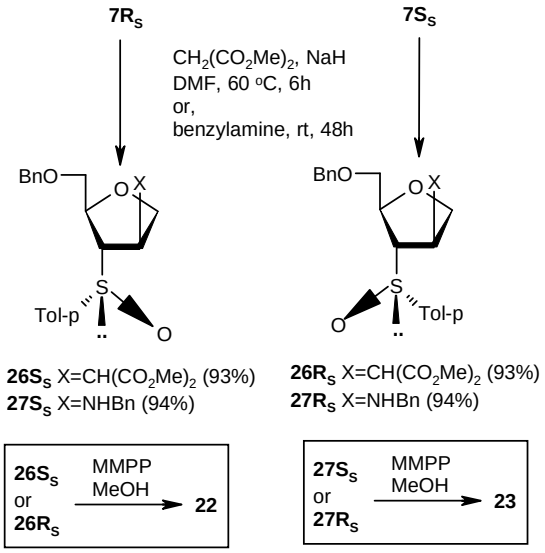
To generalize the study, vinyl sulfone **6** was reacted with nitromethane/KO^{t}Bu or dimethylmalonate/ KO^{t}Bu to afford single diastereomers **21** and **22** in excellent yields (Scheme 6). Compound **6** was also reacted with benzylamine, isopropylamine and morpholine in methanol at an ambient temperature to afford adducts **23**-**25** respectively in excellent yields (Scheme 6). The structure of compound **21** was confirmed by X-ray crystallography and that of compound **22** was confirmed by comparing its spectral data with those of **21**. Similarly, the structure of the morpholino derivative **25** was confirmed by X-ray crystallography. The structures of **23** and **24** were confirmed by comparing their spectral data with those of **25**. Vinyl sulfoxide **7R$_S$** and **7S$_S$** were separately reacted with



Scheme 6. Michael type addition of C- and N-nucleophiles to vinyl sulfone-modified tetrahydrofuran **6**.

dimethylmalonate/NaH in DMF at 60 ^{o}C to generate single diastereomers **26S$_S$** and **26R$_S$** in excellent yields (Scheme 7); benzylamine afforded the addition products **27S$_S$** and **27R$_S$** respectively (Scheme 7). Once again **26S$_S$**/**26R$_S$** and **27S$_S$**/**27R$_S$** pairs were oxidized with MMPP to afford the corresponding addition products **22** and **23** respectively (Scheme 7) obtained from vinyl sulfone **6**. It should be noted that the oxidation reactions of amino compounds were terminated within 0.5h to avoid over- oxidation. These experiments established once again that like the addition pattern of methoxide, the diastereoselectivity of

addition of *C*- and *N*-nucleophiles to **6**, **7R$_S$** and **7S$_S$** afforded thermodynamically more stable products.



Scheme 7. Michael type addition of C- and N-nucleophiles to vinyl sulfoxide-modified tetrahydrofuran **6**.

Conclusion

We have devised a simple strategy for the synthesis of enantiomerically pure 2-hydroxymethylene substituted -2,5-dihydro-3-(arylsulfonyl)- and 2-hydroxymethylene substituted -2,5-dihydro-3-(arylsulfinyl)- furans from easily accessible carbohydrate derivatives. Using carefully designed experiments with vinyl sulfone- and vinyl sulfoxide-modified tetrahydrofurans, we have also established that the hydroxymethylene group is sufficient to afford diastereoselective all *trans* products. The addition pattern is general in nature because *C*- and *N*-nucleophiles also reacted in the similar fashion. Although α,β-unsaturated sulfoxides are known as efficient chiral auxiliaries, our experiments with vinyl sulfoxide-derived tetrahydrofurans have established that at least in our system, chirally pure sulfoxides do not play any role to control the diastereoselectivity of addition products because vinyl sulfoxide-modified tetrahydrofurans also afforded all *trans* products. From a

synthetic point of view the well studied vinyl sulfone-modified tetrahydrofuran **6** is now a new addition to a class of highly reactive Michael acceptors[1,2,17] capable of efficiently reacting with a wide range of nucleophiles to afford enantiomerically pure products.

Experimental Section

General methods: All reactions were conducted under N_2 atmosphere. Melting points were determined in open-end capillary tubes and are uncorrected. Carbohydrates and other fine chemicals were obtained from commercial suppliers and are used without purification. Solvents were dried and distilled following the standard procedures. TLC was carried out on pre-coated plates (Merck silica gel 60, f_{254}) in ethylacetate(EA)/pet ether (PE) mixture and the spots were visualized with UV light or by charring the plate dipped in 5% H_2SO_4-MeOH solution. Column chromatography was performed on silica gel (230-400 mesh). ^1H and ^{13}C NMR for new compounds were recorded at 200/400 and 50/100 MHz respectively using $CDCl_3$ as the solvent. DEPT experiments had been carried out to identify the methylene carbons. Optical rotations were recorded at 589 nm. Mass spectroscopy data were obtained from mass analyzer consisting of TOF and quadrupole in either ESI^+ or ESI^- mode.

(2*S*,3*S*,4*R*)-5-(Benzyloxy)-3-(*p*-tolylthio)pentane-1,2,4-triol (10): A solution of thiocresol (13.1 g, 105.9 mmol) and TMG (10.6 ml, 84.72 mmol) in DMF (30 mL) was stirred at room temperature for 0.5h. Compound **8** (5 g, 21.16 mmol) was added and the solution was heated for 5h at 100 ^oC. The mixture was partitioned between satd. aq. $NaHCO_3$ solution and EtOAc. Organic layers were pooled together, dried over anhyd. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue, thus obtained was purified over silica gel column to afford **9** (6.1 g, 80%).[15] A mixture of compound **9** (3.5 g, 9.71 mmol) and 70% TFA in water (10 mL) was stirred at room temperature for 10h. After completion of the

reaction (TLC), the reaction mixture was poured into the ice cold satd. aq. $NaHCO_3$ solution and the product was extracted with EtOAc (3 X 10 mL). The combined organic layers were dried over anhydr. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to get a residue. $NaBH_4$ (1.5 g, 38.9 mmol) was added to an ethanolic solution (40 mL) of this residue at 0 ^oC and the mixture was stirred at room temperature. After 4h the reaction mixture was concentrated under reduced pressure to get a residue. The residue was poured into satd. aq. $NaHCO_3$ solution and the product was extracted with EtOAc (3 X 10 mL). The combined organic layers were dried over anhydr. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (40% EA/PE) to get the sulfide **10** (1.96 g, 58%) as a colorless gum; Rf (40% EA/PE) 0.30; $[\alpha]_D^{25.1}$ (+) 12.07 (c 1.5, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.31 (3 H, s), 3.38 (1 H, s), 3.63-3.69 (2 H, m), 3.77-3.81 (1 H, m), 3.94-4.01 (2 H, m), 4.27 (1 H, t, *J* 4.0 Hz), 4.46 (2 H, q, *J* 11.6 Hz), 7.07 (2 H, d, *J* 7.6 Hz), 7.25-7.35 (7 H, m); δC (100 MHz, $CDCl_3$) 21.0, 56.2, 63.2 (CH_2), 70.5, 71.6 (CH_2), 72.6, 73.4 (CH_2), 127.9, 128.4, 129.9, 130.0, 131.6, 131.8, 137.2, 137.5; HRMS [ES^+, $(M+Na)^+$]: for $C_{19}H_{24}O_4NaS$ found 371.1275, requires 371.1293.

(3*S*,4*S*,5*R*)-5-(Benzyloxymethyl)-4-(*p*-tolylthio)-tetrahydrofuran-3-ol (11): A solution of compound **10** (3.15 g, 9.04 mmol) in a mixture of anhydr. pyridine and toluene (1:1; 10 mL) was treated drop-wise at 0 ^oC with a solution of tosyl chloride (2.6 g, 13.6 mmol) in dry tolune (10 ml) and the mixture was stirred for 0.5h. The reaction mixture was stored at +4 ^oC for 72h. The mixture was filtered through celite and the filtrate was evaporated to dryness. Residual pyridine was co-evaporated with toluene. The residue was purified by flash chromatography (25% EA/PE) to afford the cyclic compound **11** (2.33 g, 78%) as a yellowish gummy compound; Rf (25% EA/PE) 0.32; $[\alpha]_D^{25.1}$ (+) 20.07 (c 1.5, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.33 (3 H, s), 3.59-3.61 (1 H, m), 3.70 (1 H, dd, *J* 9.6, 12.0 Hz), 3.75-3.77 (2 H, m),

4.27-4.31 (1 H, m), 4.38-4.39 (1 H, m), 4.52-4.55 (2 H, m), 4.62 (1 H, d, *J* 11.6 Hz), 7.11 (2 H, d, *J* 8 Hz), 7.26-7.35 (7 H, m); δC (100 MHz, $CDCl_3$) 21.0, 57.1, 70.3 (CH_2), 73.5 (CH_2), 73.7 (CH_2), 77.3, 78.7, 127.6, 127.8, 128.3, 130.0, 131.1, 131.3, 137.2, 138.0; HRMS [ES^+, $(M+Na)^+$]: for $C_{19}H_{22}O_3NaS$ found 353.1188, requires 353.1187.

(3*S*,4*S*, 5*R*)-5-(Benzyloxymethyl)-4-tosyl-tetrahydrofuran-3-ol (12): To a solution of compound **11** (4.39 g, 13.28 mmol) in MeOH (20 mL), MMPP (19.8 g, 40.03 mmol) was added and the mixture was stirred for 6h at room temperature. After completion of the reaction, the mixture was evaporated under reduced pressure. The solid residue was then taken in a mixture of EtOAc and satd. aq. $NaHCO_3$ solution and the mixture was stirred for 1h. Then organic part was separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue thus obtained was purified by flash chromatography (33% EA/PE) to afford compound **12** (4.23 g, 88%) as a white solid; Rf (33% EA/PE) 0.31; Mp 119 ^oC; $[\alpha]_D^{27.3}$ (+) 21.31 (c 1.1, MeOH); δH (400 MHz, $CDCl_3$) 2.44 (3 H, s), 3.59-3.63 (1 H, m), 3.71-3.74 (1 H, m), 3.91-3.94 (2 H, m), 4.26-4.30 (1 H, m), 4.44-4.51 (2 H, m), 4.62 (1 H, d, *J* 11.6 Hz), 4.84-4.88 (1 H, m), 7.26-7.35 (7 H, m), 7.76 (2 H, d, *J* 8 Hz); δC (100 MHz, $CDCl_3$) 21.6, 68.6 (CH_2), 72.8, 73.4 (2 X CH_2), 78.6, 127.6, 127.8, 128.1, 128.3, 130.1, 136.1, 137.8, 145.2; HRMS [ES^+, $(M+H)^+$]: for $C_{19}H_{23}O_5S$ found 363.1279, requires 363.1266.

(*R*)-2-(Benzyloxymethyl)-3-tosyl-2,5-dihydrofuran (6): A stirred solution of compound **12** (2.0 g, 5.52 mmol) in dry pyridine (10 mL) was treated drop-wise at 0 ^oC with a solution of mesyl chloride (1.4 ml, 16.9 mmol) in dry pyridine (6 mL). After 0.5h the solution was stored at +4 ^oC for 24h. After completion (TLC), the reaction mixture was poured into ice-cold water and the compound was extracted with EtOAc. The organic layer was separated, dried

over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. Residual pyridine was co-evaporated with toluene. The residue thus obtained was purified by flash chromatography (33% EA/PE) to afford **6** (1.62 g, 85%) as a yellowish gum; Rf (33% EA/PE) 0.30; $[\alpha]_D^{25.1}$ (+) 41.25 (c 1.28, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.42 (3 H, s), 3.53-3.57 (1 H, m), 3.74 (1 H, d, *J* 10.8 Hz), 4.40 (2 H, s), 4.70-4.74 (1 H, m), 4.81-4.86 (1 H, m), 4.99 (1 H, s), 6.92 (1 H, s), 7.22-7.34 (8 H, m), 7.75 (2 H, d, *J* 8 Hz); δC (100 MHz, $CDCl_3$) 21.6, 70.9 (CH_2), 73.1 (CH_2), 74.5 (CH_2), 83.9, 127.3, 127.4, 128.0, 128.2, 129.9, 136.4, 138.0, 140.5, 141.5, 144.9; HRMS [ES^+, $(M+Na)^+$]: for $C_{19}H_{20}O_4NaS$ found 367.0974, requires 367.0980.

(3*S*,4*S*,5*R*)-5-(Benzyloxymethyl)-4-((*S*)-*p*-tolylsulfinyl)-tetrahydrofuran-3-ol ($13S_S$) and (3*S*,4*S*,5*R*)-5-(Benzyloxymethyl)-4-((*R*)-*p*-tolylsulfinyl)-tetrahydrofuran-3-ol ($13R_S$): To a well-stirred solution of compound **11** (3.86 g, 11.69 mmol) in MeOH (30 mL) was added $NaIO_4$ (3.75 g, 17.54 mmol) in H_2O (8 mL) and the mixture was stirred at room temperature. After 5h volatile matters were removed under reduced pressure and the residual aq. mixture was partitioned between aq. satd. $NaHCO_3$ solution and EtOAc (3 X 10 mL). The combined organic layer was separated, dried over anhyd. Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to get a residue. The residue was purified over silica gel to afford the required sulfoxides. **Compound $13S_S$:** Yellowish gum; Yield (2.26 g, 50%); Rf (60% EA/PE) 0.3; $[\alpha]_D^{25.3}$ (–) 27.21 (c 0.99, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.39 (3 H, s), 3.31-3.34 (1 H, m), 3.59-3.63 (1 H, m), 3.65-3.69 (1 H, m), 3.76-3.80 (1 H, m), 4.24 (1 H, q, *J* 6.8 Hz), 4.33 (1 H, q, *J* 12.4 Hz), 4.58 (2 H, s), 4.93 (1 H, q, *J* 5.2 Hz), 7.27 (2 H, d, *J* 8.0 Hz), 7.31-7.36 (5 H, m), 7.48 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.4 69.5 (CH_2), 71.2, 72.2, 73.6 (CH_2), 73.8 (CH_2), 77.6, 124.6, 127.9, 128.0, 128.4, 130.1, 137.4, 139.8, 142.0; HRMS [ES^+, $(M+H)^+$]: for $C_{19}H_{23}O_4S$ found 347.1304, requires 347.1317.

Compound 13R$_S$: White solid; Yield (1.98 g, 49%); Rf (80% EA/PE) 0.31; Mp 109 ^oC; $[\alpha]_D^{25.3}$ (+) 54.46 (c 1.01, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.42 (3 H, s), 3.38-4.40 (1 H, m), 3.50-3.54 (1 H, m), 4.00-4.06 (3 H, m), 4.15-4.18 (1 H, m), 4.53-4.57 (1 H, m), 4.64, (2 H, q, *J* 12.0 Hz), 7.28-7.41 (7 H, m), 7.60 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.5, 69.6 (CH_2), 71.3, 73.6 (CH_2), 74.3 (CH_2), 74.7, 79.2, 125.6, 127.7, 127.9, 128.4, 130.2, 137.8, 138.6, 142.8; HRMS [ES^+, $(M+H)^+$]: for $C_{19}H_{23}O_4S$ found 347.1334, requires 347.1317.

(3*S*,4*S*,5*R*)-5-(Benzyloxymethyl)-4-((*S*)-*p*-tolylsulfinyl)-tetrahydrofuran-3-yl methanesulfonate (14S$_S$): Following the procedure described for the preparation of **6**, sulfoxide **13S$_S$** (2.0 g, 5.78 mmol) was converted to **14S$_S$** (2.18 g, 89%). White solid; Rf (50% EA/PE) 0.31; Mp 88 ^oC; $[\alpha]_D^{25.3}$ (–) 35.95 (c 1.05, $CHCl_3$); δH(400 MHz, $CDCl_3$) 2.36 (3 H, s), 2.45 (3 H, s), 3.42 (1 H, d, *J* 6.4 Hz), 3.83-3.90 (2 H, m), 3.94-3.99 (1 H, m), 4.28-4.32 (1 H, m), 4.46 (1 H, q, *J* 6.4 Hz), 4.56 (2 H, s), 5.40-5.42 (1 H, m), 7.25-7.30 (7 H, m), 7.41 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.4, 37.6, 68.8 (CH_2), 70.0, 73.9 (2 X CH_2), 78.1, 78.1, 124.4, 128.1, 128.1, 128.6, 130.3, 137.4, 139.1, 142.0; HRMS [ES^+, $(M+H)^+$]: for $C_{20}H_{25}O_6S_2$ found 425.1085, requires 425.1093.

(3*S*,4*S*,5*R*)-5-(Benzyloxymethyl)-4-((*R*)-*p*-tolylsulfinyl)-tetrahydrofuran-3-yl methanesulfonate (14R$_S$): Following the procedure described for the preparation of **6**, sulfoxide **13R$_S$** (1.5 g, 4.33 mmol) was converted to **14R$_S$** (1.69 g, 92%). Yellowish gum; Rf (60%EA/PE) 0.32; $[\alpha]_D^{25.3}$ (+) 49.57 (c 0.95, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.41 (3 H, s), 2.52 (3 H, s), 3.67-3.70 (1 H, m), 3.86-3.89 (1 H, m), 3.99-4.08 (2 H, m), 4.22-4.27 (1 H, m), 4.56-4.71 (3 H, m), 4.92-4.95 (1 H, m), 7.30-7.38 (7 H, m), 7.65 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.4, 37.7, 69.5 (CH_2), 71.3, 73.4 (CH_2), 73.7 (CH_2), 78.3, 79.1, 126.0, 127.8,

128.5, 130.2, 137.5, 138.6, 146.1; HRMS [ES^+, $(M+H)^+$]: for $C_{20}H_{25}O_6S_2$ found 425.1085, requires 425.1093.

(*R*)-2-(Benzyloxymethyl)-3-((*R*)-*p*-tolylsulfinyl)-2,5-dihydrofuran ($7R_S$): The mesylated compound **$14S_S$** (2.15 g, 5.07 mmol) was treated with DBU (1.5 mL, 10.14 mmol) in DCM (15 mL) at ambient temperature for 3h. Solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (40% EA/PE) to afford corresponding vinyl sulfoxides **$7R_S$** (1.51 g, 91%) as a brown solid; Rf (40% EA/PE) 0.34; Mp 131 ^oC; $[\alpha]_D^{25.3}$ (–) 60.21 (c 0.98, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.36 (3 H, s), 3.44-3.52 (2 H, m), 4.45 (2 H, q, *J* 12.0 Hz), 4.55 (1 H, bs), 4.69-4.74 (1 H, m), 4.81-4.86 (1 H, m), 6.68 (1 H, s), 7.22 (2 H, d, *J* 8.0 Hz), 7.29-7.36 (5 H, m), 7.45 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.4, 71.5 (CH_2), 73.5 (CH_2), 75.5 (CH_2), 88.3, 125.6, 127.7, 127.8, 128.3, 130.0, 131.4, 137.6, 138.6, 142.3, 146.3; HRMS [ES^+, $(M+Na)^+$]: for $C_{19}H_{20}O_3NaS$ found 351.1004, requires 351.1031.

(*R*)-2-(Benzyloxymethyl)-3-((*S*)-*p*-tolylsulfinyl)-2,5-dihydrofuran ($7S_S$): Following the procedure described for the preparation of **$7R_S$**, compound **$14R_S$** (1.2 g, 2.83 mmol) was converted to **$7S_S$** (0.85 g, 92%). Colorless gum; Rf (40% EA/PE) 0.30; $[\alpha]_D^{25.3}$ (+) 28.94 (c 0.93, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.33 (3 H, s), 3.44-3.48 (1 H, m), 3.63 (1 H, d, *J* 10.8 Hz), 4.41 (2 H, q, *J* 12.4 Hz), 4.59-4.63 (1 H, m), 4.74-4.77 (2 H, m), 6.56 (1 H, s), 7.20-7.27 (7 H, m), 7.39 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.4, 71.8 (CH_2), 73.2 (CH_2), 74.7 (CH_2), 84.0, 124.7, 127.4, 127.5, 128.2, 130.0, 136.3, 138.1, 138.3, 141.8, 143.3; HRMS [ES^+, $(M+H)^+$]: for $C_{19}H_{21}O_3S$ found 329.1190, requires 329.1211.

