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TETRAHEDRON: *ASYMMETRY*

# Enantioselective synthesis of antibiotic (+)-rancinamycin III derivative and two protected carbasugars of the α-D-talo-series from furan

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**Abstract**

The synthesis of (+)-**1**, a carbasugar related to rancinamycin III, has been achieved from diene (+)-**3** in two steps using as the key step the transformation of alkyne (−)-**2**, obtained by resolution of alcohol **6**, into diene (+)-**3** by treatment with Na/MeOH. Moreover, reduction of the carbonyl group in (+)-**1** affords diol (+)-**19**, in which different protection strategies of the hydroxy groups allows one to obtain, selectively, protected derivatives of α-D-carbatalopyranose (+)-**4a** and its 6-desoxy derivative (+)-**4b** to be obtained selectively. 

## 1. Introduction

The term ‘carbasugar’ is commonly used for designing a class of compounds wherein the ring oxygen atom of a cyclic monosaccharide is replaced by a methylene group.[1] In some cases, a carbasugar might be accepted by enzymes or biological systems in the place of a true sugar. Thus, some of them show interesting biological activities in the area of enzyme inhibitors. In addition, several of them have been used as sweeteners, antibiotics, antiviral and anticancer agents.[2] Consequently, much attention has been bestowed on devising methodologies for gaining rapid entry to carbasugars in a regio- and stereoselective manner.[3]

## 2. Results and discussion

Within this research field, we have recently reported the synthesis, in racemic form, of the carbasugar **1** related to rancimamycin III.[4] Rancinamycins[5] are a group of secondary metabolites produced by

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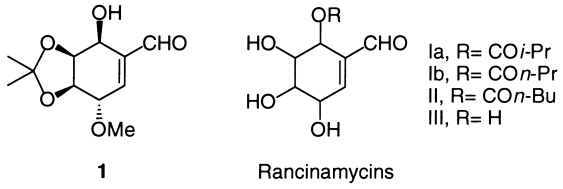
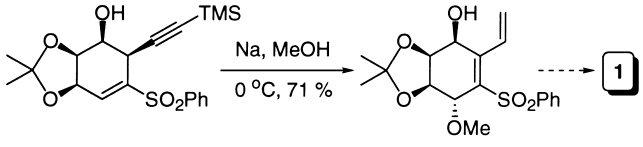
*Streptomyces lincolnensis* in a sulfur-depleted culture medium. They have important antibiotic activity in vitro against *Proteus vulgaris*, *Proteus rettgeri* and *Staphylococcus aureus* (Scheme 1).




**1** Rancinamycins

Scheme 1.

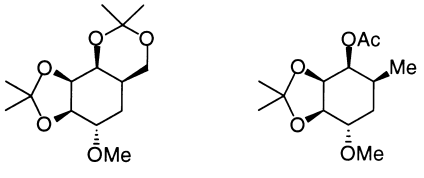
The key step of this synthesis is the unprecedented transformation of alkynylcyclohexenylsulfones such as **2** into dienylsulfone **3** by reaction with Na/MeOH (Scheme 2). This transformation involves in one step a Michael addition, vinylsulfone isomerization and triple bond reduction.[4]




**2** **3**

Scheme 2.

On the basis of this novel transformation, we envisioned diene **3** as a potential precursor to different families of carbasugars. In this paper we wish to account for the synthesis, in enantiomerically pure form, of carbasugar (+)-**1**, the protected derivative of α-D-carbatalopyranose (+)-**4a** and the protected derivative of the hitherto unknown α-D-6-desoxycarbatalopyranose (+)-**4b**[6] (Scheme 3), which were in turn obtained from the 7-oxanorbornene derivative **5**,[7] the Diels–Alder adduct of furan and *trans*-1,2-*bis*-(phenylsulfonyl)ethylene.[8]



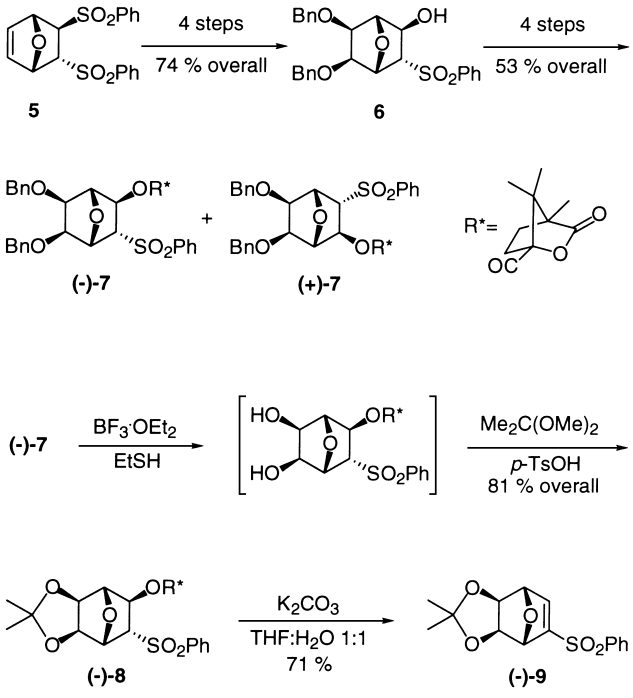

**(+)-4a** **(+)-4b**

Scheme 3.

Our starting material was the enantiomerically pure vinylsulfone (−)-**9**, prepared by resolution of alcohol **6** (Scheme 4).[9] Treatment of **6** with (1*S*)-(−)-camphanic acid chloride gave a 1:1 mixture of diastereomeric esters (+)-**7** and (−)-**7**, which were separated by column chromatography on silica gel. Removal of the benzyl groups on (−)-**7** with $BF_3 \cdot OEt_2$ and protection of the resulting diol as the acetonide afforded camphanic derivative (−)-**8**. Elimination of the chiral auxiliary was performed with $K_2CO_3$ giving vinylsulfone (−)-**9**.

Ring opening of (−)-**9** with lithium trimethylsilylacetylide afforded compound (−)-**2**. Transformation of (−)-**2** into diene (+)-**3** was performed by treatment with MeONa in MeOH at 0°C. A possible mechanism proposed for this reaction[4] involves deprotection of the acetylenic moiety to give the tridentade anion **10**. Reprotonation at the terminal allenic position gives **11**, which after conjugate addition of methoxide anion affords compound (+)-**3** (Scheme 5).

The stereochemical configuration of (+)-**3** (Scheme 5) was established on the basis on the multiplicity of the signal of H-4, which appears as a singlet in the $^1H$ NMR spectrum. The absence of coupling




Scheme 4.

between H-4 and H-5 suggests that the dihedral angle between both protons is near 90°. The *s-trans* configuration of the diene was deduced from the absence of an NOE effect between the H-*trans* of the vinyl group and the aromatic protons of the phenylsulfonyl substituent.