(2*R*,3*R*,4*R*)-2-(Benzyloxymethyl)-4-methoxy-3-tosyl-tetrahydrofuran (15): Sodium methoxide (0.02 g, 0.36 mmol) was added to an anhyd. methanolic solution (5 mL) of vinyl sulfone **6** (0.043 g, 0.09 mmol) and the mixture was stirred at room temperature for 36h. Volatile matters were removed under reduced pressure. The solid residue was then taken in a mixture of EtOAc and satd. aq. $NaHCO_3$ solution and the mixture was stirred for 1h. Organic layers were separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated. The residue thus obtained, was purified by flash chromatography (20% EA/PE) to afford compound **15** (0.04 g, 86%) as a white solid; Rf (20% EA/PE) 0.32; Mp 82 ^oC; $[\alpha]_D^{25.1}$ (+) 29.81 (c 1.02, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.43 (3 H, s), 3.18 (3 H, s), 3.28-3.32 (1 H, m), 3.50 (1 H, dd, *J* 3.2, 10.8 Hz), 3.67 (1 H, d, *J* 6.0 Hz), 3.80-3.84 (1 H, m), 4.03 (1 H, d, *J* 10.0 Hz), 4.35-4.41 (3 H, m), 4.52 (1 H, d, *J* 12.0 Hz), 7.23-7.33 (7 H, m), 7.74 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.6, 56.9, 69.8, 69.9 (CH_2), 73.0 (CH_2), 73.3 (CH_2), 78.6, 82.2, 127.6, 127.7, 128.3, 128.5, 130.0, 135.0, 137.8, 145.2; HRMS [ES^+, $(M+Na)^+$]: for $C_{20}H_{24}O_5NaS$ found 399.1248, requires 399.1242.

(2*R*,3*R*,4*R*,5*S*)-2-(Benzyloxymethyl)-4,5-dimethoxy-3-(*p*-tolylthio)-tetrahydrofuran (17): Sodium hydride (0.88 g, 18.5 mmol) was added to an ice-cold solution of compound **16**[15] (2.66 g, 7.4 mmol) in anhyd. DMF (15 mL) and the mixture was stirred for 0.5h. Methyl iodide (1.6 mL, 22.2 mmol) was added slowly to the mixture and it was stirred at room temperature for 2.5h. After completion of the reaction, the whole mixture was poured into ice-cold water and the compound was extracted with EtOAc. Organic layers were separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography (20% EA/PE) to afford compound **17** (2.38 g, 86%) as colorless gum; Rf (20% EA/PE) 0.32; $[\alpha]_D^{25.1}$ (+) 91.74 (c 1.2, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.33 (3 H, s), 3.30 (3 H, s), 3.12-3.40 (1 H, m), 3.42 (3 H, s), 3.54 (1 H, dd, *J* 5.2,

10.8 Hz), 3.67 (1 H, dd, *J* 2.4, 10.8 Hz), 3.79 (1 H, d, *J* 4.0 Hz), 4.13-4.17 (1 H, m), 4.53 (2 H, q, *J* 12.0 Hz), 4.96 (1 H, s), 7.09 (2 H, d, *J* 8.0 Hz), 7.27-7.37 (7 H, m); δC (100 MHz, $CDCl_3$) 21.3, 51.7, 55.2, 58.0, 69.8 (CH_2), 73.6 (CH_2), 82.5, 91.9, 107.4, 127.8, 127.9, 128.5, 130.0, 130.7, 132.7, 137.8, 138.3; HRMS [ES^+, $(M+Na)^+$]: for $C_{21}H_{26}O_4NaS$ found 397.1433, requires 397.1450.

(2*R*,3*R*,4*R*)-5-(Benzyloxy)-2-methoxy-3-(*p*-tolylthio)-pentane-1,4-diol (18): Following the procedure described for the synthesis of **10**, compound **17** (1.97 g, 5.3 mmol) was converted to compound **18** (1.16 g, 61%).Colorless gum; Rf (33% EA/PE) 0.30; $[\alpha]_D^{27.4}$ (+) 12.99 (c 1.0, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.31 (3 H, s), 3.43-3.47 (1 H, m), 3.49 (3 H, s), 3.70-3.77 (2 H, m), 3.87-4.02 (4 H, m), 4.37 (2 H, q, *J* 11.6 Hz), 7.07 (2 H, d, *J* 8.0 Hz), 7.21 (2 H, d, *J* 6.4 Hz), 7.26-7.34 (5 H, m); δC (100 MHz, $CDCl_3$) 21.0, 53.3, 58.8, 62.1 (CH_2), 71.5, 71.7 (CH_2), 73.2 (CH_2), 80.8, 127.7, 127.8, 128.3, 129.8, 131.4, 132.1, 137.0, 137.7; HRMS [ES^+, $(M+H)^+$]: for $C_{20}H_{27}O_4S$ found 363.1626, requires 363.1630.

(2*R*,3*S*,4*R*)-2-(Benzyloxy)-4-methoxy-3-(*p*-tolylthio)-tetrahydrofuran (19): Following the procedure described for the preparation of **11**, compound **18** (1.23 g, 3.39 mmol) was converted to **19** (0.89 g, 76%); Colorless gum; Rf (20% EA/PE) 0.33; $[\alpha]_D^{27.4}$ (+) 91.89 (c 1.01, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.34 (3 H, s), 3.20 (3 H, s), 3.43-3.47 (1 H, m), 3.56-3.65 (2 H, m), 3.85-4.02 (4 H, m), 4.56 (2 H, s), 7.12 (2 H, d, *J* 7.6 Hz), 7.27-7.37 (7 H, m); δC (100 MHz, $CDCl_3$) 21.4, 52.5, 57.1, 71.1 (CH_2), 71.9 (CH_2), 73.6 (CH_2), 83.7, 87.3, 127.8, 128.0, 128.6, 130.1, 130.6, 132.6, 137.9, 138.4; HRMS [ES^+, $(M+H)^+$]: for $C_{20}H_{25}O_3S$ found 345.1515, requires 345.1524.

Alternative synthesis of compound 15 from 19: Following the procedure described for the preparation of **12**, compound **19** (0.21 g, 0.50 mmol) was converted to **15** (0.19 g, 84%).

(2*R*,3*R*,4*R*)-2-(Benzyloxymethyl)-4-methoxy-3-((*S*)-*p*-tolylsulfinyl)-tetrahydrofuran (20S$_S$): Following the procedure described for the preparation of **15**, vinyl sulfoxide **7R$_S$** (0.07 g, 0.21 mmol) was converted to **20S$_S$** (0.07 g, 92%). White solid; Rf (33% EA/PE) 0.30; Mp 97 ^oC; $[\alpha]_D^{25.3}$ (–) 77.31 (c 1.1, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.37 (3 H, s), 2.78-2.82 (1 H, m), 3.17-3.22 (2 H, m), 3.33 (3 H, s), 3.69-3.73 (1 H, m), 3.98-4.01 (1 H, m), 4.26-4.32 (3 H, m), 4.42 (1 H, d, *J* 12.4 Hz), 7.19-7.33 (8 H, m), 7.42 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.4, 57.1, 67.5, 70.8 (CH_2), 71.9 (CH_2), 73.1 (CH_2), 74.8, 82.8, 124.0, 127.5, 127.6, 128.2, 129.9, 137.7, 137.9, 141.7; HRMS [ES^+, $(M+H)^+$]: for $C_{20}H_{25}O_4S$ found 361.1445, requires 361.1474.

(2*R*,3*R*,4*R*)-2-(Benzyloxymethyl)-4-methoxy-3-((*R*)-*p*-tolylsulfinyl)-tetrahydrofuran (20R$_S$): Following the procedure described for the preparation of **15**, vinyl sulfoxide **7S$_S$** (0.054 g, 0.16 mmol) was converted to **20R$_S$** (0.053 g, 91%). White solid; Rf (33% EA/PE) 0.30; Mp 103 ^oC; $[\alpha]_D^{25.3}$ (+) 134.56 (c 1.1, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.43 (3 H, s), 3.00 (3 H, s). 3.19 (1 H, d, *J* 6.4 Hz), 3.45-3.56 (2 H, m), 3.81-3.84 (1 H, m), 4.05 (1 H, d, *J* 10.4 Hz), 4.21-4.25 (1 H, m), 4.28-4.29 (1 H, m), 4.54 (2 H, q, *J* 12.4 Hz), 7.28-7.38 (7 H, m), 7.53 (2 H, d, *J* 8.4 Hz); δC (100 MHz, $CDCl_3$) 21.7, 56.7, 70.4 (CH_2), 70.7, 73.6 (CH_2), 73.7 (CH_2), 78.4, 80.4, 124.8, 127.9, 127.9, 128.6, 130.2, 138.1, 138.8, 142.3; HRMS [ES^+, $(M+H)^+$]: for $C_{20}H_{25}O_4S$ found 361.1486, requires 361.1474.

Compound 15 from 20R$_S$ or 20S$_S$: To a solution of **20S$_S$** or **20S$_S$** (0.2 g, 0.56 mmol) in MeOH (7 mL), MMPP (0.56 g, 1.11 mmol) was added and the mixture was stirred for 2h at

room temperature. After completion of the reaction, the mixture was evaporated under reduced pressure. The solid residue was then taken in a mixture of EtOAc and satd. aq. $NaHCO_3$ solution and the mixture was stirred for 1h. Then organic part was separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue thus obtained was purified over silica gel column to afford compound **15** (0.19 g, 91%).

(2*R*,3*R*,4*R*)-2-(Benzyloxymethyl)-4-(nitromethyl)-3-tosyl-tetrahydrofuran (21): A mixture of nitromethane (0.09 mL, 1.74 mmol) and KO^{t}Bu (0.16 g, 1.45 mmol) in DMF (5 mL) was stirred at room temperature under N_2 atmosphere. After 0.5h compound **6** (0.2 g, 0.58 mmol) in THF (4mL) was added to the mixture and stirred at room temperature for 4h. After completion of reaction, the mixture was evaporated under reduced pressure. The residue was then taken in a mixture of EtOAc and satd. aq. NH_4Cl solution and the mixture was stirred for 0.5h. The organic part was separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue thus obtained was purified by flash chromatography(20% EA/PE) to afford the compound **21** (0.21g, 90%) as white solid; Rf (20% EA/PE) 0.34; Mp 94 ^oC; $[\alpha]_D^{25.1}$ (+) 41.21 (c 0.99, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.45 (3 H, s), 3.21-3.24 (1 H, m), 3.34 (1 H, bs), 3.56-3.59 (1 H, m), 3.65 (1 H, d, *J* 12.0 Hz), 3.81-3.83 (1 H, m), 4.00-4.04 (1 H, m), 4.36-4.55 (5 H, m), 7.24 (2 H, d, *J* 6.4 Hz), 7.33-7.35 (5 H, m), 7.70 (2 H, d, *J* 7.6 Hz); δC (100 MHz, $CDCl_3$) 21.7, 40.4, 66.1, 69.7 (CH_2), 71.0 (CH_2), 73.5 (CH_2), 75.6 (CH_2), 78.7, 127.8, 127.9, 128.5, 128.5, 130.2, 134.1, 137.3, 145.7; HRMS [ES$^+$, $(M+H)^+$]: for $C_{20}H_{24}NO_6S$ found 406.1313, requires 406.1324.

Dimethyl-2-((3*R*,4*R*,5*R*)-5-(benzyloxymethyl)-4-tosyl-tetrahydrofuran-3-yl)malonate (22): A mixture of dimethylmalonate (0.2 mL, 1.74 mmol) and KO^{t}Bu (0.16 g, 1.45 mmol) in DMF (5 mL) was reacted with compound **6** (0.2 g, 0.58 mmol) in THF (4 mL) following the

procedure described for **21** to afford compound **22** (0.25 g, 91%) as white solid; Rf (20% EA/PE) 0.31; Mp 113 ^{o}C; $[\alpha]_D^{25.1}$ (+) 41.21 (c 0.99, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.42 (3 H, s), 3.22 (1 H, dd, *J* 4.0, 10.4 Hz), 3.28-3.32 (1 H, m), 3.51 (1 H, dd, *J* 2.0, 10.8 Hz), 3.58 (3 H, s), 3.63-3.70 (4 H, m), 3.77-3.79 (1 H, m), 3.84 (1 H, dd, *J* 2.8, 9.6 Hz), 3.98-4.01 (1 H, m), 3.47-3.52 (3 H, m), 7.26-7.35 (7 H, m), 7.71 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.6, 41.3, 52.6, 52.7, 52.8, 66.3, 70.0 (CH_2), 71.5 (CH_2), 73.4 (CH_2), 79.0, 127.7, 127.8, 128.3, 128.8, 130.0, 134.6, 137.5, 145.2, 167.9, 168.1; HRMS [ES^+, $(M+Na)^+$]: for $C_{24}H_{28}O_8NaS$ found 499.1397, requires 499.1403.

(3*R*,4*R*,5*R*)-N-benzyl-5-(benzyloxymethyl)-4-tosyl-tetrahydrofuran-3-amine (23): Benzyl amine (0.6 mL, 5.8 mmol) was added to an anhyd. methanolic solution (5 mL) of vinyl sulfone **6** (0.2 g, 0.58 mmol) and the mixture was stirred at room temperature for 4h. Volatile matters were removed under reduced pressure. The residue was then taken in a mixture of EtOAc and satd. aq. NH_4Cl solution and the mixture was stirred for 1h. Then organic part was separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue thus obtained was purified by falsh chromatography to afford the compound **23** (0.23 g, 90%) as brown solid; Rf (20% EA/PE) 0.32; Mp 103 ^{o}C; $[\alpha]_D^{25.1}$ (+) 53.30 (c 1.03, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.45 (3 H, s), 3.32 (1 H, dd, *J* 2.8, 10.4 Hz), 3.51 (2 H, q, *J* 13.6 Hz), 3.65-3.71 (3 H, m), 3.85-3.92 (2 H, m), 4.41-4.56 (3 H, m), 7.09 (2 H, d, *J* 4.8 Hz), 7.22-7.34 (10 H, m), 7.68 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.6, 50.8 (CH_2), 60.4, 69.3, 70.3 (CH_2), 73.5 (CH_2), 77.9, 127.0, 127.7, 127.8, 128.0, 128.3, 128.4, 128.5, 130.0, 134.9, 137.4, 138.9, 145.1; HRMS [ES^+, $(M+H)^+$]: for $C_{26}H_{30}NO_4S$ found 452.1915, requires 452.1895.

(3*R*,4*R*,5*R*)-5-(Benzyloxymethyl)-N-isopropyl-4-tosyl-tetrahydrofuran-3-amine (24): Isopropylamine (0.9 mL, 11.6 mmol) was reacted with **6** (0.2 g, 0.58 mmol) following the procedure described for **23** to afford the compound **24** (0.21 g, 91%) as colorless gum; Rf (20% EA/PE) 0.30; $[\alpha]_D^{25.1}$ (+) 39.15 (c 0.97, $CHCl_3$); δH (400 MHz, $CDCl_3$) 0.76 (6 H, t, J 6.0 Hz), 2.43 (3 H, s), 2.47-2.53 (1 H, m), 3.22 (1 H, dd, *J* 3.2, 10.4 Hz), 3.61-3.70 (3 H, m), 3.82 (1 H, d, *J* 9.2 Hz), 3.87-3.91 (2 H, m), 4.38-4.54 (3 H, m), 7.24-7.33 (7 H, m), 7.73 (2 H, d, *J* 8.4 Hz); δC (100 MHz, $CDCl_3$) 21.6, 21.7, 22.8, 45.4, 58.2, 69.0, 70.2 (CH_2), 73.6 (CH_2), 74.3 (CH_2), 77.8, 127.9, 127.9, 128.4, 128.4, 130.0, 135.1, 137.4, 145.0; HRMS [ES^+, $(M+H)^+$]: for $C_{22}H_{30}NO_4S$ found 404.1909, requires 404.1896.

4-((3*R*,4*R*,5*R*)-5-(Benzyloxymethyl)-4-tosyl-tetrahydrofuran-3-yl)morpholine (25): Morpholine (0.5 mL, 5.8 mmol) was reacted with **6** (0.2 g, 0.58 mmol) following the procedure described for **23** to afford the compound **25** (0.22 g, 91%) as a brownish solid; Rf (20% EA/PE) 0.32; Mp 121 ^oC; $[\alpha]_D^{25.1}$ (+) 47.91 (c 1.00, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.35-2.42 (7 H, m), 2.18 (1 H, dd, *J* 4.4, 10.8 Hz), 3.47 (1 H, dd, *J* 2.0, 10.8 Hz), 3.52-3.55 (4 H, m), 3.74-3.85 (3 H, m), 4.08 (1 H, d, *J* 10.0 Hz), 4.22-4.24 (1 H, m), 4.39 (2 H, q, *J* 12.0 Hz), 7.21 (2 H, d, *J* 6.8 Hz), 7.26-7.33 (5 H, m), 7.72 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.6, 49.5 (CH_2), 63.8, 66.8 (CH_2), 67.5, 69.6 (CH_2), 70.4 (CH_2), 73.4 (CH_2), 79.1, 127.6, 127.7, 128.3, 128.5, 129.9, 135.2, 137.6, 145.1; HRMS [ES^+, $(M+Na)^+$]: for $C_{23}H_{29}NO_5NaS$ found 454.1680, requires 454.1664.

Dimethyl-2-((3*R*,4*R*,5*R*)-5-(benzyloxymethyl)-4-((*S*)-*p*-tosylsufinyl)-tetrahydrofuran-3-yl)malonate ($26S_S$): A mixture of dimethylmalonate (0.3 mL, 2.73 mmol) and NaH (0.1 g, 2.26 mmol) in DMF (5 mL) in DMF (3 mL) was stirred at room temperature under N_2 atmosphere. After 0.5 h compound $\mathbf{7R_S}$ (0.3 g, 0.91 mmol) was added to the mixture and

heated at 60 ^{o}C for 6h. After completion of reaction, the mixture was partitioned between EtOAc and satd. aq. $NaHCO_3$ solution. Then organic part was separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue thus obtained was purified by flash chromatography (25% EA/PE) to afford the compound **26S$_S$** (0.39 g, 93%) as a yellowish gum; Rf (25% EA/PE) 0.30; $[\alpha]_D^{25.3}$ (–) 85.96 (c 0.89, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.37 (3 H, s), 2.47-2.50 (1 H, m), 3.16-3.22 (2 H, m), 3.32-3.37 (1 H, m), 3.67 (1 H, d, *J* 8.8 Hz), 3.71-3.77 (7 H, m), 3.95-3.99 (1 H, m), 4.17 (1 H, d, *J* 12.0 Hz), 4.31-4.33 (1 H, m), 4.40 (1 H, d, *J* 12.0 Hz), 7.15-7.41 (10 H, m); δC (100 MHz, $CDCl_3$) 21.3, 42.7, 52.7, 52.7, 53.3, 65.1, 70.9 (CH_2), 71.3 (CH_2), 73.1 (CH_2), 74.8, 123.7, 127.6, 127.6, 128.2, 129.8, 137.7, 138.3, 141.3, 168.3, 168.6; HRMS [ES^+, $(M+H)^+$]: for $C_{24}H_{29}O_7S$ found 461.1620, requires 461.1634.

(3*R*,4*R*,5*R*)-N-benzyl-5-(benzyloxymethyl)-4-((*S*)-*p*-tolylsulfinyl)-tetrahydrofuran-3-amine (27S$_S$): A mixture of vinyl sulfoxide **7R$_S$** (0.3 g, 0.91 mmol) and benzylamine (3.0 mL, 27.3 mmol) was stirred at room temperature for 48h. After completion of reaction, the mixture was partitioned between EtOAc and satd. aq. NH_4Cl solution. Then organic part was separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue thus obtained was purified by flash chromatography (40% EA/PE) to afford the compound **27S$_S$** (0.37 g, 94%) as a yellowish gum; Rf (40% EA/PE) 0.32; $[\alpha]_D^{25.3}$ (–) 71.87 (c 0.98, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.40 (3 H, s), 2.70 (1 H, dd, *J* 3.2, 10.8 Hz), 3.16-3.17 (1 H, m), 3.45 (1 H, d, *J* 10.4 Hz), 3.63-3.65 (3 H, m), 3.79 (1 H, dd, *J* 5.2, 8.0 Hz), 3.93 (1 H, d, *J* 9.2 Hz), 4.26-4.31 (2 H, m), 4.47 (1 H, d, *J* 12.0 Hz), 7.17-7.28 (13 H, m), 7.37 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.5, 51.4 (CH_2), 61.4, 68.1, 71.1 (CH_2), 73.0 (CH_2), 73.4 (CH_2), 75.3, 124.2, 127.1, 127.8, 127.9, 128.1, 128.4, 128.5, 130.0, 137.7, 138.4, 139.4, 141.6; HRMS [ES^+, $(M+H)^+$]: for $C_{26}H_{30}NO_3S$ found 436.1935, requires 436.1946.

Dimethyl-2-((3*R*,4*R*,5*R*)-5-(benzyloxymethyl)-4-((*R*)-*p*-tolylsulfinyl)-tetrahydrofuran-3-yl)malonate ($26R_S$): Dimethylmalonate (0.3 mL, 2.73 mmol) was reacted with compound $7S_S$ (0.3 g, 0.91 mmol) following the procedure described for $26S_S$ to afford the compound $26R_S$ (0.40 g, 93%) as a colorless gum; Rf (25% EA/PE) 0.34; $[\alpha]_D^{25.3}$ (+) 143.57 (c 0.98, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.38 (3 H, s), 3.24-3.36 (4 H, m), 3.42 (1 H, dd, *J* 3.6, 10.4 Hz), 3.61 (6 H, d, *J* 10.0 Hz), 3.85 (2 H, d, *J* 5.2 Hz), 4.17-4.21 (1 H, m), 4.48 (2 H, q, *J* 12.4 Hz), 7.26-7.35 (7 H, m), 7.48 (2 H, d, *J* 8.4 Hz); δC (100 MHz, $CDCl_3$) 21.4, 39.2, 52.5, 52.6, 53.2, 66.6, 70.6 (CH_2), 71.6 (CH_2), 73.4 (CH_2), 78.1, 124.8, 127.7, 127.7, 128.3, 130.0, 137.6, 138.0, 142.2, 168.2; HRMS [ES^+, $(M+H)^+$]: for $C_{24}H_{29}O_7S$ found 461.1617, requires 461.1634.

(3*R*,4*R*,5*R*)-N-benzyl-5-(benzyloxymethyl)-4-((*R*)-p-tolylsulfinyl)-tetrahydrofuran-3-amine ($27R_S$): Benzylamine (3.0 mL, 27.3 mmol) was reacted with $7S_S$ (0.3 g, 0.91 mmol) following a procedure described for $27S_S$ to afford $27R_S$ (0.35 g, 94%) as a yellowish gum; Rf (40% EA/PE) 0.30; $[\alpha]_D^{25.3}$ (–) 131.89 (c 0.98, $CHCl_3$); δH (400 MHz, $CDCl_3$) 2.40 (3 H, s), 3.20-3.27 (2 H, m), 3.42-3.52 (3 H, m), 3.74-3.92 (3 H, m), 4.15-4.18 (1 H, m), 4.47 (2 H, q, *J* 12.0 Hz), 7.10 (2 H, d, *J* 6.4 Hz), 7.21-7.33 (10 H, m), 7.47 (2 H, d, *J* 8.0 Hz); δC (100 MHz, $CDCl_3$) 21.4, 51.3 (CH_2), 59.0, 69.9, 70.2 (CH_2), 73.4 (CH_2), 73.9 (CH_2), 77.8, 124.6, 126.9, 127.5, 127.8, 128.0, 128.4, 128.7, 130.1, 137.5, 138.6, 139.3, 142.1; HRMS [ES^+, $(M+H)^+$]: for $C_{26}H_{30}NO_3S$ found 436.1967, requires 436.1946.

Compound 22 from $26S_S$ or $26R_S$: To a solution of compound $26S_S$ (0.2 g, 0.43 mmol) in MeOH (5 mL), MMPP (0.43 g, 0.86 mmol) was added and the mixture was stirred for 2h at room temperature. After completion of the reaction, the mixture was evaporated under reduced pressure. The solid residue was then taken in a mixture of EtOAc and satd. aq.

$NaHCO_3$ solution and the mixture was stirred for 1h. Then organic part was separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue thus obtained was purified over silica gel column to afford compound **22** (0.19 g, 88%). All the data were same as stated earlier in compound **22**. Compound **26R$_S$** was converted to **22** in a similar fashion.

Compound 23 from 27S$_S$ or 27R$_S$: To a solution of compound **27S$_S$** (0.5 g, 1.15 mmol) in MeOH (5 mL), MMPP (0.68 g, 1.37 mmol) was added and the mixture was stirred for 0.5h at room temperature. After completion of the reaction, the mixture was evaporated under reduced pressure. The solid residue was then taken in a mixture of EtOAc and satd. aq. $NaHCO_3$ solution and the mixture was stirred for 1h. Then organic part was separated, dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue thus obtained was purified over silica gel column to afford compound **23** (0.16 g, 31%). All the data were same as stated earlier in compound **23**. Compound **27R$_S$** was converted to **23** in a similar fashion.

Crystallographic data (excluding structure factors) for the structures **7R$_S$** (CCDC 931612), **21** (CCDC 949569) and **25** (CCDC 949570) in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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Supporting Information: NMR spectra of all new compounds and ORTEP diagram of compounds **7R$_S$**, **21** and **25**.

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Vinyl sulfone- and vinyl sulfoxide-modified tetrahydrofurans: A Preliminary Account of the Enantiomeric synthesis of and Diastereoselectivity of addition to a New Class of Michael Acceptors

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S36-S37: ^{1}H-/^{13}C-/DEPT-NMR spectra of compound **22**

S38-S39: ^{1}H-/^{13}C-/DEPT-NMR spectra of compound **23**

S40-S41: ^{1}H-/^{13}C-/DEPT-NMR spectra of compound **24**

S42-S43: ^{1}H-/^{13}C-/DEPT-NMR spectra of compound **25**

S44-S45: ^{1}H-/^{13}C-/DEPT-NMR spectra of compound **26S$_S$**

S46-S47: ^{1}H-/^{13}C-/DEPT-NMR spectra of compound **26R$_S$**

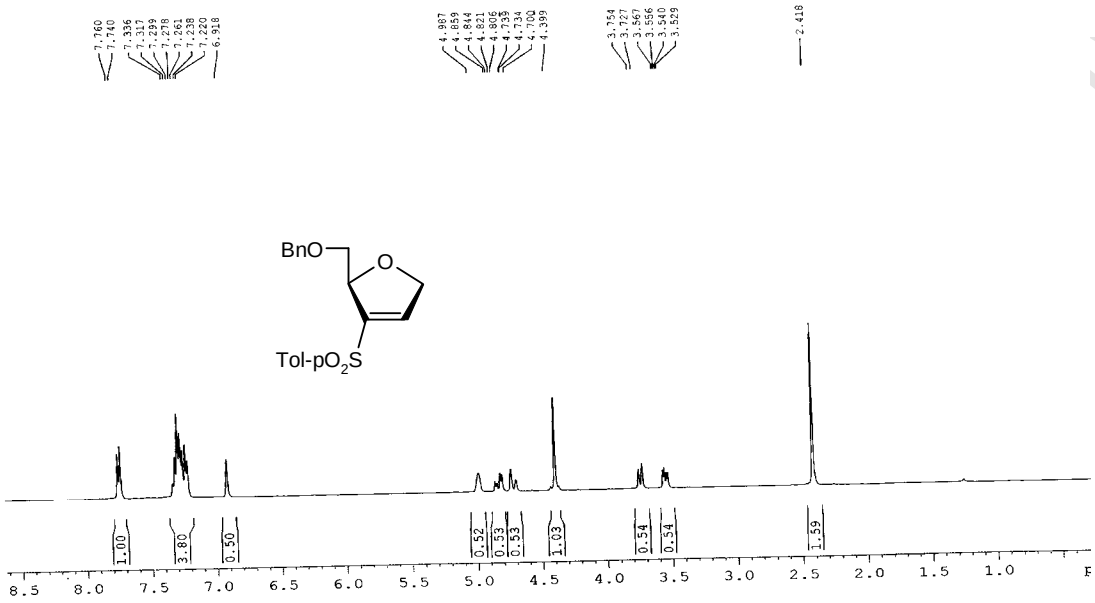
S48-S49: ^{1}H-/^{13}C-/DEPT-NMR spectra of compound **27S$_S$**

S50-S51: ^{1}H-/^{13}C-/DEPT-NMR spectra of compound **27R$_S$**

S52: ORTEP diagram of compound **7R$_S$** and **21**

S53: ORTEP diagram of compound **25**

Compound 6


7.760
7.740
7.336
7.317
7.299
7.278
7.261
7.238
7.220
6.918
4.987
4.859
4.844
4.821
4.806
4.739
4.734
4.700
4.399
3.754
3.727
3.567
3.556
3.540
3.529
2.418
BnO
O
Tol-pO2S
1.00
3.80
0.50
0.52
0.53
0.53
1.03
0.54
0.54
1.59
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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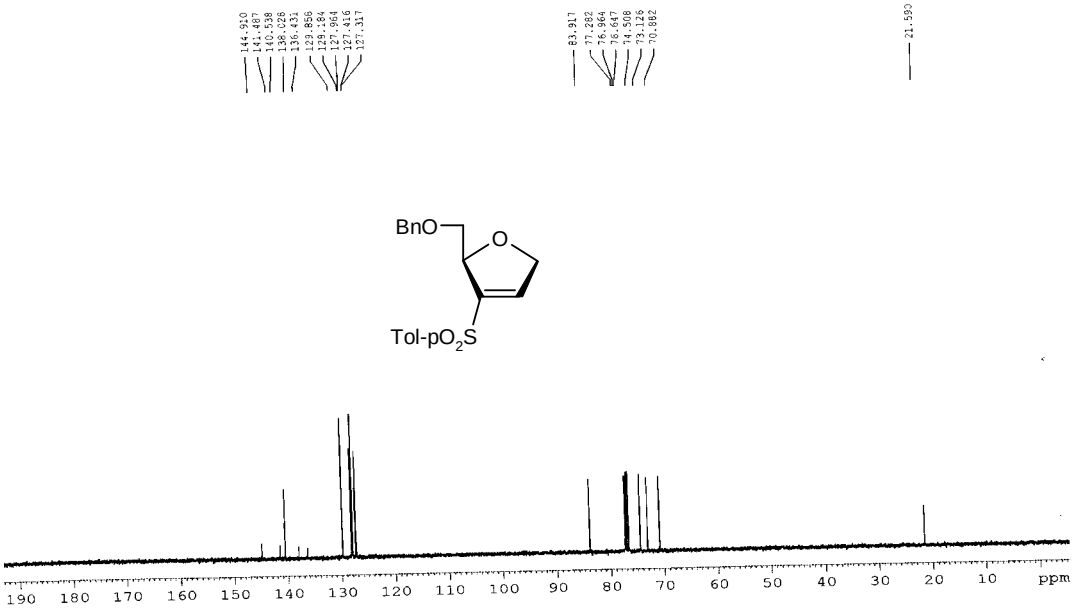
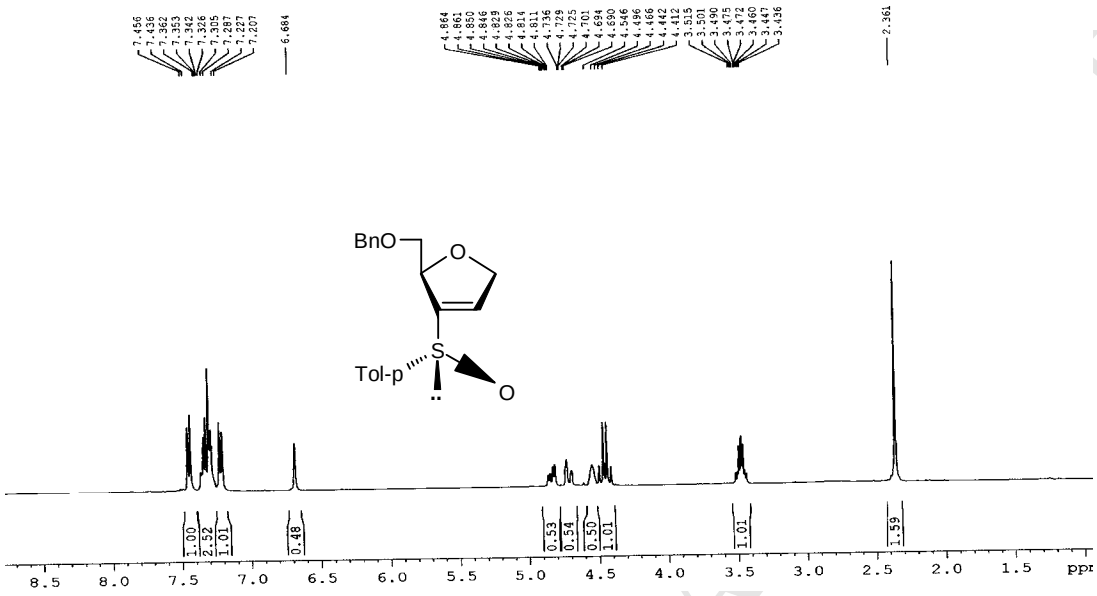
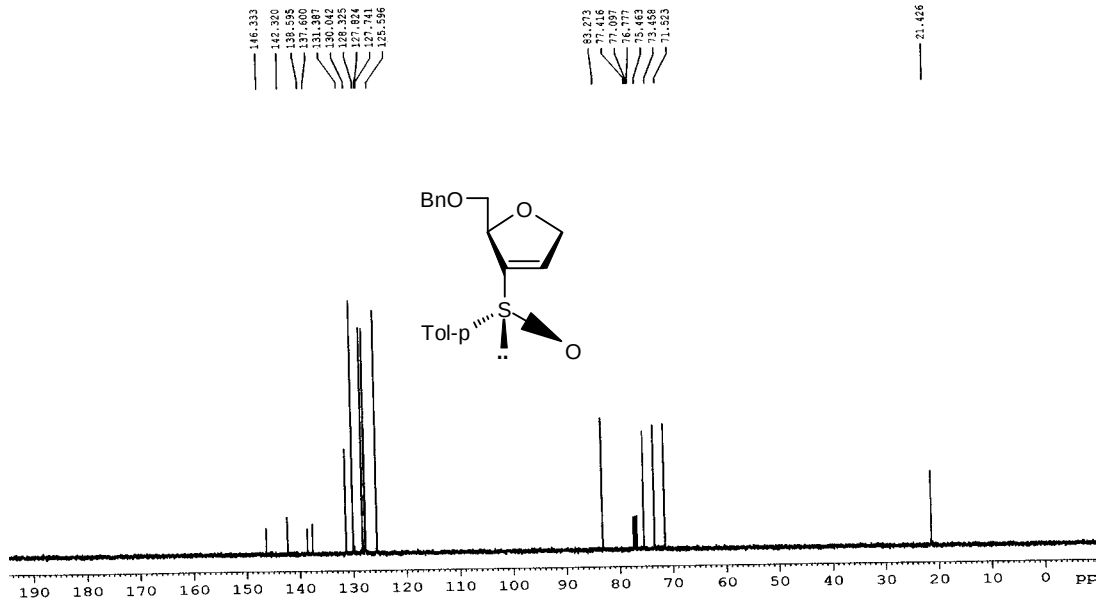
3.5
3.0
2.5
2.0
1.5
1.0

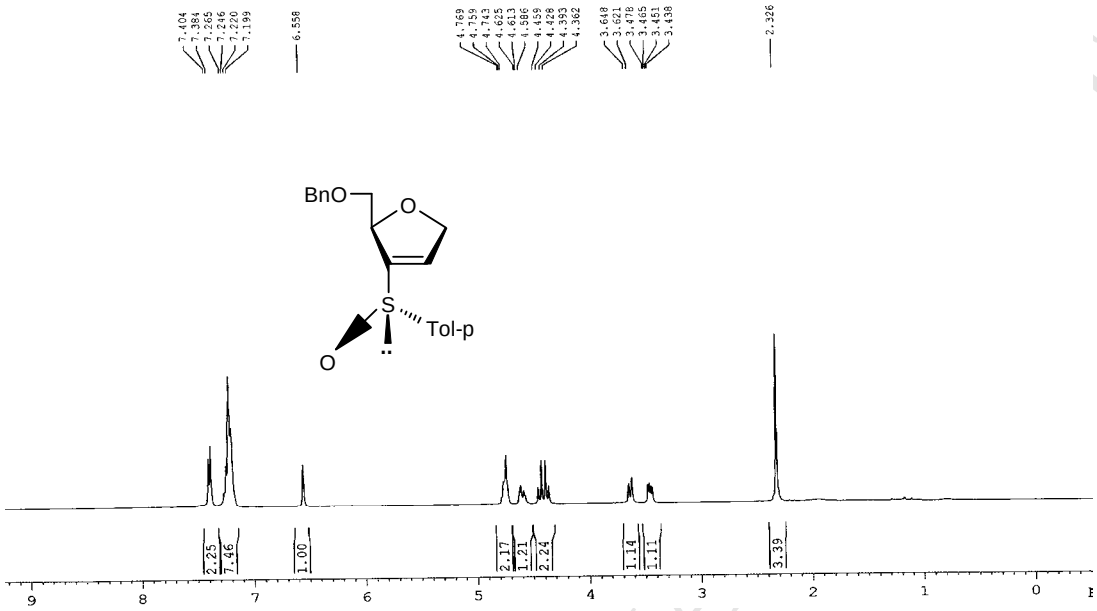

144.910
141.487
140.538
138.028
136.431
129.856
129.384
128.664
127.416
127.317
83.917
77.282
76.964
76.647
74.588
73.126
70.882
21.590
BnO
O
Tol-pO2S
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