In order to achieve the synthesis of our target molecules, we accomplished first the oxidation of the exocyclic double bond in **3** to the related aldehyde **14**. In this way, bishydroxylation of **3** afforded a 12:1 mixture of compounds **12** and **13**. Oxidation of **12** with $NaIO_4$ gave aldehyde **14**. This compound could be prepared in a one-pot procedure by treatment of diene **3** with $NaIO_4$ and $RuCl_3$[10] (Scheme 6).

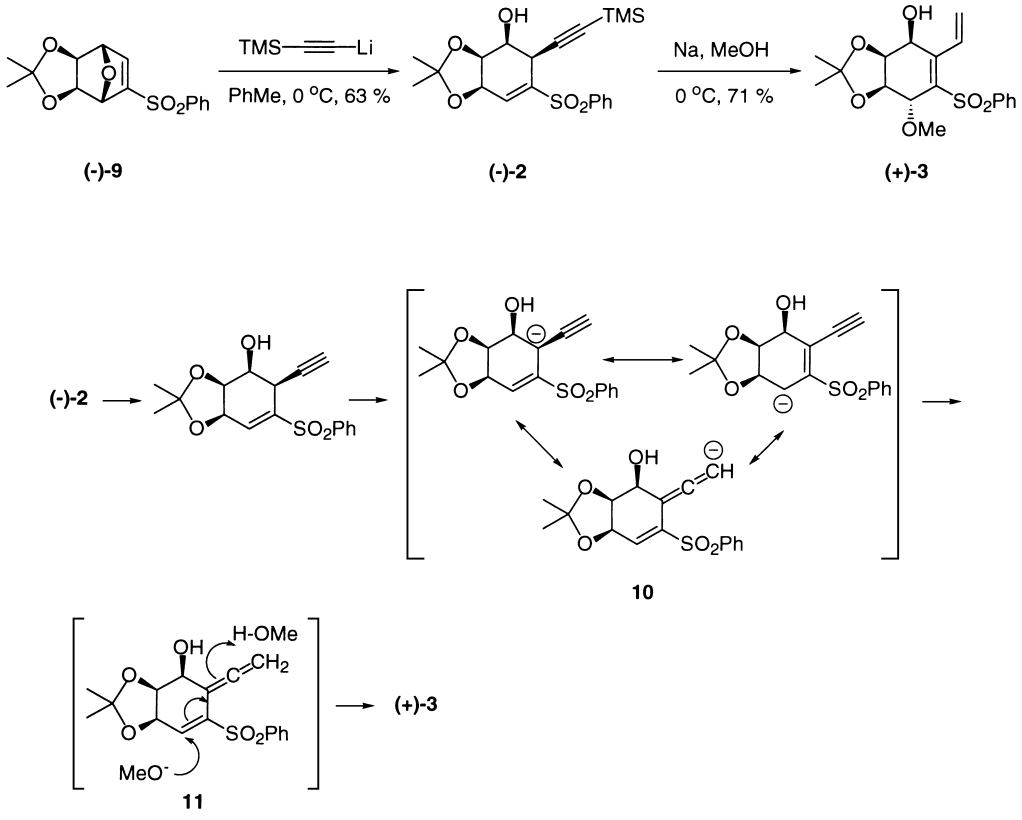
At this stage, desulfonylation of **14** was not possible because of extensive decomposition of starting material under a variety of experimental conditions. Therefore, in order to obtain carbatalopyranose derivatives, we decided to carry out a total reduction of aldehyde **14** by transformation into alcohol **15** followed by 1,4-hydride addition to the vinylsulfone moiety.[11] This new strategy would involve the desulfonylation process in a further step of the synthesis. Reduction of **14** was performed using different conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$; $LiAlH_4$; $NaBH_4$; $LiEt_3BH$; DIBALH). In all cases the isolated final product was alcohol **15** instead of the desired fully reduced product **16** (Scheme 7).

Completion of the synthesis of compounds **4** from alcohol **15** would require desulfonylation and hydrogenation of the double bond. However, treatment of **15** with Na–Hg or $H_2$, Pd/C did not produce the expected products. Compounds **12**–**15** were not obtained in enantiomerically pure form.

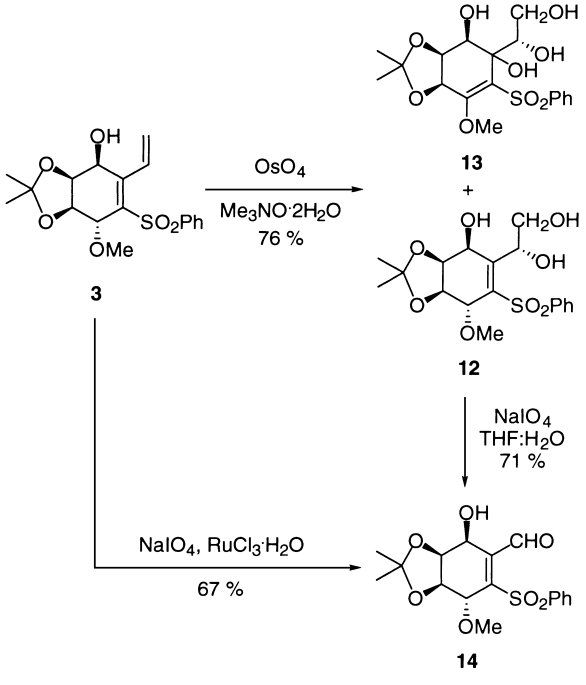
Finally, the synthesis was completed as follows (Scheme 8). Desulfonylation of (+)-**3** afforded diene (+)-**17**. Oxidation of the exocyclic double bond in (+)-**17** to obtain aldehyde (+)-**1** was carried out by reaction with $NaIO_4$ and $RuCl_3$. This transformation was also achieved by bishydroxylation of the exocyclic double bond in (+)-**17** and oxidation of the remittant diol (+)-**18** with $NaIO_4$.

Thus, we have obtained the general structure of rancinamycin III with a well defined stereochemistry of the four stereogenic centers and in enantiomerically pure form.