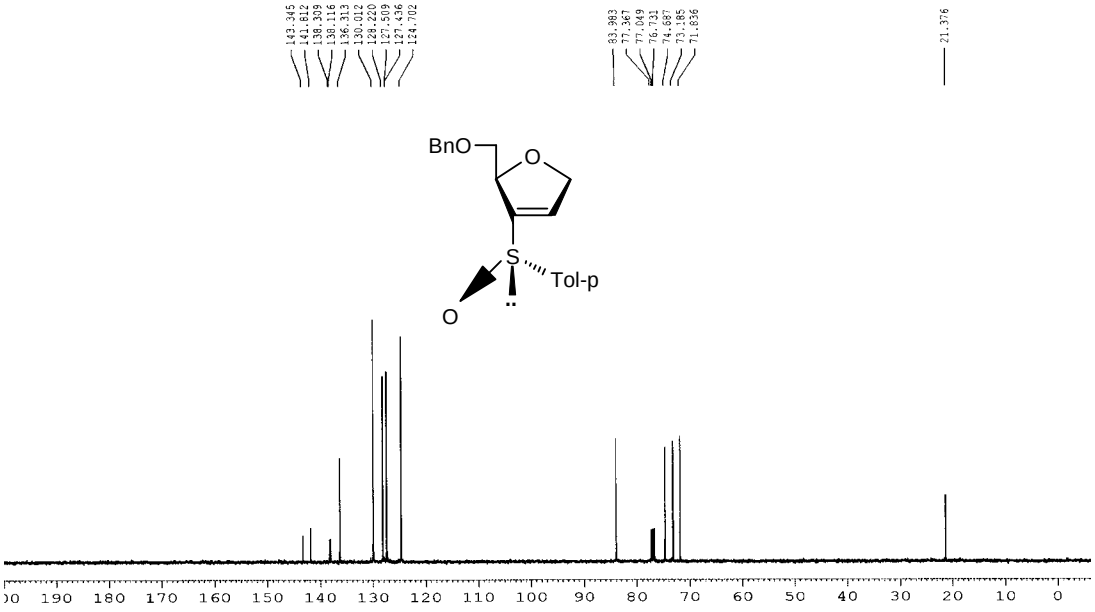
Compound 7R$_S$



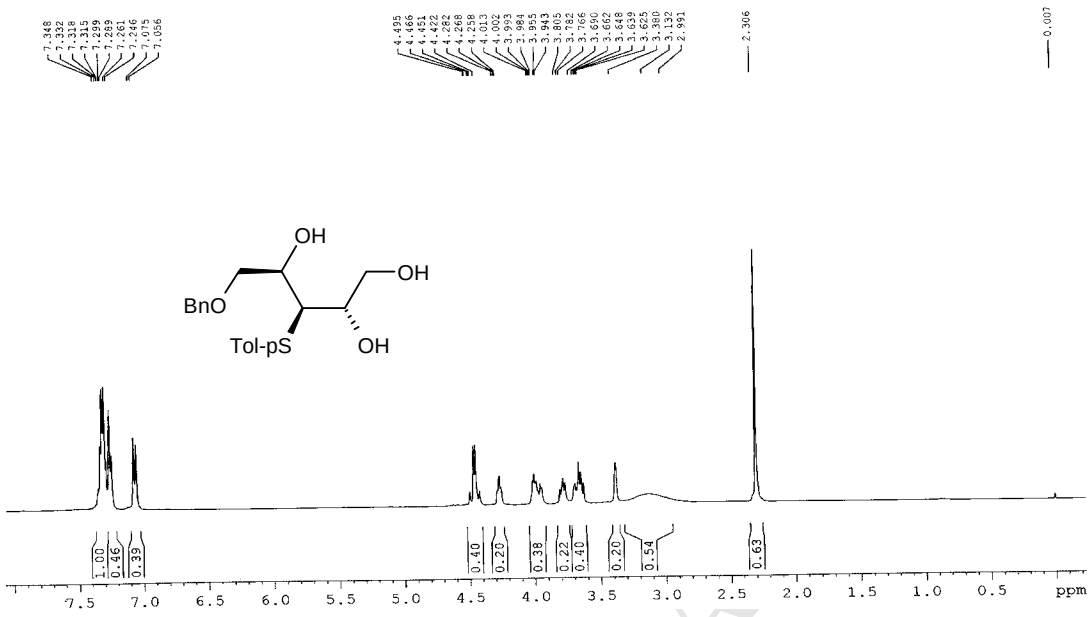


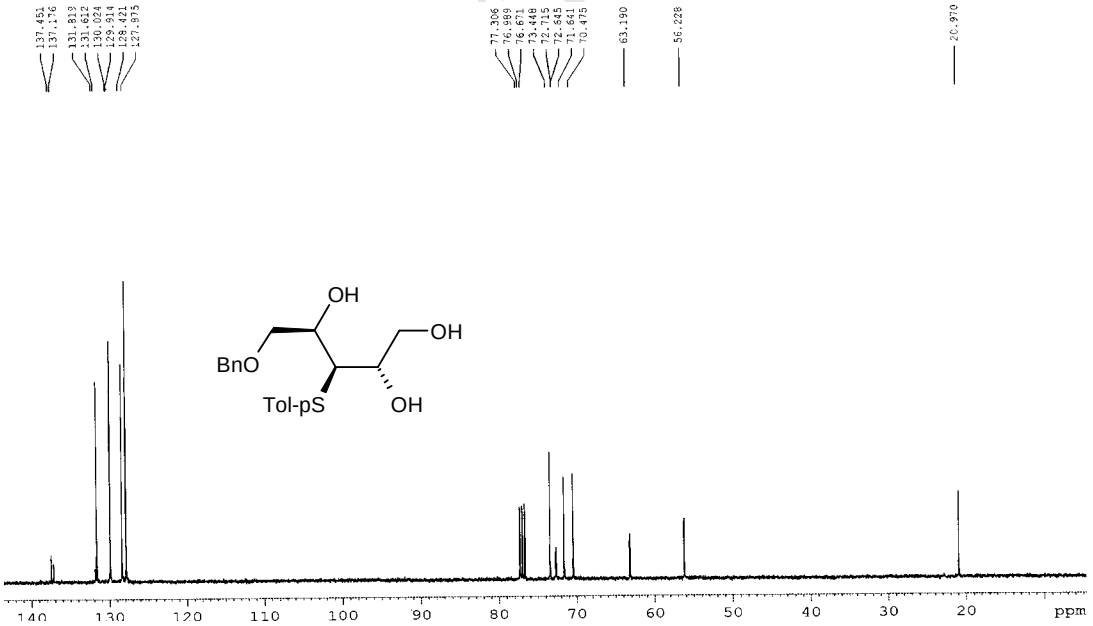
Compound 7S$_S$



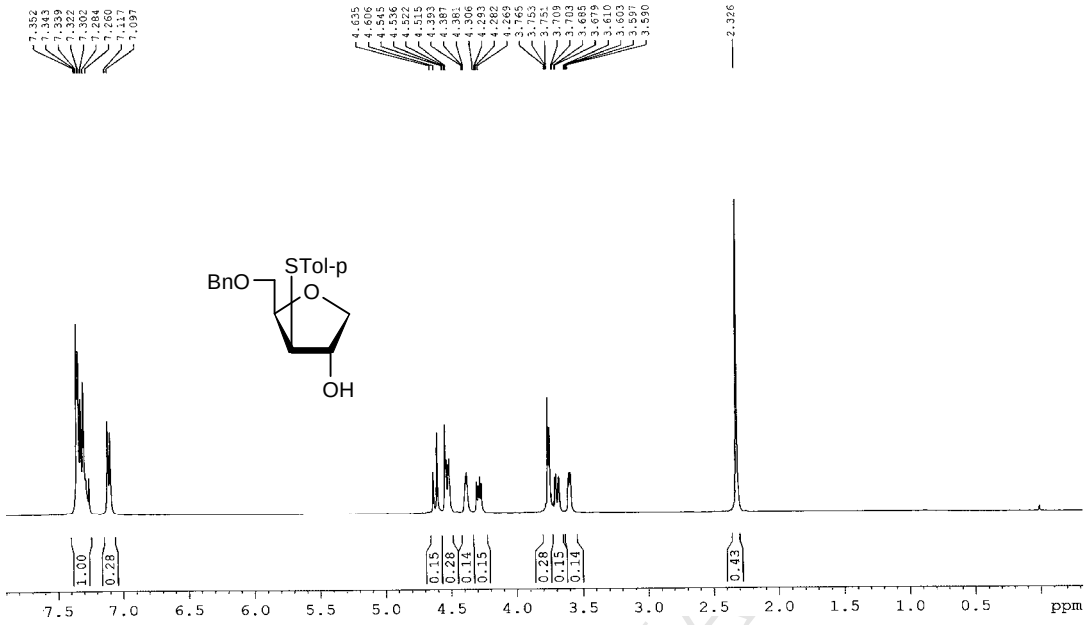


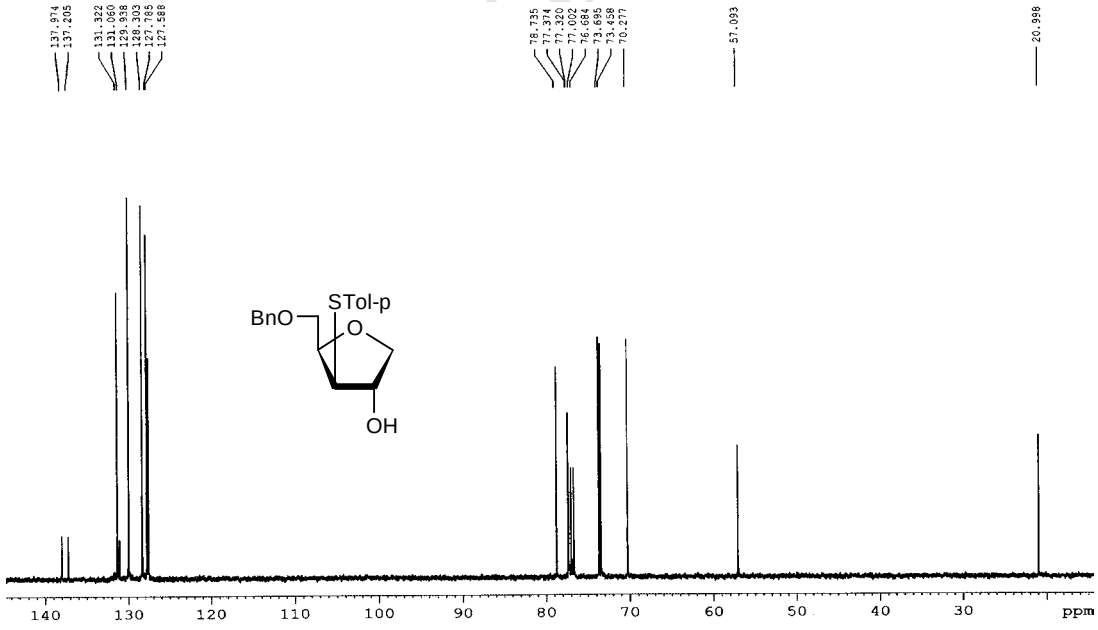
Compound 10



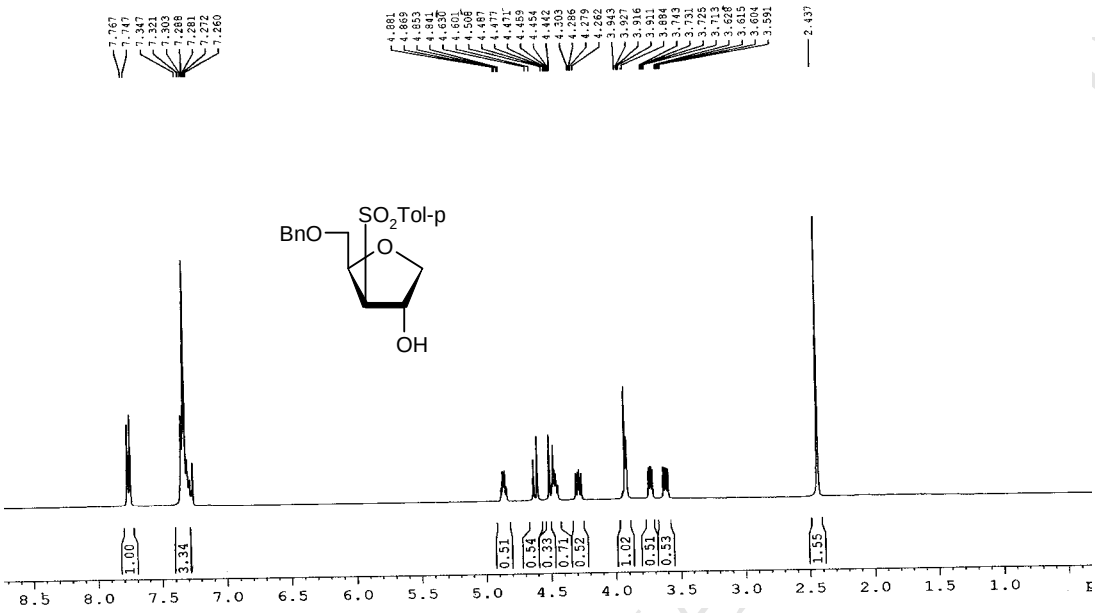


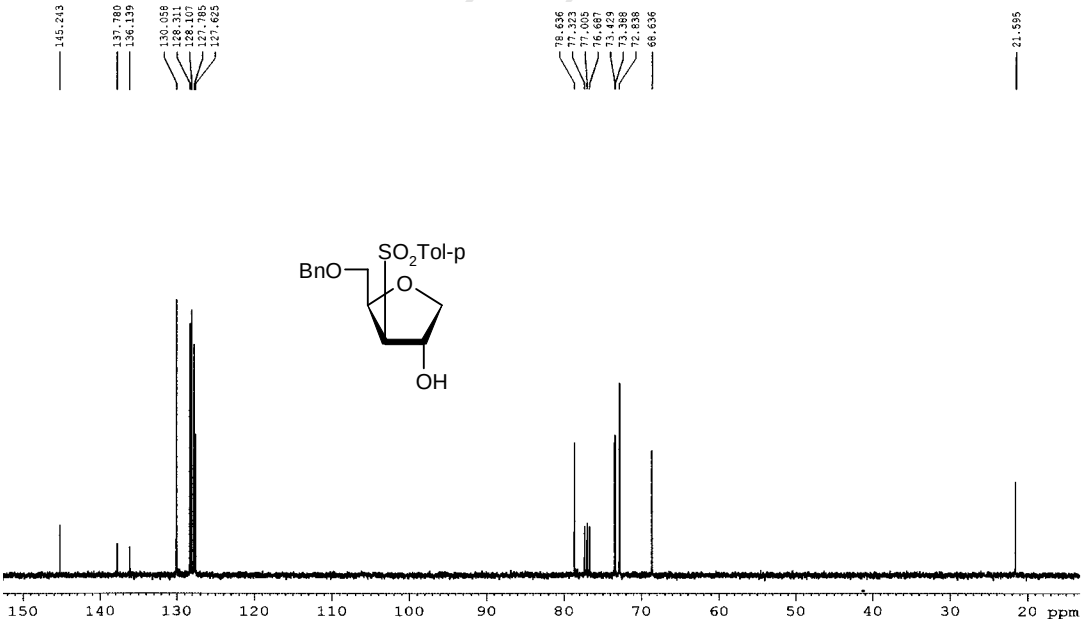
Compound 11


7.352
7.343
7.339
7.322
7.302
7.284
7.260
7.117
7.097
4.635
4.606
4.545
4.536
4.522
4.515
4.393
4.387
4.381
4.306
4.293
4.282
4.269
4.265
3.753
3.751
3.709
3.703
3.685
3.679
3.610
3.603
3.597
3.590
2.326
BnO
STol-p
O
OH
1.00
0.28
0.15
0.28
0.14
0.15
0.28
0.15
0.14
0.43
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

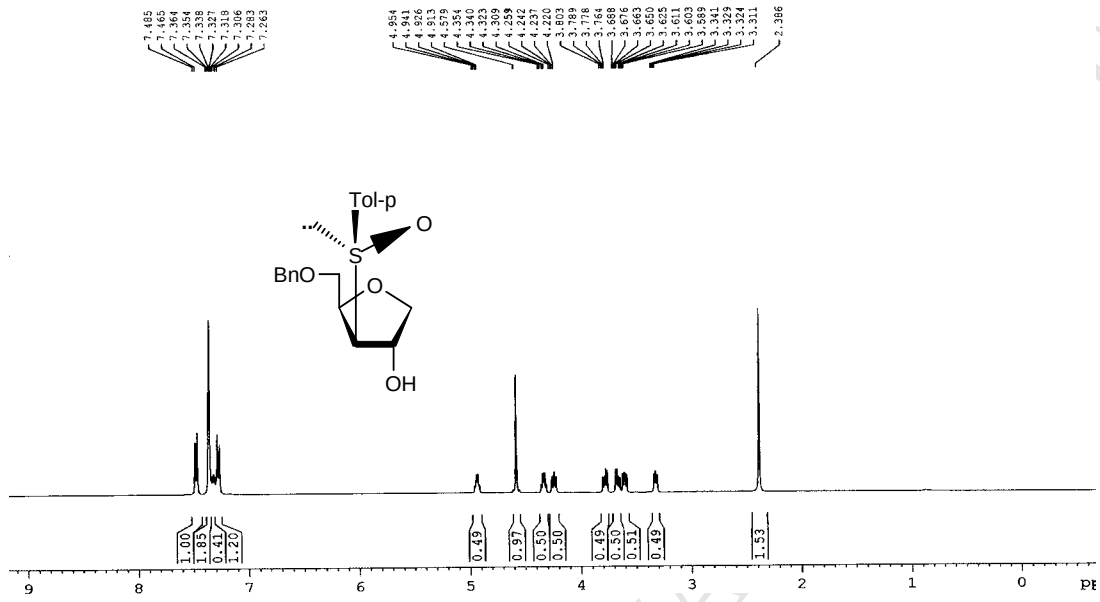

137.974
137.205
131.322
131.060
129.938
128.303
127.785
127.588
78.735
77.374
77.320
77.002
76.684
73.695
73.458
70.277
57.093
20.998
BnO
STol-p
O
OH
140
130
120
110
100
90
80
70
60
50
40
30
ppm

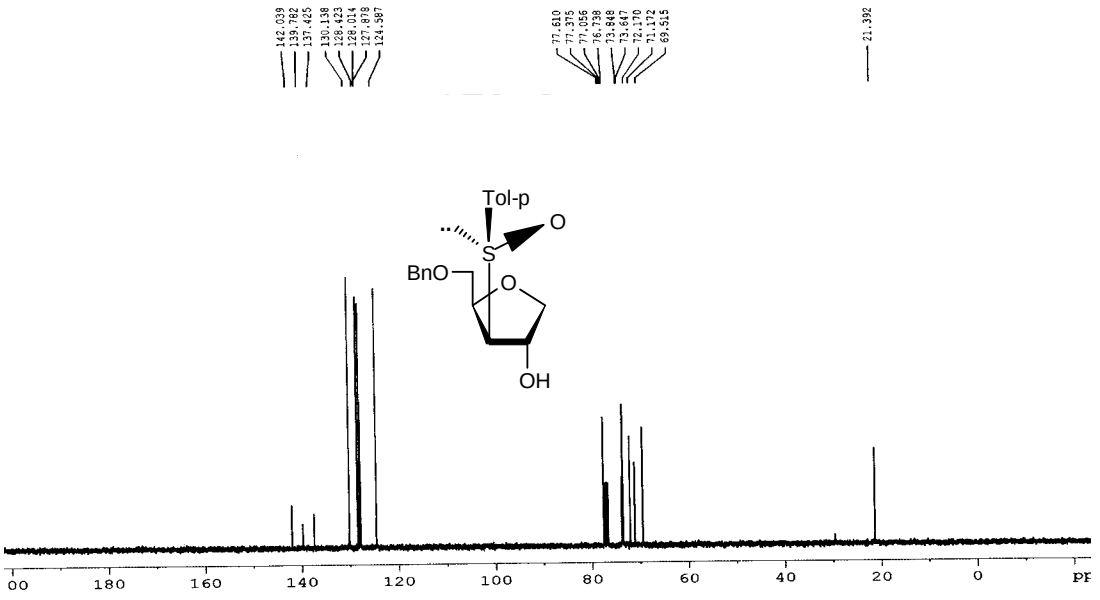
Compound 12


7.767
7.747
7.347
7.321
7.303
7.288
7.281
7.272
7.260
4.881
4.869
4.853
4.841
4.635
4.601
4.506
4.487
4.477
4.471
4.459
4.454
4.442
4.303
4.286
4.279
4.262
4.243
3.927
3.916
3.911
3.884
3.743
3.731
3.725
3.713
3.628
3.615
3.604
3.591
2.437
SO2Tol-p
BnO
O
OH
1.00
3.34
0.51
0.54
0.33
0.71
0.52
1.02
0.51
0.53
1.55
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

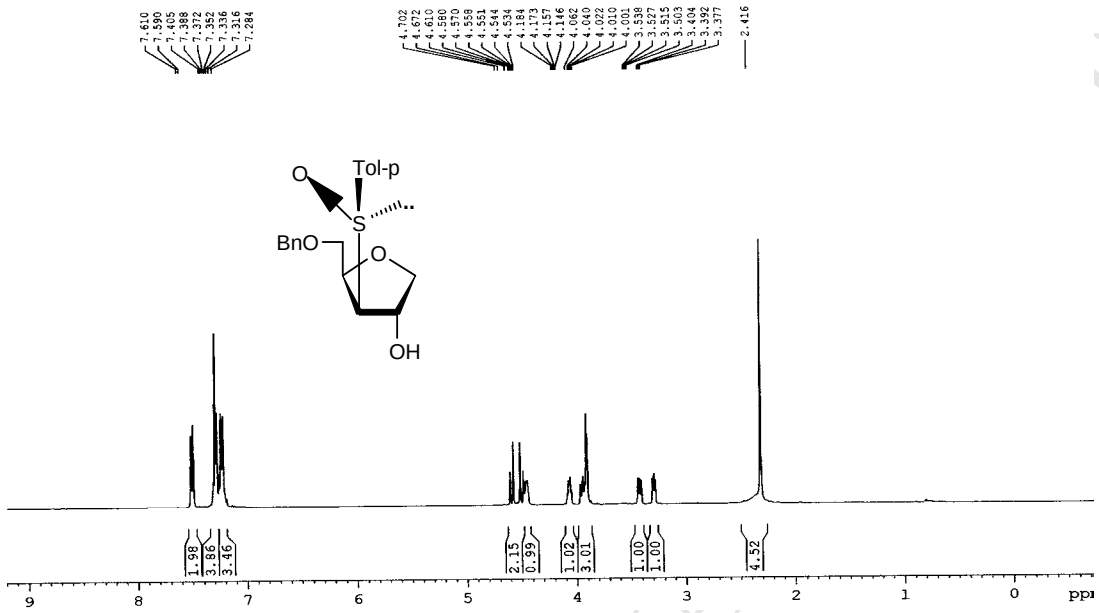

145.243
137.780
136.139
130.068
128.311
128.107
127.785
127.625
78.636
77.323
77.005
76.687
73.429
73.388
72.838
68.636
21.585
SO2Tol-p
BnO
O
OH
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