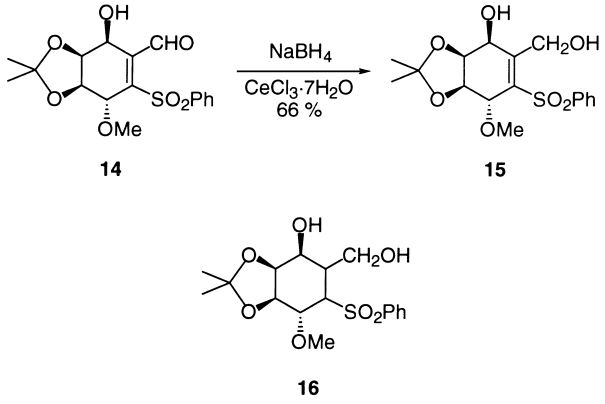
To synthesize α-D-carbatalopyranose, we decided to reduce the α,β-unsaturated system in (+)-**1**.



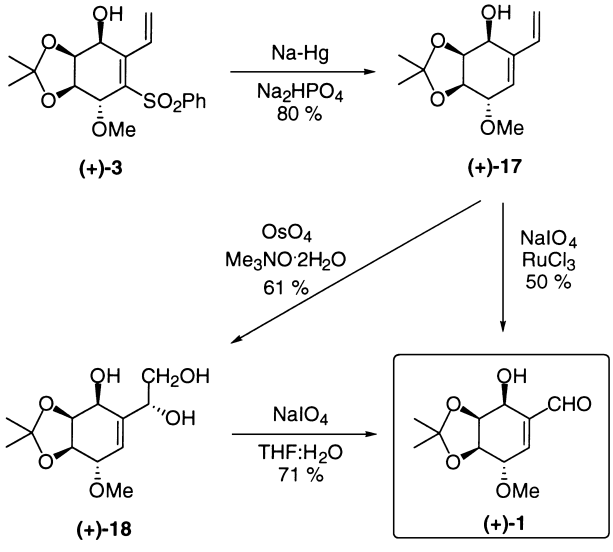

Scheme 5.




Scheme 6.



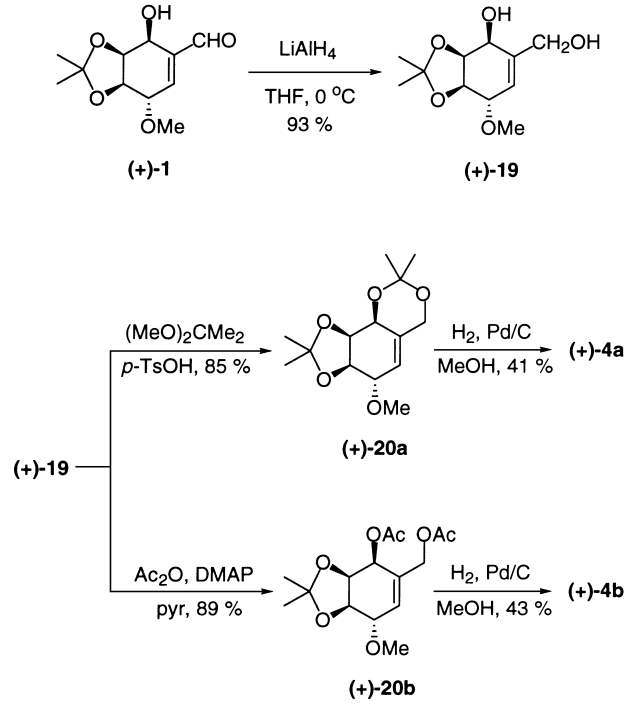

Scheme 7.




Scheme 8.

However, using reagents for this transformation such as $NaBH_4$ or $NaCNBH_3$, complex mixtures of products were obtained. With other reducing reagents only diol (+)-**19** was observed. The best conditions for this transformation were found on treating (+)-**1** with $LiAlH_4$ in THF at 0°C (Scheme 9). At this stage, appropriate protection of diol (+)-**19** allowed us to obtain selectively the carbasugars **4a** or **4b**. Thus, when (+)-**19** was protected as a diacetonide, the hydrogenation of the resulting product (+)-**20a** afforded the α-D-carbatalopyranose derivative (+)-**4a**. In contrast, protection of diol with $Ac_2O$ afforded (+)-**20b**, which, after catalytic hydrogenation (Pd/C 10% as catalyst), produced the 6-desoxy derivative (+)-**4b**. This result has a precedent in the literature[12] and can be explained admitting hydrogenolysis of the acetoxy group, catalyzed by Pd, followed by hydrogenation of the alkene moiety.

In summary, the synthesis of a protected derivative of α-D-carbatalopyranose (+)-**4a**, α-D-6-desoxycarbatalopyranose (+)-**4b** and one stereoisomer of rancinamycin III (+)-**1** has been accomplished from furan and *trans*-1,2-*bis*-(phenylsulfonyl)ethylene.




Scheme 9.

## 3. Experimental

### *3.1. General methods*

Reagents and solvents were handled by using standard syringe techniques. THF was distilled over Na/benzophenone; $CH_2Cl_2$, PhMe, $Et_3N$, pyridine and $Ac_2O$ were distilled over $CaH_2$ before use. The remaining solvents and chemicals were commercial and used as received. $^1H$ NMR and $^{13}C$ NMR were recorded at 300 MHz and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm from internal $(CH_3)_4Si$. Flash chromatography was performed using 230–400 mesh silica gel. Analytical TLC was carried out on silica gel plates. Melting points are uncorrected. Elemental analyses were performed at the Universidad Complutense de Madrid.

### *3.2. (1*S*,2*R*,3*R*,4*R*,5*S*,6*S*)-2*-exo-*Camphanoyloxy-5,6*-exo-*(isopropylidene-dioxy)-3*-endo-*phenyl-sulfonyl-7-oxabicyclo[2.2.1]heptane, (−)-**8**

To a solution of (−)-**7** (1.37 g, 2.12 mmol) in EtSH (6.4 ml), $BF_3 \cdot OEt_2$ (0.78 ml, 6.36 mmol) was added. The mixture was stirred for 15 min and then $H_2O$ was added. The crude was extracted with AcOEt, the organic layer was dried over $MgSO_4$, filtered and then the solvent was evaporated under reduced pressure. The solid obtained was dissolved in acetone (21.0 ml) and 2,2-dimethoxypropane (0.52 ml, 4.24 mmol) and *p*-TsOH (catalytic amounts) were added. After 30 min of stirring, solvent was eliminated in vacuo. The crude product was purified by column chromatography (hexane:AcOEt 2:1) to produce (−)-**8** (0.87 g, 81%) as a white solid. $[\alpha]_D$ −41.0 (*c* 1.4, $CHCl_3$). Mp: 224–225°C. $^1H$ NMR ($CDCl_3$, 300 MHz): δ 0.67 (s, 3H), 0.91 (s, 3H), 1.05 (s, 3H), 1.36 (s, 3H), 1.47 (s, 3H), 1.62–2.07 (m, 4H), 3.69 (dd, 1H, *J*=3.4, 5.4 Hz), 4.42 (s, 1H), 4.59 (d, 1H, *J*=5.4 Hz), 4.80 (dd, 1H, *J*=1.8, 5.4 Hz),

5.24 (d, 1H, *J*=5.9 Hz), 5.31 (d, 1H, *J*=3.4 Hz), 7.60 (t, 2H, *J*=7.3 Hz), 7.70 (t, 1H, *J*=7.3 Hz), 7.92 (d, 2H, *J*=6.8 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 9.7, 16.4, 16.6, 25.0, 25.6, 28.7, 30.3, 54.2, 54.6, 69.1, 74.0, 78.3, 79.3, 86.0, 90.1, 112.7, 128.0, 129.8, 134.6, 136.6, 139.1, 166.5, 177.4. IR (KBr): ν 1790, 1440, 1105 cm$^{-1}$. Anal. calcd for $C_{25}H_{30}O_9S$: C, 59.29; H, 5.93. Found: C, 59.16; H, 5.88.

### *3.3. 5,6-*exo*-(Isopropylidenedioxy)-2-phenylsulfonyl-7-oxabicyclo[2.2.1]hept-2-ene, (−)-**9***

To a solution of (−)-**8** (160 mg, 0.32 mmol) in a mixture of THF:$H_2O$ 20:1 (3.20 ml of THF, 0.10 ml of $H_2O$), $K_2CO_3$ (190 mg, 1.58 mmol) was added. The mixture was stirred at room temperature for 2 days and then quenched with $H_2O$. The crude was extracted with AcOEt, organic layers were dried over $MgSO_4$, filtered and solvent was evaporated in vacuo. The crude product was purified by column chromatography (hexane:AcOEt 5:1) to afford sulfone (−)-**9** (69 mg, 71%) as a white solid. $[\alpha]_D$ −39.1 (*c* 0.8, $CHCl_3$). Mp: 112–114°C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 3H), 1.45 (s, 3H), 4.44 (d, 1H, *J*=5.1 Hz), 4.55 (d, 1H, *J*=5.1 Hz), 4.77 (d, 1H, *J*=0.6 Hz), 4.94 (dd, 1H, *J*=0.6, 2.0 Hz), 7.05 (d, 1H, *J*=2.0 Hz), 7.58 (t, 2H, *J*=7.0 Hz), 7.66 (d, 1H, *J*=7.5 Hz), 7.90 (d, 2H, *J*=7.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 25.6, 31.5, 79.2, 79.5, 81.2, 83.1, 116.5, 127.9, 129.6, 134.3, 138.4, 143.3, 150.4. IR (KBr): ν 3050, 1520, 1420 cm$^{-1}$. Anal. calcd for $C_{15}H_{16}O_5S$: C, 58.44; H, 5.20. Found: C, 58.40; H, 5.13.

### *3.4. (1*S*,2*R*,5*R*,6*S*)-5,6-(Isopropylidenedioxy)-2-(trimethylsilylethynyl)-3-phenyl-sulfonylcyclohex-3-enol, (−)-**2***

To a solution of trimethylsilylacetylene (0.27 ml, 1.94 mmol) in THF (5 ml), *n*-BuLi (1.46 ml, 2.33 mmol) was added dropwise at 0°C. After 30 min of stirring, lithium trimethylsilylacetylide was added via cannula over a solution of (−)-**9** (200 mg, 0.65 mmol) in PhMe (13 ml) cooled at 0°C. The mixture was stirred for 5 min, quenched with saturated aqueous solution of $NH_4Cl$ and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Compound (−)-**2** (163 mg, 63%) was obtained as a colorless oil after purification by column chromatography (hexane:AcOEt 5:1). $[\alpha]_D$ −6.4 (*c* 0.9, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): δ −0.08 (s, 9H), 1.22 (s, 3H), 1.32 (s, 3H), 2.85 (d, 1H, *J*=12.4 Hz), 3.82 (ddd, 1H, *J*=2.4, 6.4, 12.4 Hz), 4.00 (d, 1H, *J*=6.4 Hz), 4.47 (dd, 1H, *J*=2.4, 5.7 Hz), 4.78 (t, 1H, *J*=2.5 Hz), 6.99 (d, 1H, *J*=3.7 Hz), 7.51 (t, 2H, *J*=7.7 Hz), 7.62 (t, 1H, *J*=7.4 Hz), 7.93 (d, 2H, *J*=7.7 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 0.0, 0.2, 0.3, 26.3, 27.8, 31.0, 67.8, 72.6, 75.4, 98.9, 110.8, 111.6, 128.9, 129.3, 130.1, 134.0, 135.5, 139.6. IR ($CHCl_3$): ν 3600, 3050, 1425 cm$^{-1}$. Anal. calcd for $C_{20}H_{26}O_5SSi$: C, 59.26; H, 6.17. Found: C, 59.18; H, 6.09.

### *3.5. (1*S*,4*R*,5*S*,6*S*)-5,6-(Isopropylidenedioxy)-4-methoxy-3-phenylsulfonyl-2-vinyl-cyclohex-2-enol, (+)-**3***

To a solution of MeONa (1 M, 3.3 ml) cooled at 0°C, sulfone (−)-**2** (267 mg, 0.66 mmol) dissolved in MeOH (3.3 ml) was added and stirred for 20 min. The reaction was quenched with saturated aqueous solution of NaCl and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The resulting crude product was purified by column chromatography (hexane:AcOEt 5:1) to afford 163 mg of (+)-**3** (71%) as a white solid. $[\alpha]_D$ +158.9 (*c* 0.9, $CHCl_3$). Mp: 131–132°C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 0.84 (s, 3H), 1.26 (s, 3H), 2.23 (d, 1H, *J*=10.0 Hz), 3.44 (s, 3H), 4.59 (bs, 1H), 4.60 (bs, 1H), 4.72 (bs, 1H), 4.75 (d, 1H, *J*=10.0 Hz), 5.44 (dd, 1H, *J*=1.5, 18.0 Hz), 5.55 (dd, 1H, *J*=1.5, 12.0 Hz), 6.79 (dd, 1H, *J*=12.0, 18.0 Hz), 7.47 (t, 2H, *J*=8.0 Hz), 7.55 (d, 1H, *J*=7.8 Hz), 7.89 (d, 2H, *J*=7.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 24.2, 25.4, 57.6, 68.8, 74.0, 74.5,

76.3, 109.5, 123.7, 128.3, 128.6, 129.5, 129.6, 133.1, 135.2, 141.6. IR (KBr): ν 3500, 3000, 1450, 1390 $cm^{-1}$. Anal. calcd for $C_{18}H_{22}O_6S$: C, 59.00; H, 6.05. Found: C, 58.87; H, 6.17.