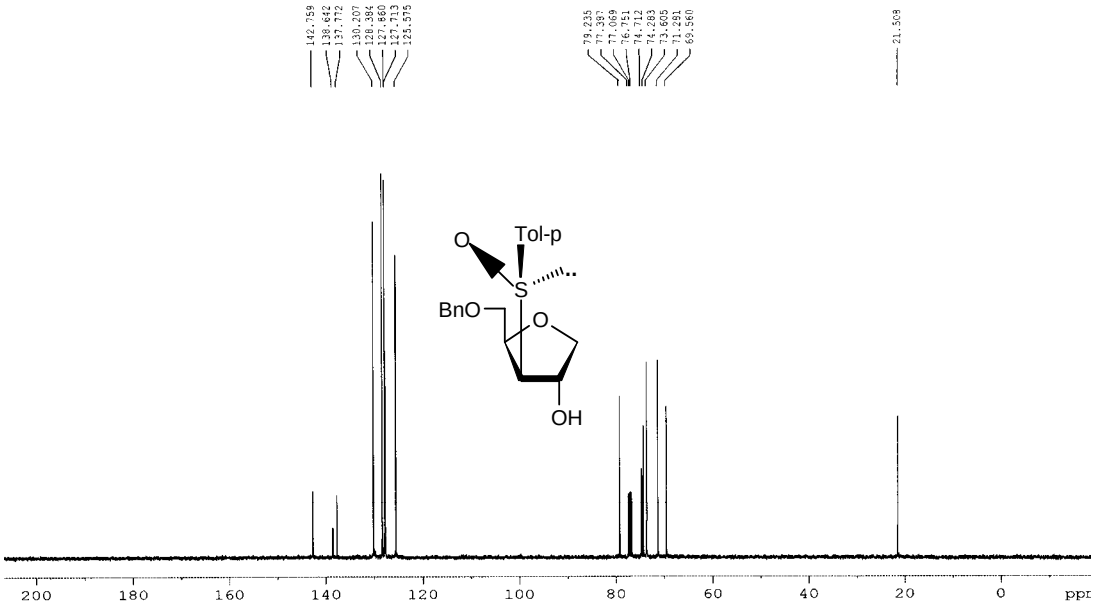
Compound 13S$_S$



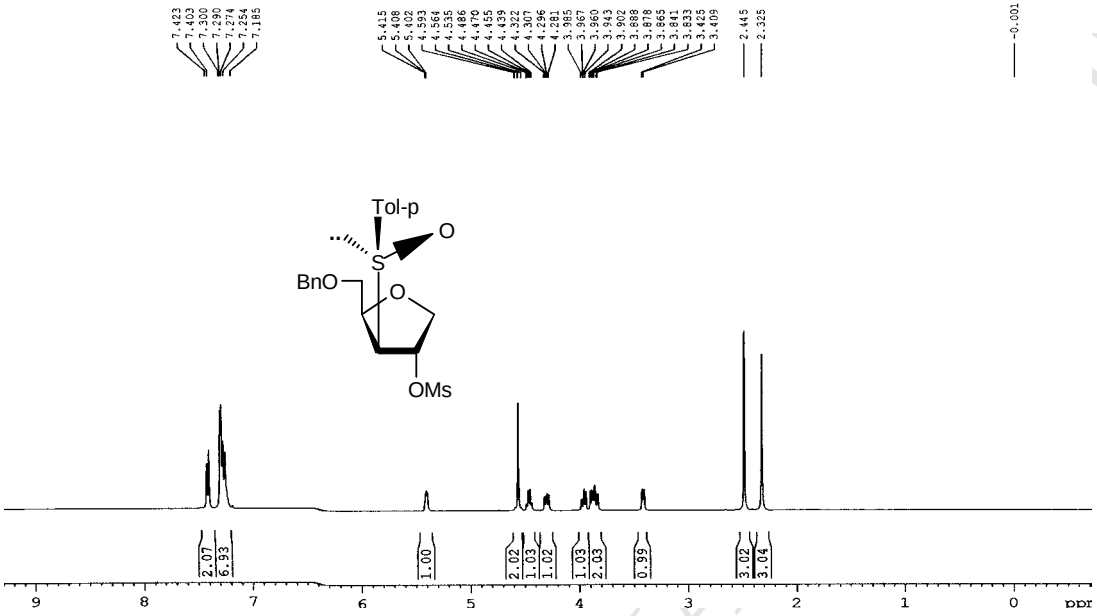


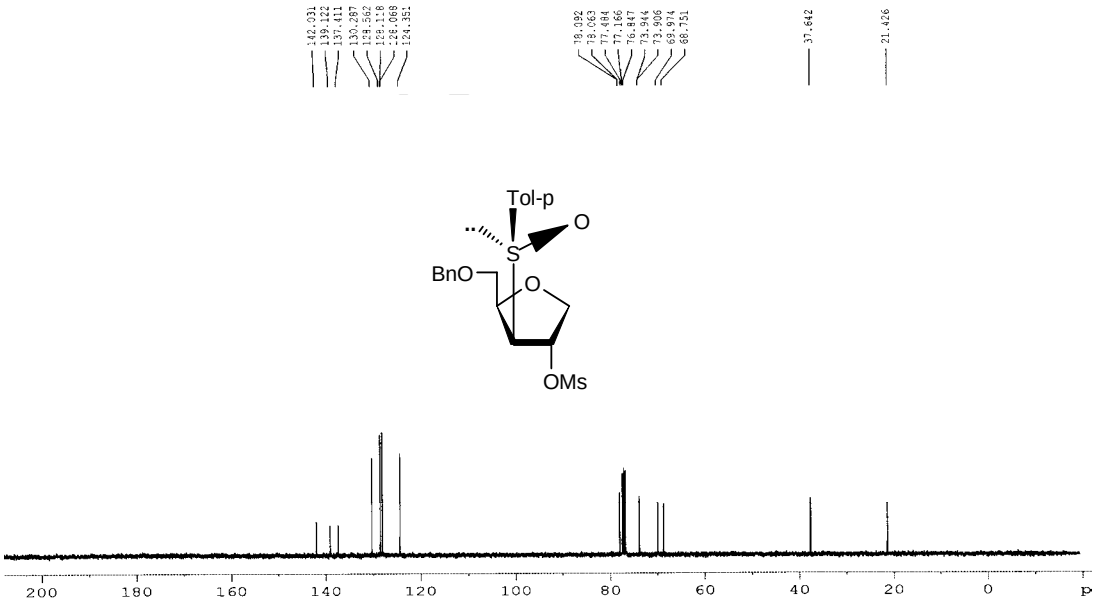
Compound 13R$_S$



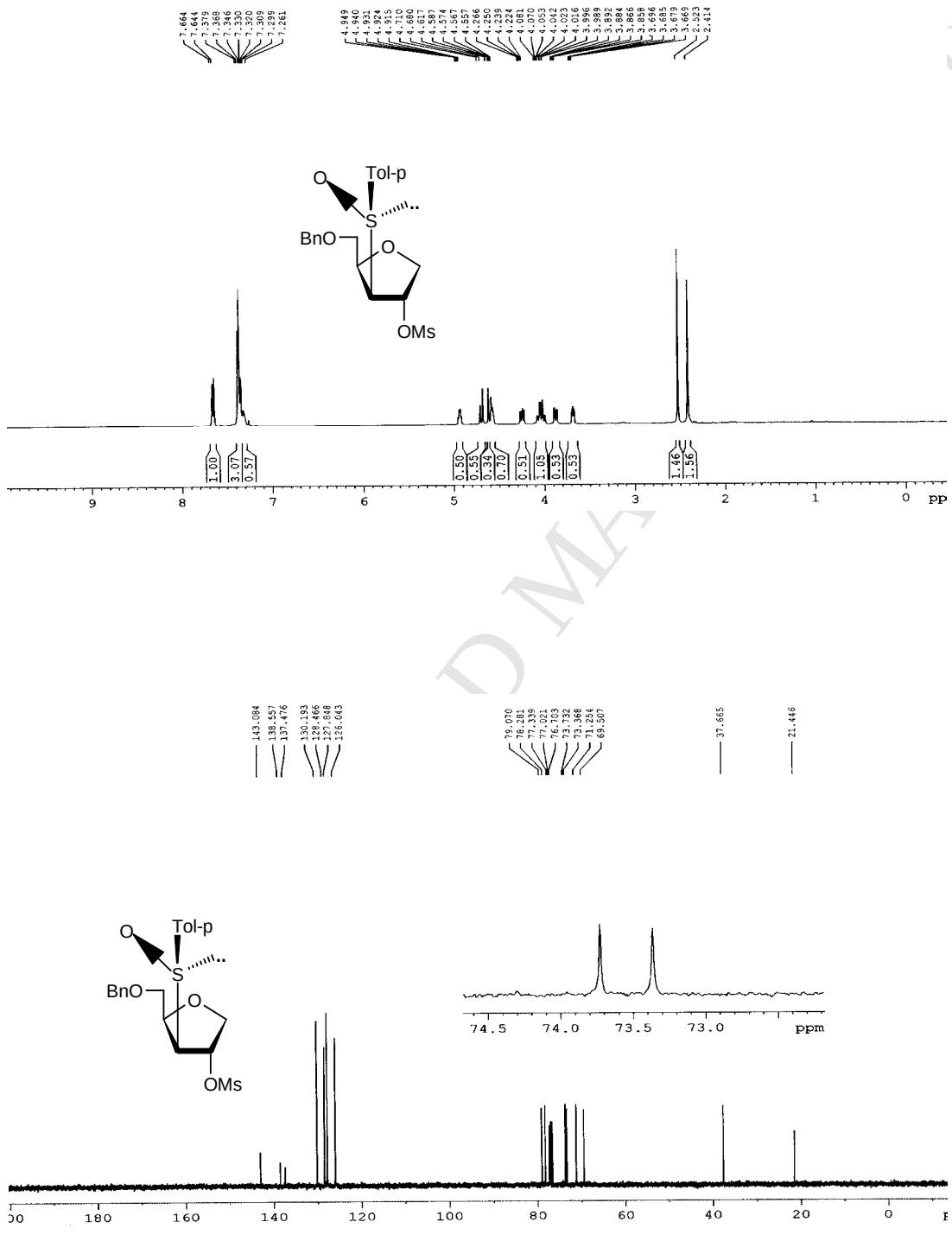


Compound 14S$_S$

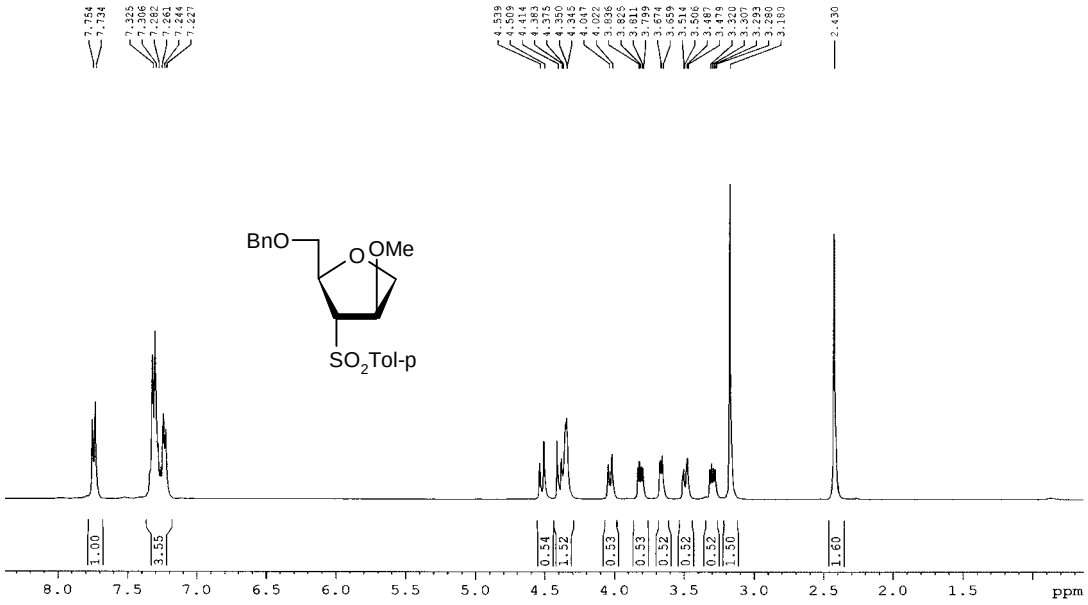


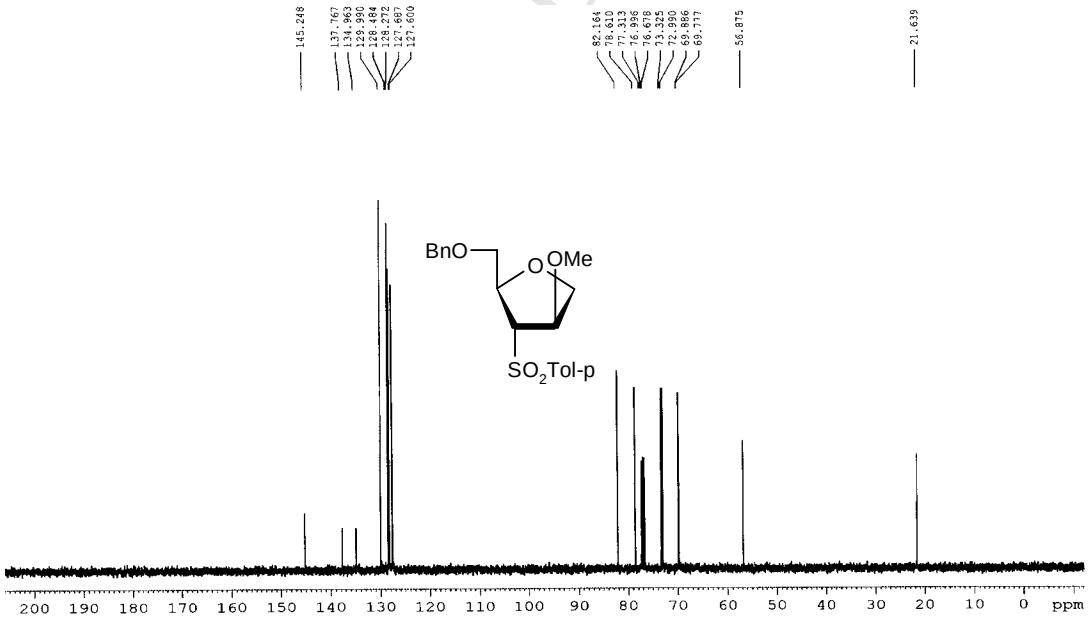


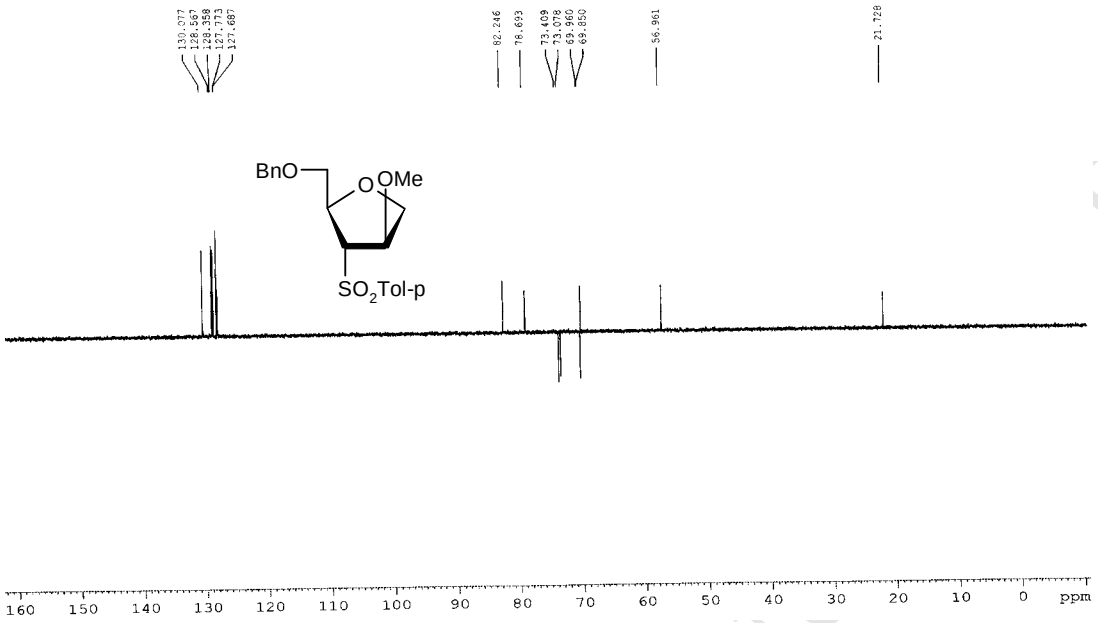
Compound 14R$_S$



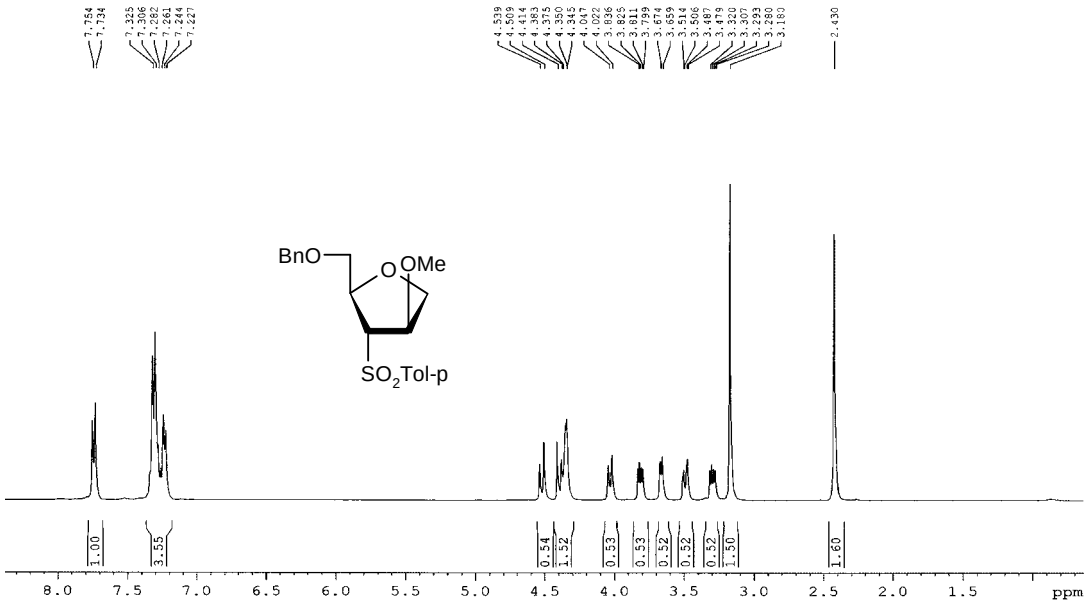
Compound 15


7.754
7.734
7.325
7.306
7.282
7.261
7.244
7.227
4.539
4.509
4.414
4.383
4.375
4.350
4.045
4.027
4.022
3.836
3.825
3.811
3.799
3.674
3.659
3.514
3.506
3.487
3.479
3.320
3.307
3.293
3.280
3.180
2.430
BnO
O
OMe
SO2Tol-p
1.00
3.55
0.54
1.52
0.53
0.53
0.52
0.52
0.52
1.50
1.60
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

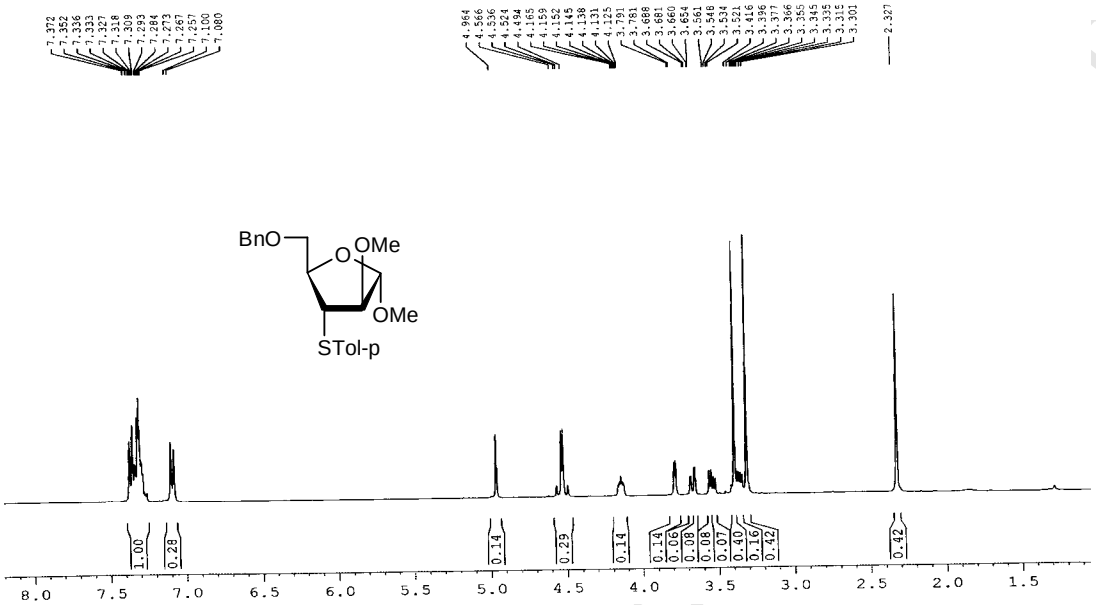

145.248
137.767
134.583
129.980
128.484
128.272
127.697
127.600
82.164
78.610
77.313
76.996
76.678
73.325
72.990
69.886
69.777
56.875
21.639
BnO
O
OMe
SO2Tol-p
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