### *3.6. (1S*,4R*,5S*,6S*,1′R*)-2-(1′,2′-Dihydroxyethyl)-5,6-(isopropylidenedioxy)-4-methoxy-3-phenylsulfonylcyclohex-2-enol **12** and (1R*,2S* or 2R*,5S*,6S*,1′S*)-2-(1′,2′-dihydroxyethyl)-5,6-(isopropylidenedioxy)-4-methoxy-3-phenylsulfonylcyclohex-3-en-1,2-diol, **13***

To a solution of **3** (55 mg, 0.15 mmol) in acetone:$H_2O$ 8:1 (0.8 ml of acetone, 0.1 ml of $H_2O$) $Me_3NO \cdot 2H_2O$ (23 mg, 0.20 ml) and $OsO_4$ (2.5% *t*-BuOH) (0.04 ml, $3.10^{-3}$ mmol) were added. The mixture was stirred for 25 min. The reaction was quenched with $NaHSO_3$ and solvent was evaporated in vacuo. The crude product was subjected to column chromatography (hexane:AcOEt 5:1) to afford **12** (42 mg, 70%) as a white solid and **13** (4 mg, 6%) as a colorless oil. Compound **12**: mp: 120–122°C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.15 (s, 3H), 1.31 (s, 3H), 3.25 (s, 3H), 3.52 (dd, 1H, *J*=3.7, 11.9 Hz), 3.76 (dd, 1H, *J*=5.8, 11.9 Hz), 3.91–3.99 (m, 3H), 4.54–4.59 (m, 2H), 4.63–4.67 (m, 1H), 4.94 (d, 1H, *J*=3.5 Hz), 5.81 (dd, 1H, *J*=3.8, 5.7 Hz), 7.55 (t, 2H, *J*=7.5 Hz), 7.63 (t, 1H, *J*=7.3 Hz), 7.94 (d, 2H, *J*=7.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 24.2, 25.6, 57.9, 66.1, 70.6, 71.7, 73.8, 74.5, 76.6, 109.8, 128.0, 129.4, 133.9, 135.6, 140.8, 156.8. IR (KBr): ν 3400, 1430, 1370 $cm^{-1}$. Anal. calcd for $C_{18}H_{24}O_8S$: C, 51.90; H, 5.77. Found: C, 51.79; H, 5.65. Compound **13**: $^1$H NMR ($CDCl_3$, 300 MHz): δ 0.78 (s, 3H), 1.21 (s, 3H), 3.41 (s, 3H), 4.21–4.26 (m, 4H), 4.50 (t, 1H, *J*=7.9 Hz), 4.54–4.61 (m, 3H), 5.25 (t, 1H, *J*=7.2 Hz), 7.60 (t, 2H, *J*=7.7 Hz), 7.68 (d, 1H, *J*=7.3 Hz), 7.96 (d, 2H, *J*=7.7 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 23.7, 25.4, 58.7, 69.3, 73.0, 75.3, 75.7, 76.6, 101.8, 109.6, 128.4, 129.6, 134.6, 136.1, 138.8, 158.5. IR ($CHCl_3$): ν 3460, 3020, 1450, 1390 $cm^{-1}$. Anal. calcd for $C_{18}H_{24}O_9S$: C, 51.92; H, 5.77. Found: C, 51.83; H, 5.66.

### *3.7. (3R*,4S*,5S*,6S*)-6-Hydroxy-4,5-(isopropylidenedioxy)-3-methoxy-2-phenyl-sulfonylcyclohex-1-enecarbaldehyde, **14***

#### *3.7.1. Procedure A*

To a solution of **12** (39 mg, 0.10 mmol) in THF:$H_2O$ 1:1 (0.5 ml of $H_2O$, 0.5 ml of THF), $NaIO_4$ (31 mg, 0.15 mmol) was added. The mixture was stirred for 1 h and was then quenched with $H_2O$. The crude was extracted with AcOEt, and the organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Aldehyde **14** (26 mg, 71%) was obtained as a colorless oil.

#### *3.7.2. Procedure B*

To a solution of **3** (163 mg, 0.44 mmol) in $CH_3CN$:$CCl_4$:$H_2O$ 3:3:4 (2.5 ml of $CH_3CN$, 2.5 ml of $CCl_4$, 3.4 ml of $H_2O$), $NaIO_4$ (188 mg, 0.88 ml) was added. After 5 min of stirring, $RuCl_3 \cdot H_2O$ (4 mg, 0.02 mmol) was added. The mixture was stirred for 30 min, quenched with saturated aqueous solution of $NaHCO_3$ and extracted with $CH_2Cl_2$. Organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography afforded aldehyde **14** (108 mg, 67%) as a colorless oil. $^1$H NMR ($CDCl_3$, 300 MHz): δ 0.82 (s, 3H), 1.20 (s, 3H), 2.98 (d, 1H, *J*=10.5 Hz), 3.40 (s, 3H), 4.31 (d, 1H, *J*=2.7 Hz), 4.51 (dd, 1H, *J*=2.7, 7.1 Hz), 4.57 (dd, 1H, *J*=4.0, 7.1 Hz), 4.87 (dd, 1H, *J*=3.9, 10.1 Hz), 7.56 (t, 2H, *J*=7.7 Hz), 7.64 (t, 1H, *J*=7.1 Hz), 7.86 (d, 2H, *J*=7.7 Hz), 10.45 (s, 1H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 24.2, 25.3, 58.3, 68.1, 73.6, 74.4, 75.6, 110.0, 128.8, 129.4, 134.2, 139.1, 139.8, 152.9, 194.0. IR ($CHCl_3$): ν 3400, 3020, 1715 $cm^{-1}$. Anal. calcd for $C_{17}H_{20}O_7S$: C, 55.43; H, 5.43. Found: C, 55.59; H, 5.56.

### 3.8. (1S*,4R*,5S*,6S*)-2-(Hydroxymethyl)-5,6-(isopropylidenedioxy)-4-methoxy-3-phenylsulfonyl-cyclohex-2-enol, **15**

To a solution of $CeCl_3 \cdot 7H_2O$ (201 mg, 0.54 mmol) in MeOH (1.4 ml) at −78°C, $NaBH_4$ (12 mg, 0.32 mmol) was added. After 5 min, **14** (101 mg, 0.27 mmol) dissolved in MeOH (1.4 ml) was added dropwise. The mixture was stirred for 3.5 h, quenched with $H_2O$ and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by column chromatography (hexane:AcOEt, 1:1) to afford **15** (66 mg, 66%) as a white solid. Mp: 105–106°C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 0.92 (s, 3H), 1.28 (s, 3H), 2.65 (m, 1H), 3.19 (d, 1H, *J*=9.2 Hz), 3.37 (s, 3H), 4.58 (dd, 1H, *J*=2.6, 7.4 Hz), 4.62–4.66 (m, 2H), 4.71–4.78 (m, 2H), 4.86 (dd, 1H, *J*=6.3, 12.9 Hz), 7.55 (t, 2H, *J*=7.0 Hz), 7.62 (t, 1H, *J*=7.0 Hz), 7.94 (d, 2H, *J*=7.0 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 24.1, 25.3, 57.4, 57.6, 69.3, 74.0, 74.1, 75.8, 109.6, 127.8, 129.1, 133.5, 136.6, 141.1, 156.5. IR (KBr): ν 3250, 2930, 1420 $cm^{-1}$. Anal. calcd for $C_{17}H_{22}O_7S$: C, 55.13; H, 5.95. Found: C, 55.24; H, 5.83.

### 3.9. (1S,4S,5R,6S)-5,6-(Isopropylidenedioxy)-4-methoxy-2-vinylcyclohex-2-enol, (+)-**17**

To a solution of (+)-**3** (333 mg, 0.90 mmol) in anhydrous MeOH (1 ml), $Na_2HPO_4$ (505 mg, 3.55 mmol) was added. After cooling the mixture to −20°C, Na–Hg 6% (2.28 g, 2.5 g/mmol) was added. The mixture was stirred for 3.5 h, quenched with $H_2O$ and extracted with $Et_2O$. The organic layer was dried over $MgSO_4$ and solvent was evaporated under reduced pressure to afford (+)-**17** as a colorless oil (164 mg, 80%). $[\alpha]_D$ +15.4 (*c* 0.02, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.42 (s, 3H), 1.57 (s, 3H), 2.59 (s, 1H), 3.52 (s, 3H), 4.21 (m, 2H), 4.33 (s, 1H), 4.71 (s, 1H), 5.17 (d, 1H, *J*=11.1 Hz), 5.43 (d, 1H, *J*=17.5 Hz), 5.94 (s, 1H), 6.41 (dd, 1H, J=11.1, 17.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 24.1, 26.4, 57.5, 62.6, 75.0, 78.5, 79.9, 110.2, 113.9, 132.3, 135.2, 137.4. IR ($CHCl_3$): ν 3420, 2920, 1480 $cm^{-1}$. Anal. calcd for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found: C, 63.61; H, 8.08.

### 3.10. (1S,4S,5R,6S,1′R)-2-(1′,2′-Dihydroxyethyl)-5,6-(isopropylidenedioxy)-4-methoxycyclohex-2-enol, (+)-**18**

To a solution of (+)-**17** (74 mg, 0.33 mmol) in acetone:$H_2O$ 8:1 (2.64 ml of acetone, 0.33 ml of $H_2O$), $Me_3NO \cdot 2H_2O$ (73 mg, 0.66 ml) and $OsO_4$ (2.5% *t*-BuOH) (0.09 ml, $6.6 \times 10^{-3}$ mmol) were added. The mixture was stirred for 1 h. The reaction was quenched with $NaHSO_3$ and solvent was evaporated in vacuo. The crude product was subjected to column chromatography (hexane:AcOEt 1:1) to afford (+)-**18** (52 mg, 61%) as a white solid. $[\alpha]_D$ +56.5 (*c* 0.01, $CHCl_3$). Mp: 92–94°C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.40 (s, 3H), 1.50 (s, 3H), 3.45 (s, 3H), 3.72–3.79 (m, 4H), 4.13 (t, 1H, *J*=3.5 Hz), 4.28–4.34 (m, 2H), 4.37–4.39 (m, 1H), 4.51 (s, 1H), 4.57 (d, 1H, *J*=3.5 Hz), 5.98 (d, 1H, *J*=2.9 Hz). $^{13}$C NMR ($CDCl_3$, 300 MHz): δ 24.3, 26.4, 57.4, 64.4, 66.0, 72.6, 74.1, 75.6, 77.9, 110.0, 128.7, 140.8. IR (KBr): ν 3600–3200, 2920, 1160 $cm^{-1}$. Anal. calcd for $C_{12}H_{20}O_6$: C, 55.38; H, 7.69. Found: C, 55.27; H, 7.59.

### 3.11. (3S,4R,5S,6S)-6-Hydroxy-4,5-(isopropylidendioxy)-3-methoxycyclohex-1-ene-carbaldehyde, (+)-**1**

#### 3.11.1. Procedure A

To a well-stirred solution of (+)-**17** (32 mg, 0.14 mmol) in a mixture of $CH_3CN$ (0.4 ml), $CCl_4$ (0.4 ml) and $H_2O$ (0.6 ml), $NaIO_4$ (60 mg, 0.28 mmol) was added. The resulting mixture was allowed to stir for 5 min and then $RuCl_3 \cdot H_2O$ (1.3 mg, 0.01 mmol) was added. The mixture turned black and was stirred

for 50 min. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and solvent was evaporated in vacuo. After purification by column chromatography (hexane:AcOEt 5:1), (+)-**1** was obtained as a colorless oil (16 mg, 50%).

### *3.11.2. Procedure B*

To a solution of (+)-**18** (39 mg, 0.10 mmol) in a mixture THF:$H_2O$ 1:1 (0.5 ml of THF, 0.5 ml of $H_2O$), $NaIO_4$ (31 mg, 0.15 mmol) was added. After 1 h of stirring, crude was hydrolyzed with $H_2O$ and extracted with AcOEt. Organic layer was dried over $MgSO_4$, filtered and solvent was evaporated under reduced pressure. Compound (+)-**1** (26 mg, 71%) was obtained as a colorless oil.

$[\alpha]_D$ +49.5 (*c* 0.01, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.42 (s, 3H), 1.57 (s, 3H), 2.68 (s, 1H), 3.57 (s, 3H), 4.17 (dd, 1H, *J*=3.7, 8.4 Hz), 4.29 (dd, 1H, *J*=5.3, 8.6 Hz), 4.51 (dd, 1H, *J*=1.3, 5.5 Hz), 4.96 (d, 1H, *J*=3.8 Hz), 6.98 (s, 1H), 9.56 (s, 1H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 24.2, 26.5, 58.1, 60.0, 74.7, 78.9, 80.3, 111.0, 140.6, 153.8, 189.8. IR ($CHCl_3$): ν 3560, 3045, 1700 $cm^{-1}$. Anal. calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.02. Found: C, 57.78; H, 6.90.