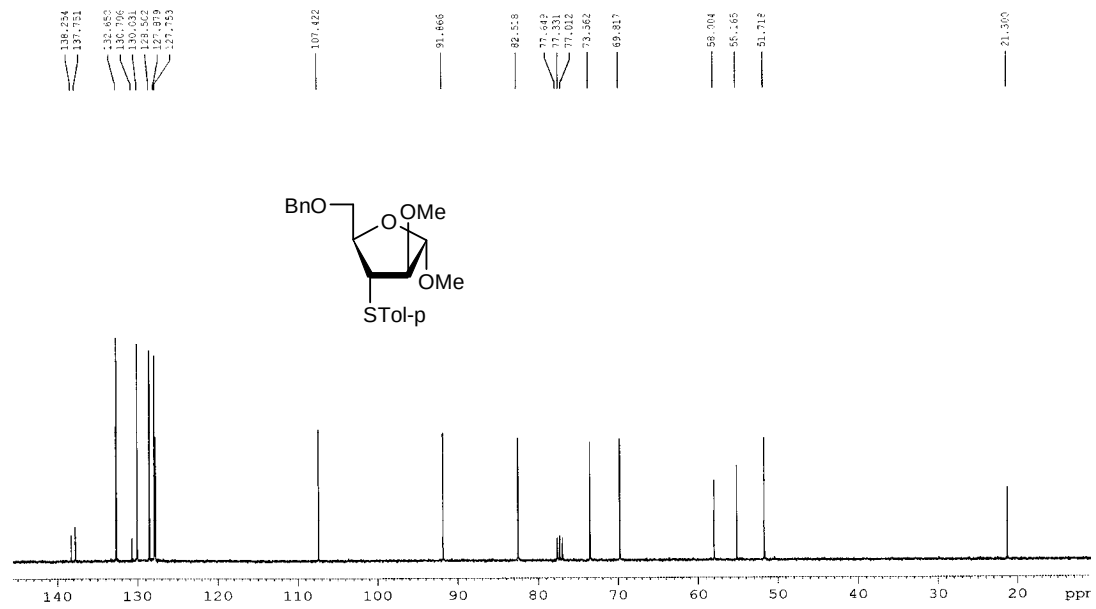


Compound 15 (Mixed ^{1}H NMR of the Michael adduct obtained from scheme 3 and the compound synthesized in alternative way in scheme 4)