### *3.12. (1S,4S,5R,6R)-2-(Hydroxymethyl)-5,6-(isopropylidenedioxy)-4-methoxycyclohex-2-enol, (+)-**19***

To a solution of (+)-**1** (23 mg, 0.10 mmol) in THF (1.0 ml), $LiAlH_4$ was added (10 mg, 0.25 mmol) at 0°C. The mixture was stirred for 20 min and quenched with $H_2O$. The aqueous layer was extracted with AcOEt. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure and purified by column chromatography (hexane:AcOEt 1:5) to afford (+)-**19** (21 mg, 93%) as a colorless oil. $[\alpha]_D$ +23.3 (*c* 0.01, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.45 (s, 3H), 3.40 (s, 3H), 4.07 (t, 1H, *J*=3.8 Hz), 4.25 (s, 2H), 4.34 (dd, 1H, *J*=3.9, 7.7 Hz), 4.43 (dd, 1H, *J*=4.1, 7.8 Hz), 4.48 (d, 1H, *J*=3.5 Hz), 5.94 (d, 1H, *J*=3.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 24.3, 26.3, 57.1, 64.4, 66.3, 67.8, 75.7, 76.3, 109.7, 125.3, 142.2. IR ($CHCl_3$): ν 3500, 2880, 1380 $cm^{-1}$. Anal. calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83. Found: C, 57.28; H, 7.70.

### *3.13. (3S,4R,5S,6S)-1-(Hydroxymethyl)-1′,6;4,5-bis-(isopropylidenedioxy)-3-methoxy-cyclohexene, (+)-**20a***

To a solution of diol (+)-**19** (32 mg, 0.14 mmol), *p*-TsOH (catalytic amount) and 2,2-dimethoxypropane (0.02 ml, 0.28 mmol) were added. After stirring for 1 h, saturated aqueous solution of $NaHCO_3$ was added. The mixture was extracted with AcOEt, and then the organic layer was dried under $MgSO_4$, filtered and solvent was eliminated in vacuo. The crude product was purified by column chromatography on silica gel (hexane:AcOEt 1:2) to produce (+)-**20a** (32 mg, 85%) as a colorless oil. $[\alpha]_D$ +20.5 (*c* 0.7, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 6H), 1.45 (s, 3H), 1.49 (s, 3H), 3.33 (s, 3H), 3.79 (dd, 1H, *J*=1.5, 5.5 Hz), 4.18 (d, 1H, *J*=13.6 Hz), 4.38 (dt, 1H, *J*=1.8, 13.9 Hz), 4.46 (dt, 1H, *J*=1.1, 6.6 Hz), 4.58 (dd, 1H, *J*=2.2, 4.0 Hz), 4.70 (dd, 1H, *J*=4.0, 6.7 Hz), 5.73 (dd, 1H, *J*=4.0, 6.7 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 23.4, 24.6, 25.7, 26.2, 56.6, 61.8, 66.3, 74.5, 75.2, 76.0, 115.8, 142.6. IR ($CHCl_3$): ν 3040, 1420, 1210 $cm^{-1}$. Anal. calcd for $C_{14}H_{22}O_5$: C, 62.22; H, 8.15. Found: C, 62.14; H, 8.06.

### 3.14. (3S,4R,5S,6S)-1-(Acetoxymethyl)-4,5-(isopropylidenedioxy)-3-methoxycyclo-hexen-1-ylacetate, (+)-**20b**

To a solution of diol (+)-**19** (13 mg, 0.06 mmol) in pyridine (0.30 ml), DMAP (catalytic amount) and $Ac_2O$ (0.02 ml, 0.18 mmol) were added. The mixture was stirred for 1 h and then the solvent was evaporated off under reduced pressure to afford (+)-**20b** (17 mg, 89%) as a colorless oil. $[\alpha]_D$ +8.4 (*c* 0.02, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 3H), 1.45 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 3.46 (s, 3H), 4.12–4.13 (m, 1H), 4.33 (dd, 1H, *J*=4.0, 8.1 Hz), 4.40 (dd, 1H, *J*=4.0, 8.1 Hz), 4.65 (s, 2H), 5.58 (d, 1H, *J*=4.0 Hz), 6.05 (d, 1H, *J*=2.9 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 20.8, 24.6, 26.1, 26.1, 57.2, 64.3, 67.4, 74.2, 77.7, 77.7, 110.2, 130.7, 134.4, 170.3. IR ($CHCl_3$): ν 2940, 1750, 1720 $cm^{-1}$. Anal. calcd for $C_{15}H_{21}O_7$: C, 57.32; H, 6.69. Found: C, 57.46; H, 6.55.

### 3.15. α-D-2,3;4,6-O-Diisopropylidene-1-O-methylcarbatalopyranose, (+)-**4a**

A solution of (+)-**20a** (17 mg, 0.06 mmol) and Pd/C 10% (67 mg, 0.06 mmol) in MeOH (1.2 ml) was hydrogenated (30 psi) for 1.5 h. The reaction mixture was filtered through a short path of $SiO_2$ with MeOH to afford (+)-**4a** as a colorless oil (7 mg, 41%). $[\alpha]_D$ +3.6 (*c* 0.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 1.52 (s, 3H), 1.48–1.57 (m, 1H), 1.70–1.75 (m, 1H), 2.08 (ddd, 1H, *J*=4.1, 6.1, 13.4 Hz), 3.45 (s, 3H), 3.63 (dd, 1H, *J*=2.9, 11.7 Hz), 3.99 (q, 1H, *J*=4.1 Hz), 4.08 (dd, 1H, *J*=3.7, 11.7 Hz), 4.13–4.16 (m, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 19.3, 25.6, 25.7, 25.8, 28.6, 29.1, 56.9, 64.9, 66.1, 75.4, 76.9, 77.6, 98.8, 109.5. IR ($CHCl_3$): ν 1458, 1200 $cm^{-1}$. Anal. calcd for $C_{14}H_{24}O_5$: C, 62.22; H, 8.89. Found: C, 62.17; H, 8.92.