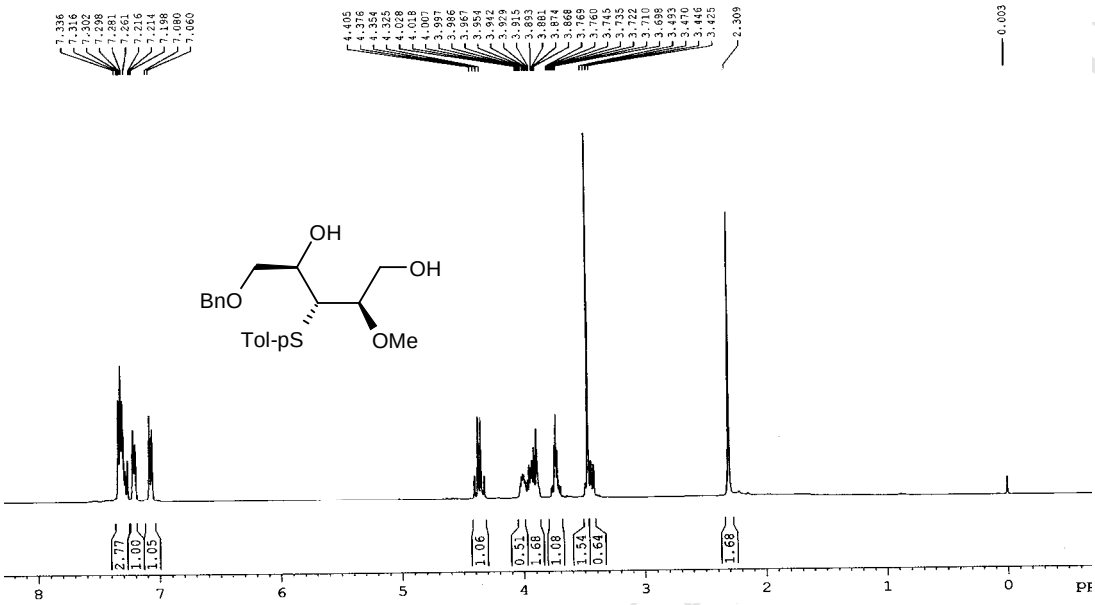


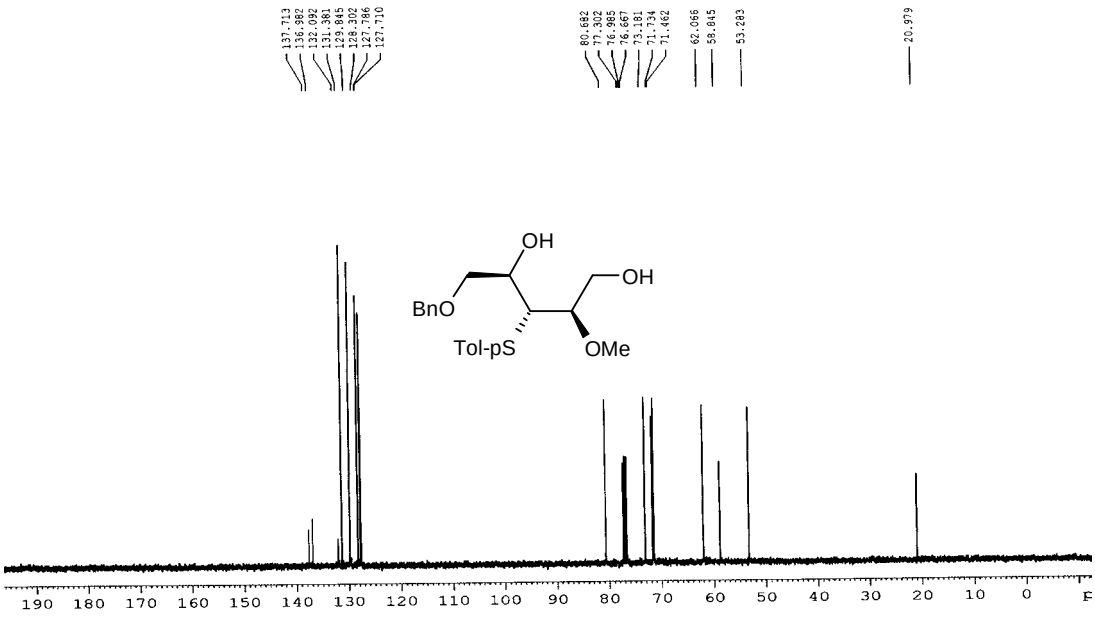
Compound 17


BnO
O
OMe
OMe
STol-p
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

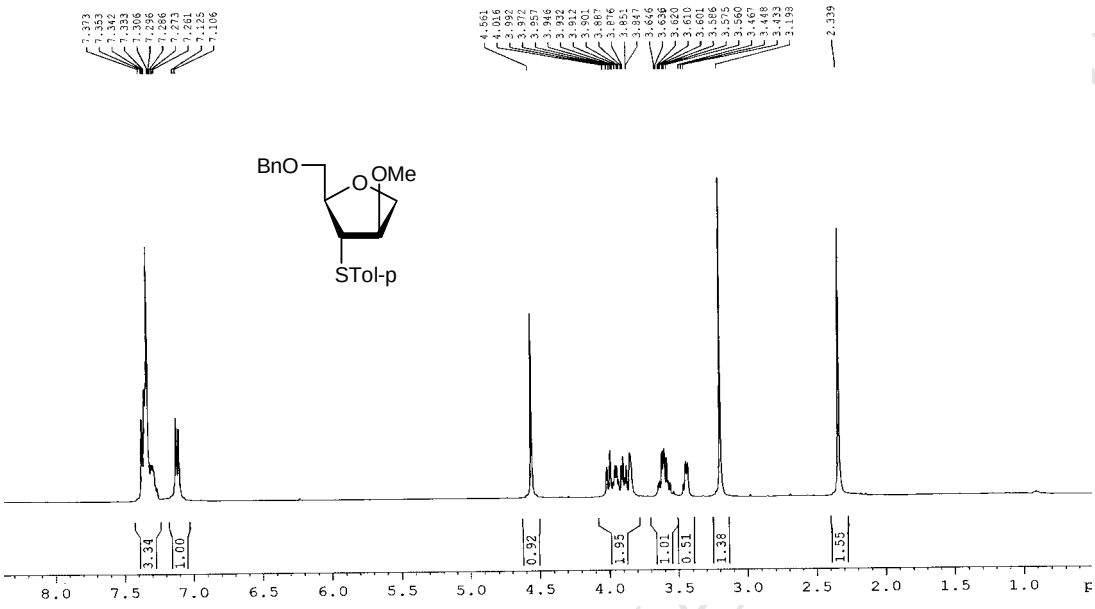

BnO
O
OMe
OMe
STol-p
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

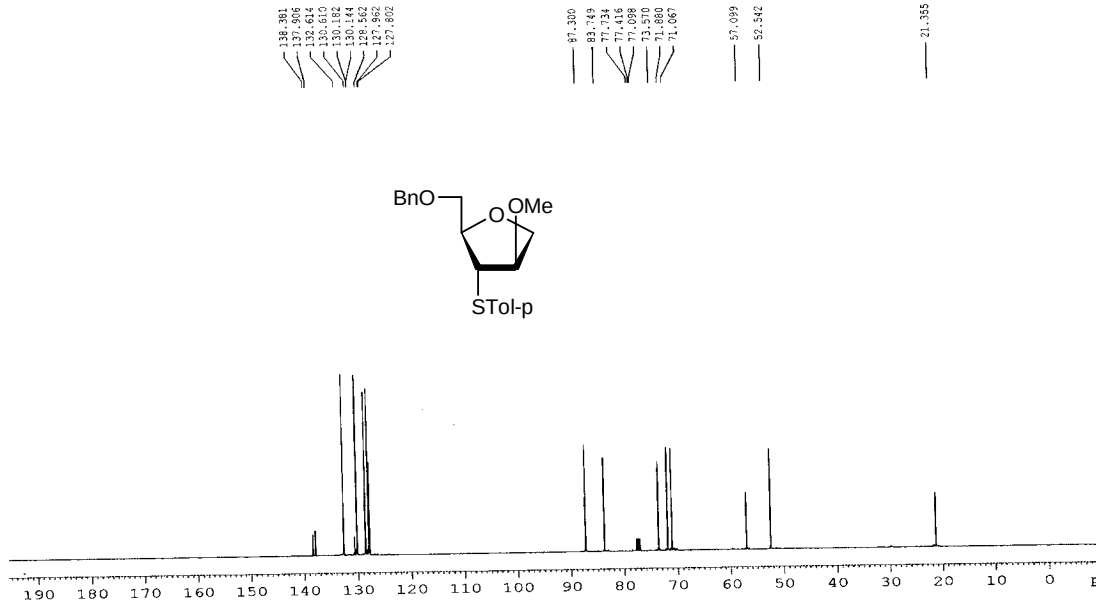
Compound 18



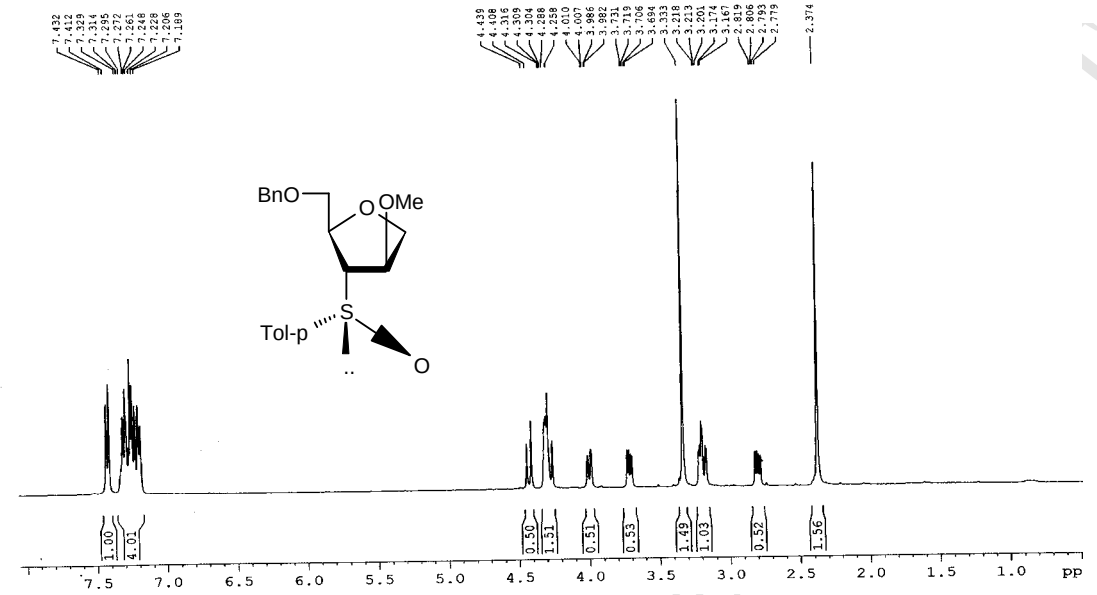


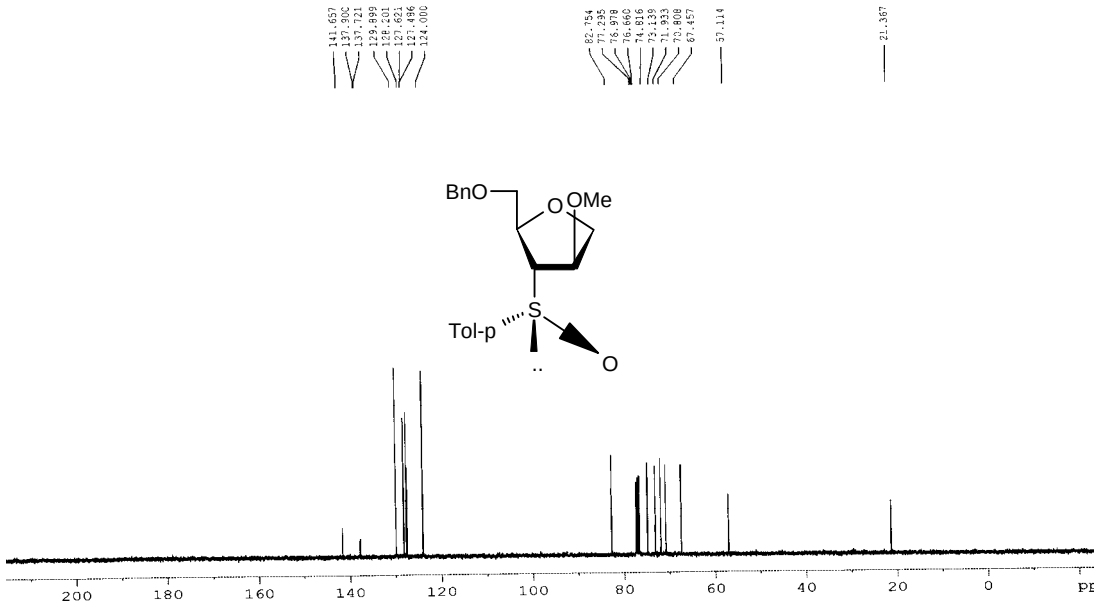
Compound 19



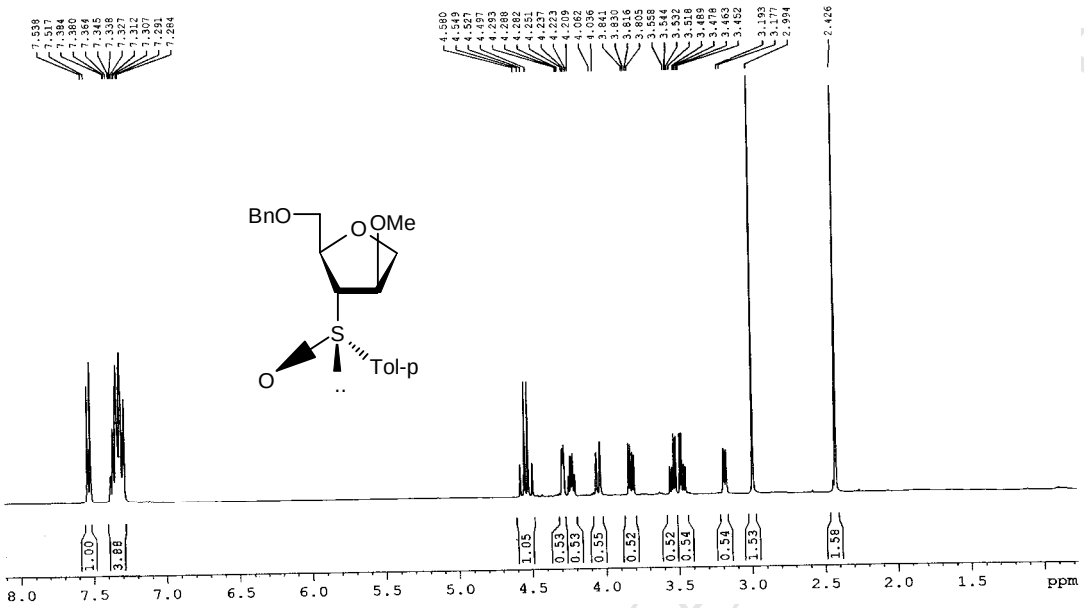


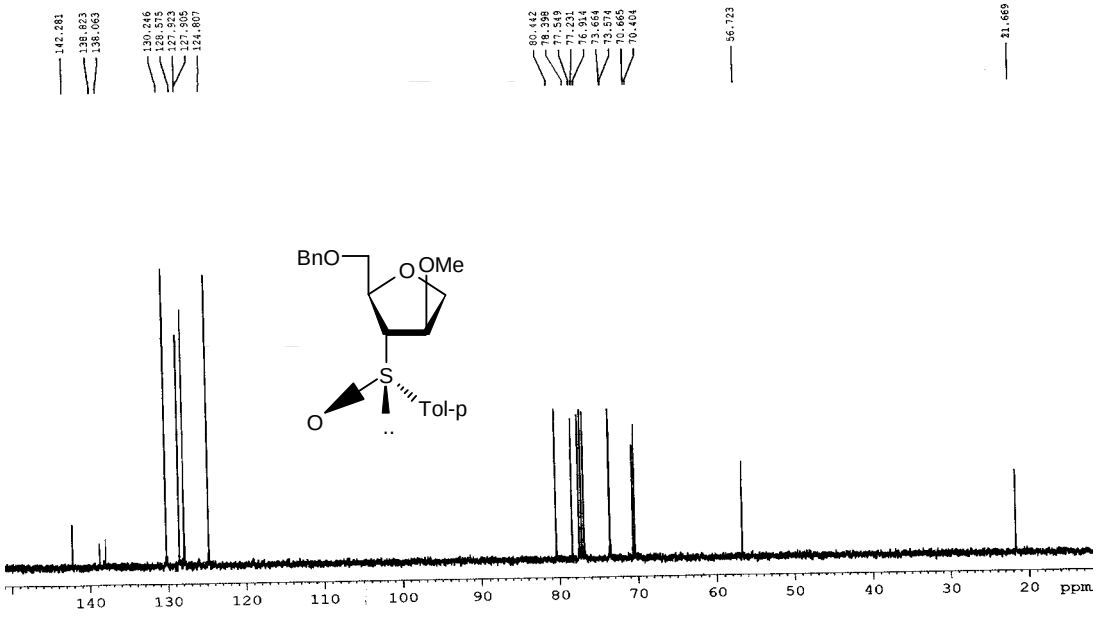
Compound 20S$_S$



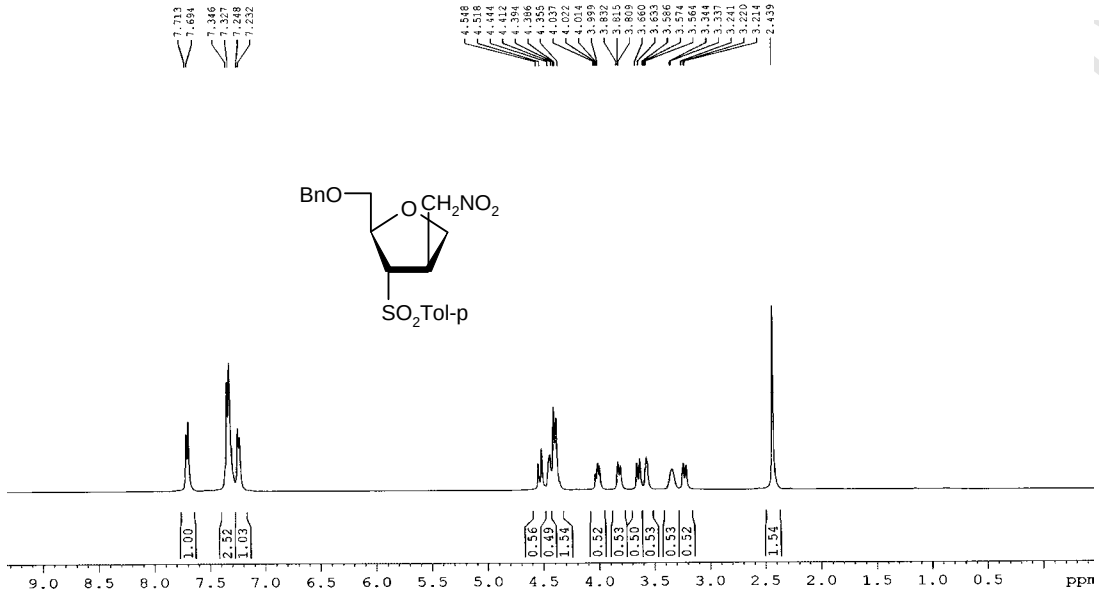


Compound 20R$_S$





Compound 21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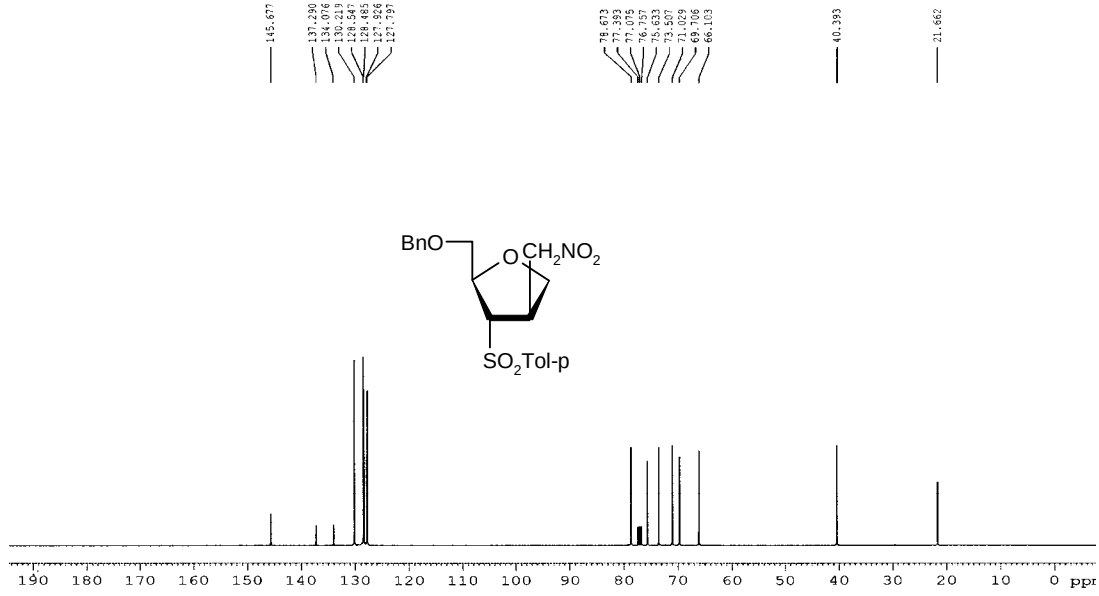
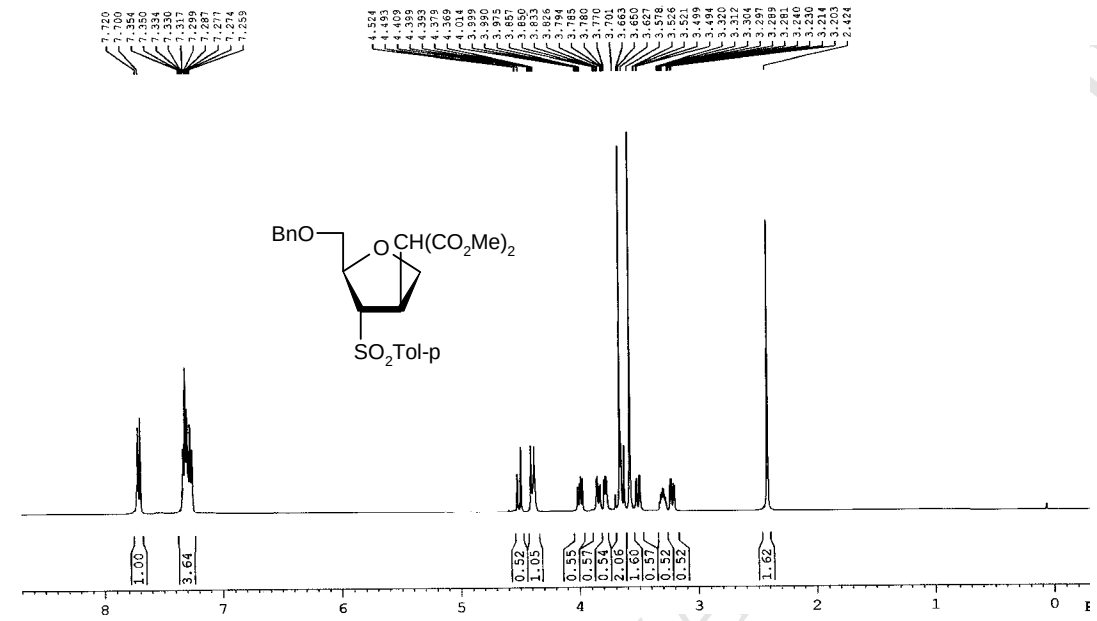
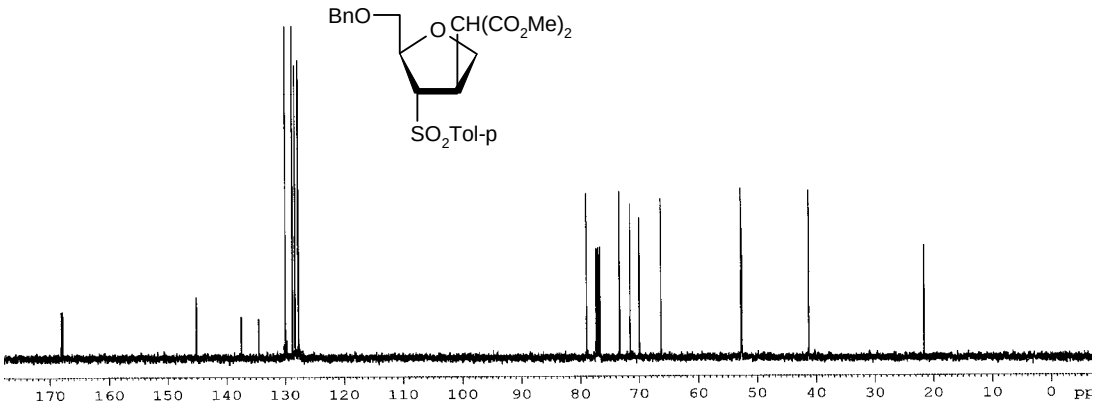
7.694
7.346
7.327
7.248
7.232
4.548
4.518
4.444
4.412
4.394
4.366
4.355
4.037
4.022
4.014
3.999
3.832
3.815
3.809
3.660
3.633
3.576
3.564
3.344
3.337
3.241
3.220
3.214
2.439
BnO
O
CH2NO2
SO2Tol-p
1.00
2.52
1.03
0.56
0.49
1.54
0.52
0.53
0.50
0.53
0.53
0.52
1.54
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

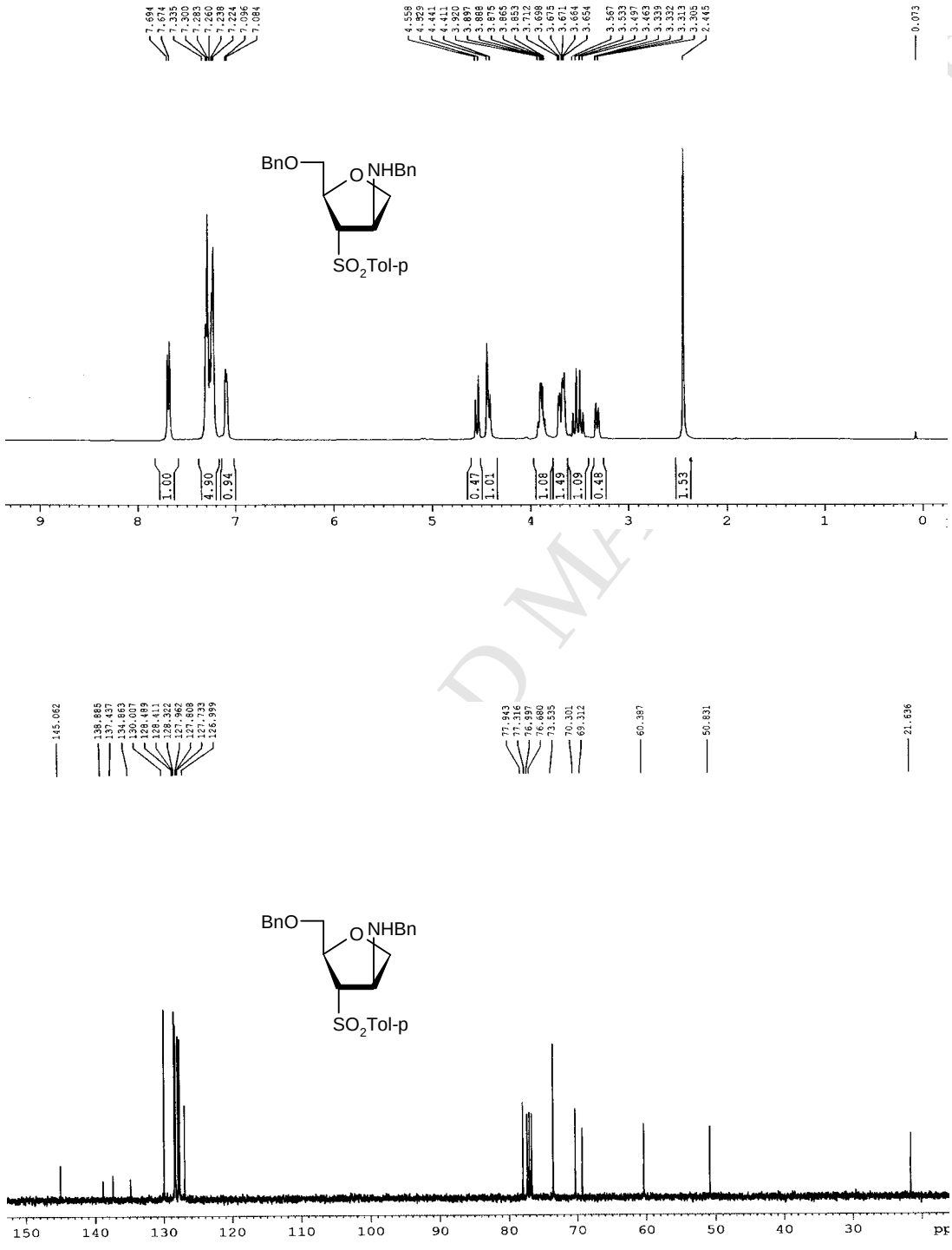

145.677
137.290
134.076
130.219
128.547
128.485
127.926
127.797
78.673
77.393
77.075
76.757
75.633
73.507
71.029
69.706
66.103
40.393
21.662
BnO
O
CH2NO2
SO2Tol-p
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

Compound 22

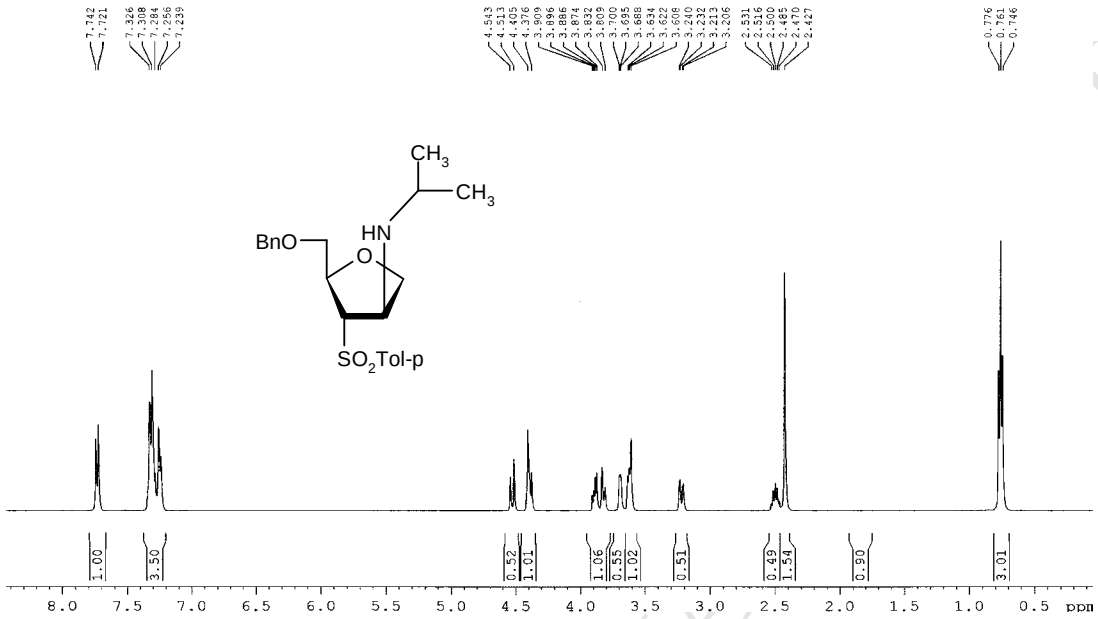


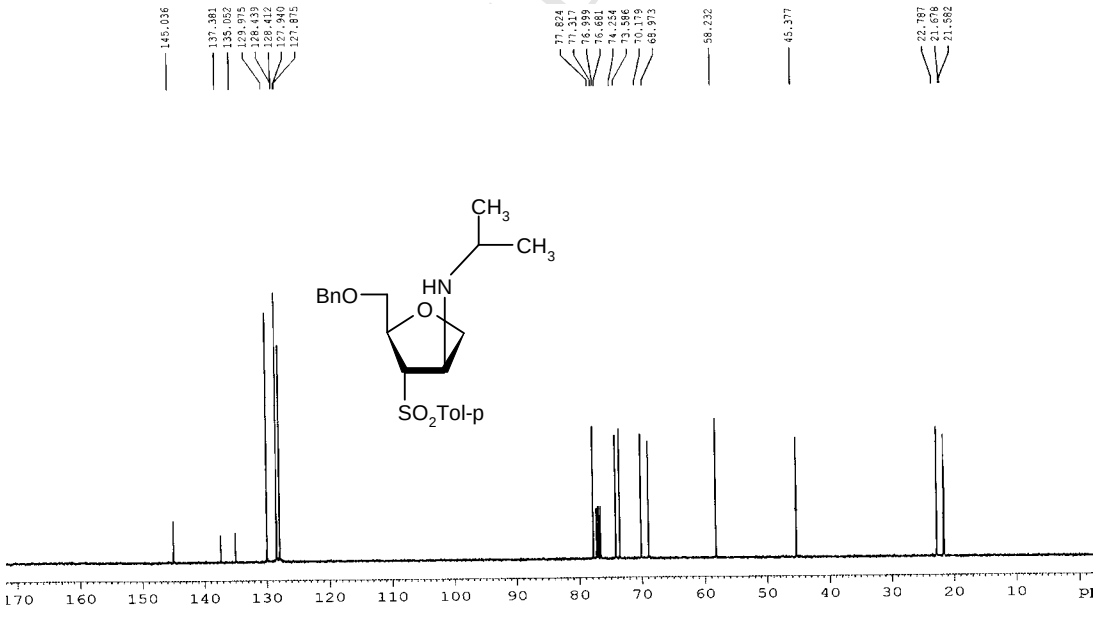


Compound 23

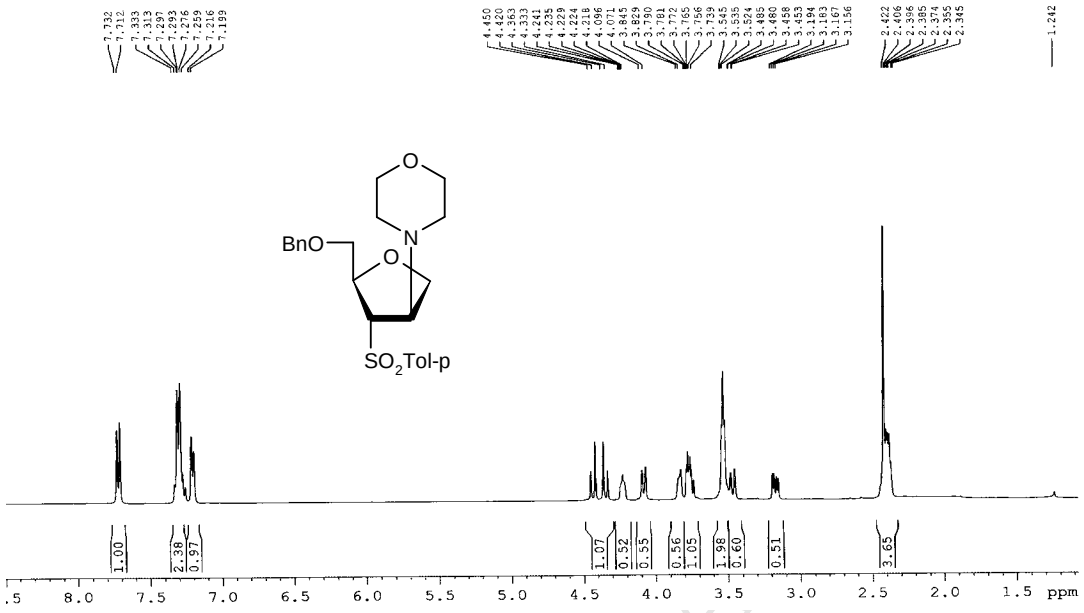


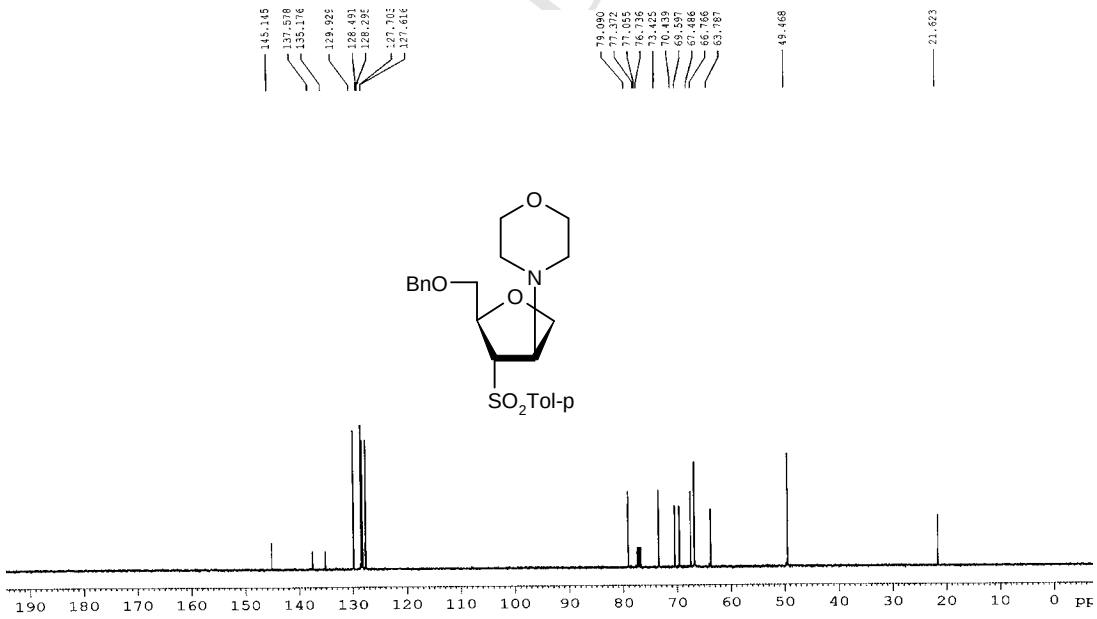
Compound 24


7.742
7.721
7.326
7.308
7.284
7.256
7.239
4.543
4.513
4.405
4.376
3.909
3.896
3.884
3.832
3.809
3.700
3.695
3.688
3.634
3.622
3.608
3.240
3.232
3.213
3.206
2.531
2.516
2.500
2.485
2.470
2.427
0.776
0.761
0.746
CH3
CH3
HN
BnO
O
SO2Tol-p
1.00
3.50
0.52
1.01
1.06
0.55
1.02
0.51
0.49
1.54
0.90
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