### 3.16. α-D-4-O-Acetyl-6-deoxy-2,3-O-isopropylidene-1-O-methylcarbatalopyranose, (+)-**4b**

A solution of (+)-**20b** (17 mg, 0.05 mmol) and Pd/C 10% (58 mg, 0.05 mmol) in MeOH (1 ml) was hydrogenated (30 psi) for 2 h. The reaction mixture was filtered through a short path of $SiO_2$ with MeOH. The resulting crude was purified by column chromatography (hexane:AcOEt 5:1) to afford (+)-**4b** (6 mg, 43%) as a colorless oil. $[\alpha]_D$ +10.9 (*c* 0.01, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.05 (d, 3H, *J*=3.0 Hz), 1.35 (s, 3H), 1.51 (s, 3H), 1.60–1.65 (m, 1H), 1.72–1.81 (m, 2H), 2.14 (s, 3H), 3.44 (s, 3H), 3.61 (dt, 1H, *J*=4.8, 8.0 Hz), 4.12 (dd, 1H, *J*=5.5, 6.6 Hz), 4.30 (dd, 1H, *J*=4.0, 7.0 Hz), 5.20 (t, 1H, *J*=4.0 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 16.9, 26.9, 27.5, 29.6, 29.7, 30.8, 70.9, 74.7, 77.1, 77.2, 77.3, 109.3, 170.1. IR ($CHCl_3$): ν 1740, 1545, 1460 $cm^{-1}$. Anal. calcd for $C_{13}H_{22}O_5$: C, 60.46; H, 8.53. Found: C, 60.31; H, 8.64.

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## References

1. McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem*. **1966**, *31*, 1516.

2. For reviews, see: (a) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem*. **1990**, *48*, 21. (b) Suami, T. *Top. Curr. Chem*. **1990**, *154*, 1257.
3. For some recent and selected references, see: (a) Cossy, J.; Ranaivosata, J. L.; Bellosta, V.; Ancerewicz, J.; Ferritto, R.; Vogel, P. *J. Org. Chem*. **1995**, *60*, 8351. (b) Aceña, J. L.; Arjona, O.; Plumet, J. *J. Org. Chem*. **1997**, *62*, 3360. (c) Lallemand, M. C.; Desjardins, M.; Freeman, S.; Hudlicky, T. *Tetrahedron Lett*. **1997**, *38*, 7693. (d) Angelaud, R.; Landais, Y. *Tetrahedron Lett*. **1997**, *38*, 8841. (e) Mehta, G.; Mohal, N. *Tetrahedron Lett*. **1998**, *39*, 3285. (f) Trost, B. M.; Chupak, L. S.; Lübbers, T. *J. Am. Chem. Soc*. **1998**, *120*, 1732. (g) Lubineau, A.; Billault, I. *J. Org. Chem*. **1998**, *63*, 5668. (h) Maudru, E.; Singh, G.; Wightman, R. H. *Chem. Commun*. **1998**, 1505. (i) André, C.; Bolte, J.; Demuynck, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3737. (j) Gómez, A. M.; Danelón, G. O.; Valverde, S.; López, J. C. *J. Org. Chem*. **1998**, *63*, 9626. (k) Renault, P.; Millet, J.; Sepulchre, C.; Theveniaux, J.; Barberousse, V.; Jeanneret, V.; Vogel, P. *Helv. Chim. Acta* **1998**, *81*, 2043. (l) Jotterand, N.; Vogel, P. *Synlett* **1998**, 1237.
4. Arjona, O.; Borrallo, C.; Iradier, F.; Medel, R.; Plumet, J. *Tetrahedron Lett*. **1998**, *39*, 1977.
5. (a) Argoudelis, A. D.; Pike, T. R.; Sprague, R. W. *J. Antibiot*. **1976**, *29*, 777. (b) Argoudelis, A. D.; Sprague, R. W.; Mizsak, S. A. *J. Antibiot*. **1976**, *29*, 787.
6. For a previous synthesis of α-D-carbatalopyranose see: Pingli, L.; Vandewalle, M. *Synlett* **1994**, 228.
7. For reviews on the use of enantiomerically pure 7-oxanorbornene derivatives in the synthesis of natural products and analogues, see for example: (a) Vogel, P.; Auberson, Y.; Bimwala, M.; De Guchteneere, E.; Vieira, E.; Wagner, J. In *Trends in Synthetic Carbohydrate Chemistry*; ACS Symposium Series 286. Horton, D.; Hawkins, L. D.; McGarvey, G. J, Eds.; American Chemical Society: Washington, DC, 1989; Chapter 13, pp. 193–241. (b) Vogel, P. *Bull. Soc. Chim. Belg*. **1990**, *99*, 395. (c) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173. (d) Nudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. *Chem. Rev*. **1996**, *96*, 1195. (e) Woo, S.; Keay, B. A. *Synthesis* **1996**, 669. (f) Chiu, P.; Lautens, M. *Topics in Current Chemistry*; Springer Verlag: Berlin, 1997; *190*, 1. (g) Jiang, S.; Singh, G. *Tetrahedron* **1998**, *54*, 4697. For more recent applications, see for example: (i) Baudat, A.; Vogel, P. *J. Org. Chem*. **1997**, *62*, 6252. (j) Mosimann, H.; Vogel, P.; Pinkerton, A. A.; Kirschbaum, K. *J. Org. Chem*. **1997**, *62*, 3002. (k) Theurillat-Moritz, V.; Guidi, A.; Vogel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3497. (l) Forster, A.; Fitremann, J.; Renaud, P. *Tetrahedron Lett*. **1998**, *39*, 7097; idem, *ibid* **1998**, *39*, 3485. (m) Pasquarello, C.; Demange, R.; Vogel, P. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 793. (n) Gerber, P.; Vogel, P. *Tetrahedron Lett*. **1999**, *40*, 3165. See also: Forster, A.; Kovac, J.; Mosimann, H.; Renaud, P.; Vogel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 567.
8. De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem*. **1984**, *49*, 596.
9. Arjona, O.; Iradier, F.; Plumet, J.; Martínez-Alcázar, M. P.; Hernández-Cano, F.; Fonseca, I. *Tetrahedron Lett*. **1998**, *39*, 6741 and references cited therein.
10. Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem*. **1981**, *46*, 3936.
11. (a) Ley, S. V.; Simpkins, N. S.; Whittle, A. J. *J. Chem. Soc., Chem. Commun*. **1983**, 503. (b) Jones, P. S.; Ley, S. V.; Simpkins, N. S.; Whittle, A. J. *Tetrahedron* **1986**, *42*, 6519. (c) Musicki, B.; Widlanski, T. S. *Tetrahedron Lett*. **1991**, *32*, 1267. For reduction of sugar-derived vinyl sulfones, see: (d) Sakakibara, T.; Takai, I.; Yamamoto, A.; Iizuka, H.; Hirasawa, K.; Ishido, Y. *Tetrahedron Lett*. **1990**, *31*, 3749.
12. Tran, C. H.; Crout, D. H. G. *Tetrahedron: Asymmetry* **1996**, *7*, 2403.