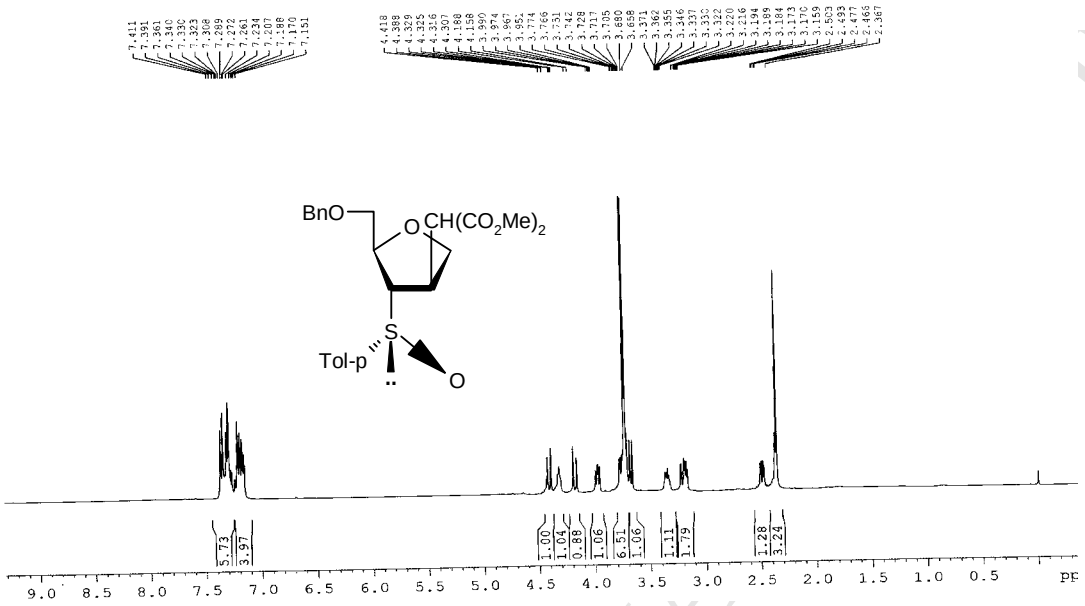

145.036
137.381
135.052
129.975
128.433
128.422
127.940
127.875
77.824
77.317
76.999
76.681
74.254
73.586
70.179
68.973
58.232
45.377
22.787
21.678
21.582
CH3
CH3
HN
BnO
O
SO2Tol-p
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

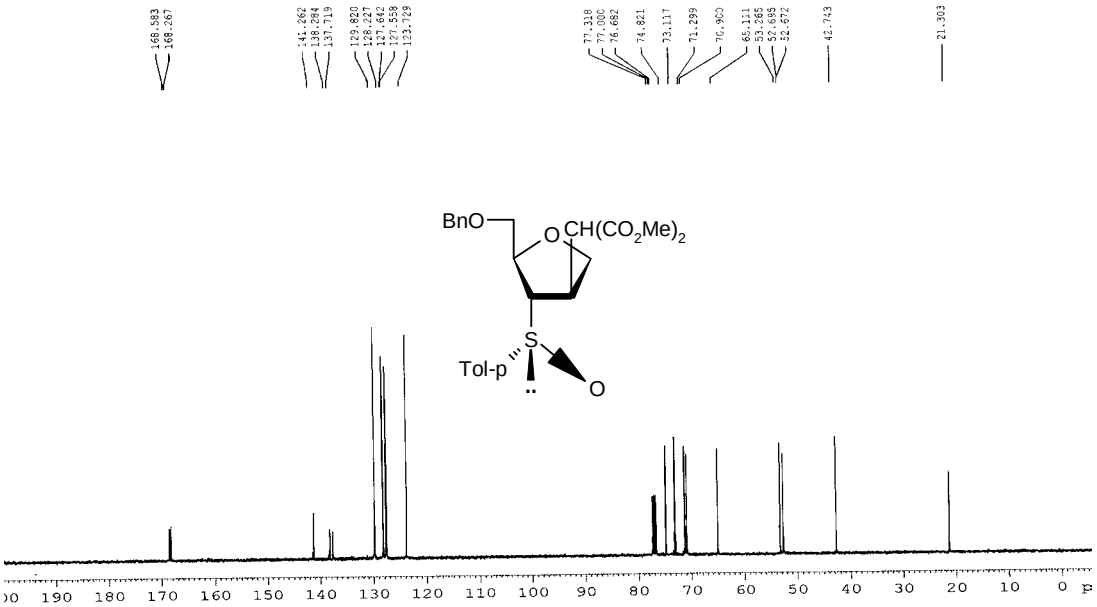
Compound 25



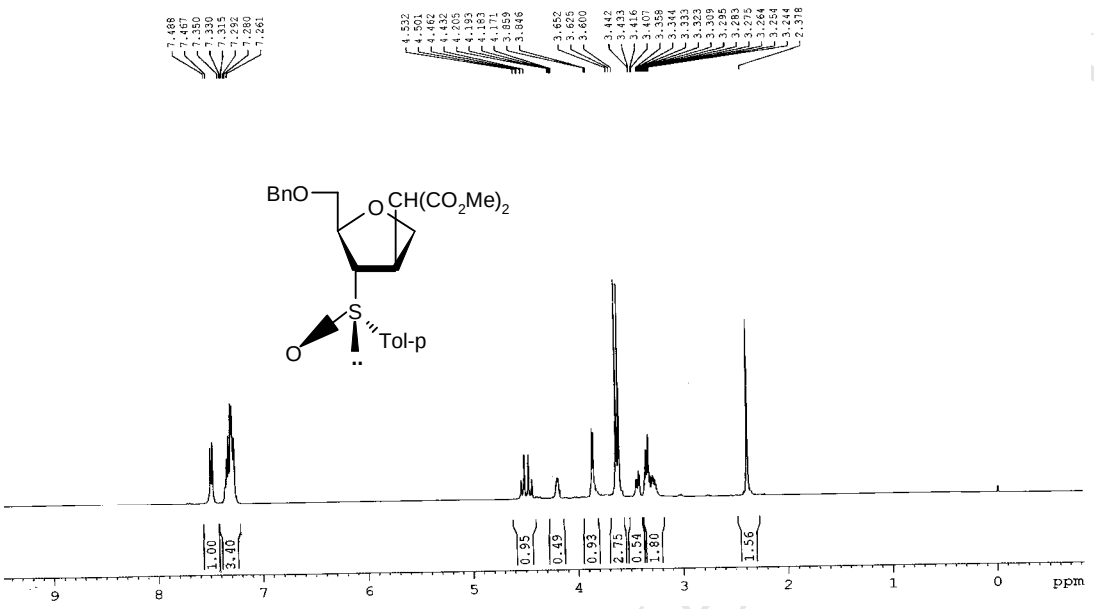


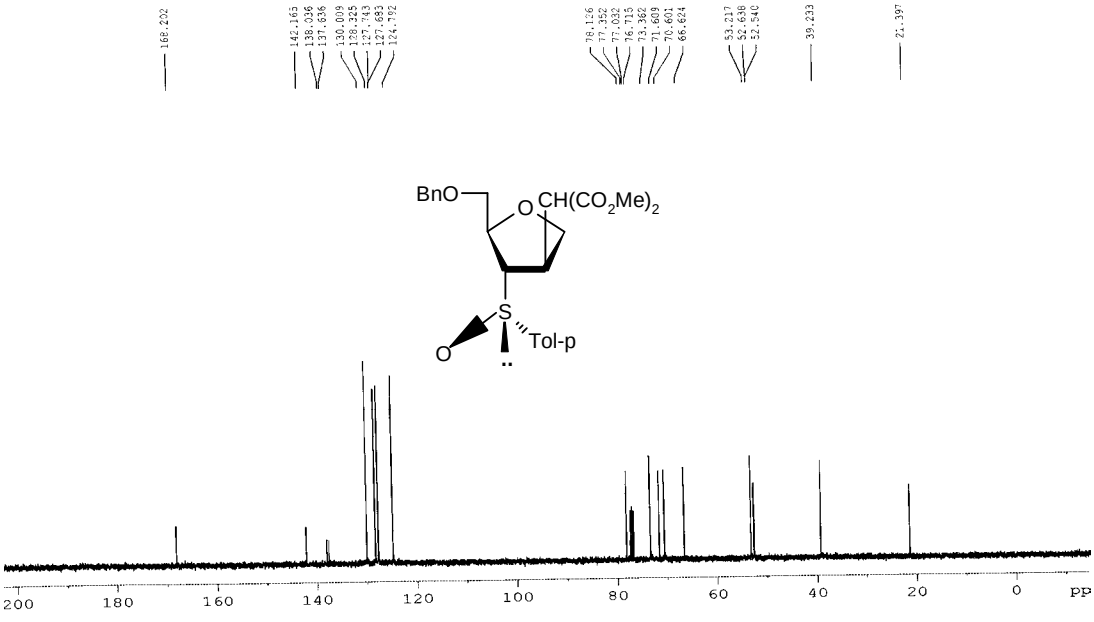
Compound 26S$_S$



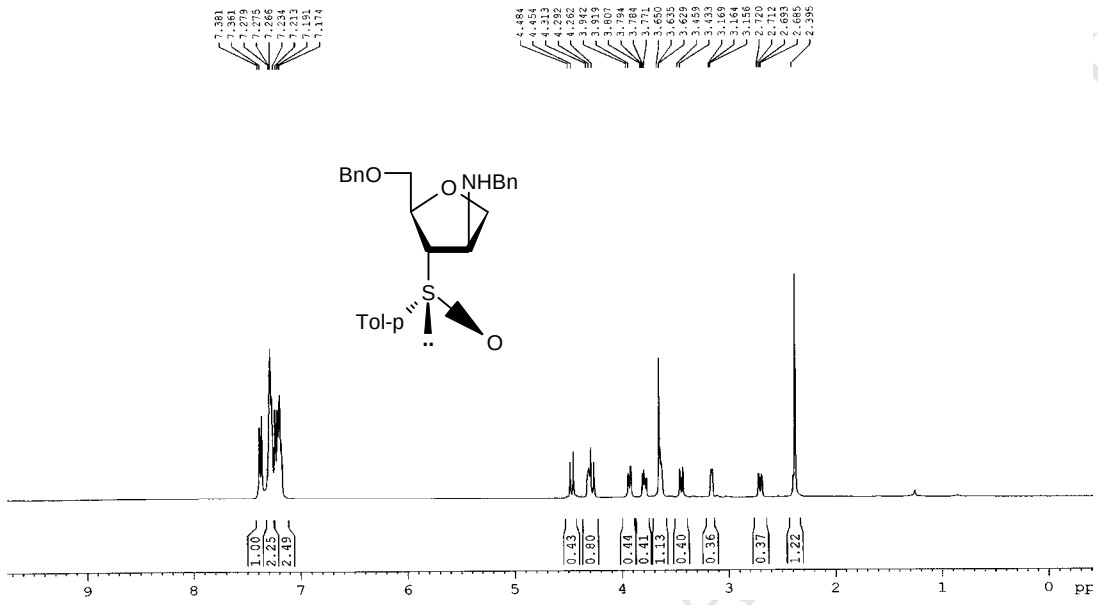


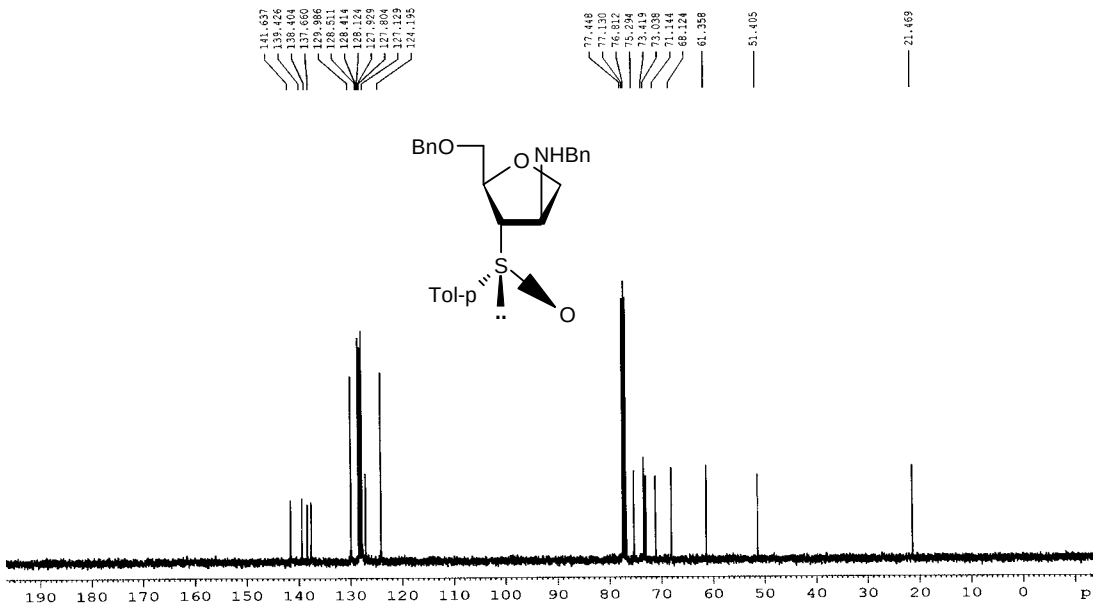
Compound 26R$_S$



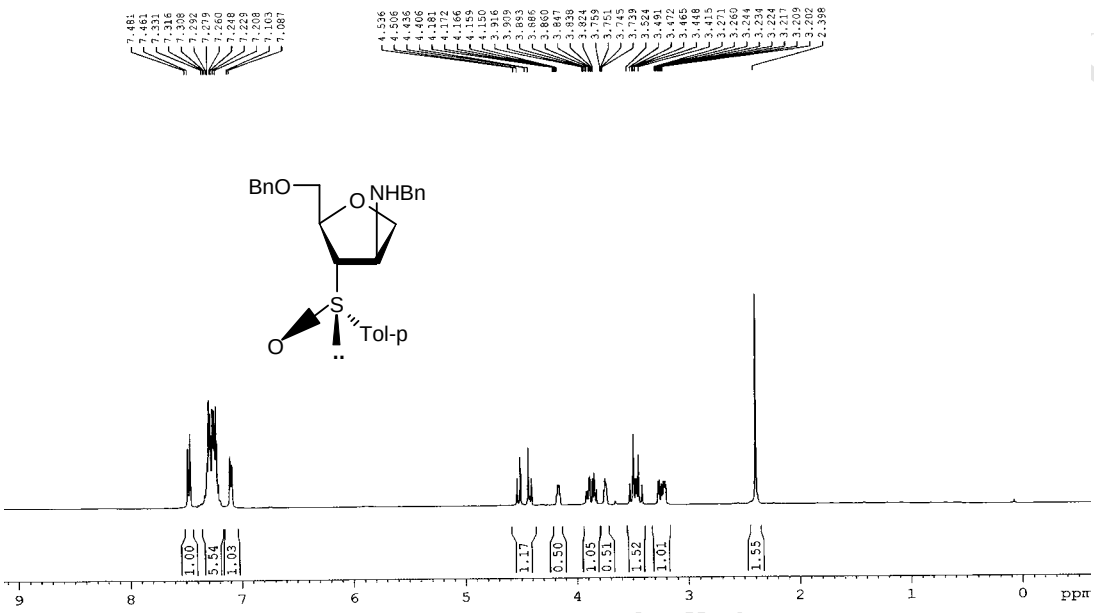


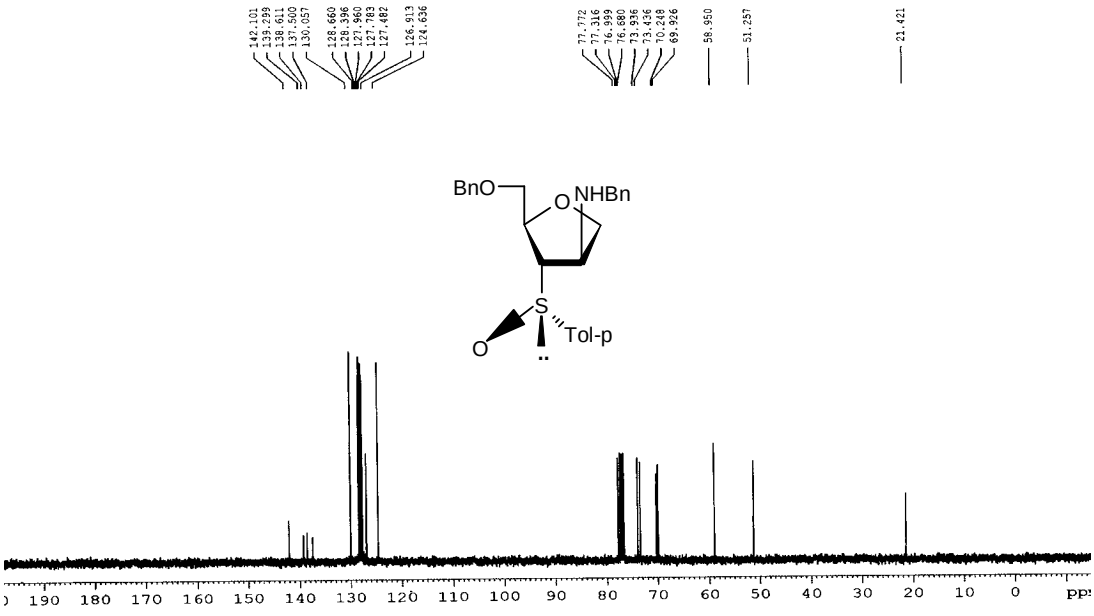
Compound 27S$_S$



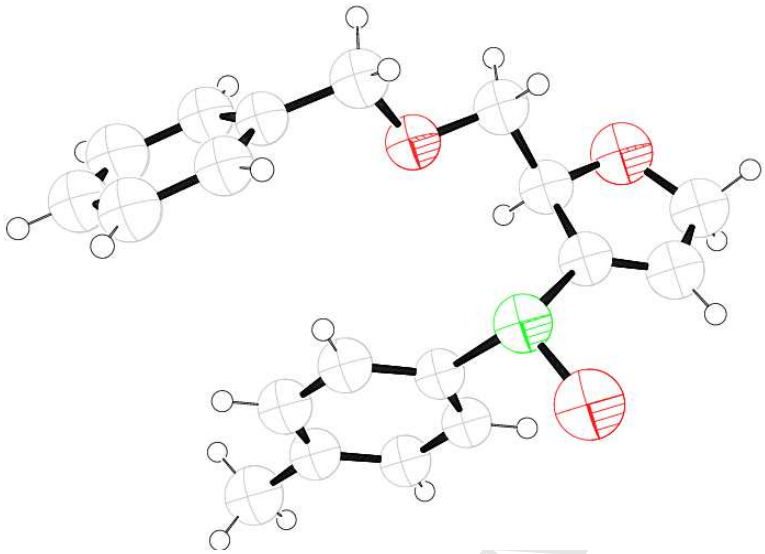


Compound 27R$_S$

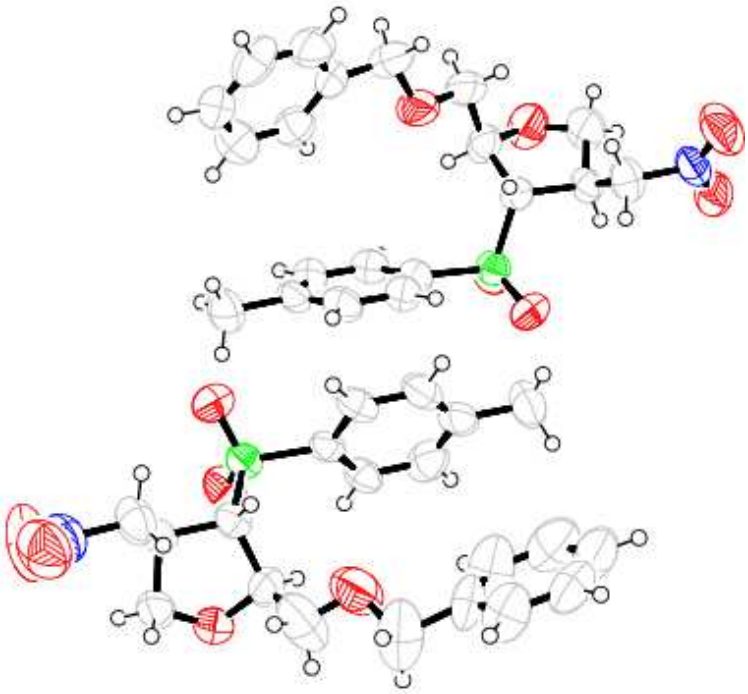




ORTEP diagram of compound 7R_S



ORTEP diagram of compound 21



ORTEP diagram of compound 25