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Total Synthesis of (+)-Pinitol.

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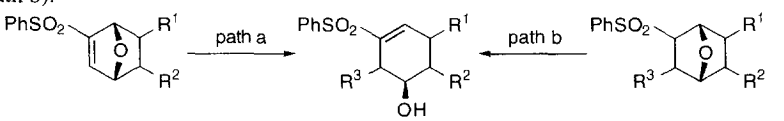
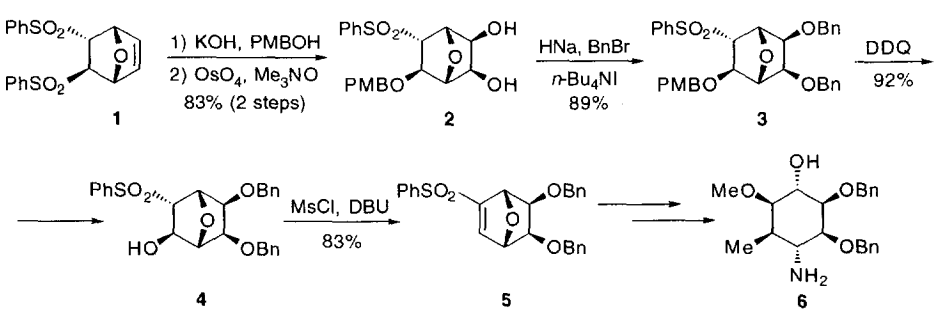
Abstract: A new synthesis of (+)-pinitol **9** has been developed starting from the 7-oxanorbornenic sulfone (+)-**5**, prepared in enantiomerically pure form by resolution of the sulfonyl-7-oxanorbornanol **4**. These precursors are available from the Diels-Alder adduct of furan and *trans*-1,2-bis-(phenylsulfonyl)-ethylene.

7-Oxabicyclo[2.2.1]hept-5-ene (7-oxanorbornene) derivatives are versatile intermediates for the synthesis of a variety of molecules of current interest.[1] In most of these transformations, the oxygen bridge cleavage constitutes a key procedure.[2] Within this general picture, highly substituted cyclohexenyl sulfones have been prepared in a regio- and stereocontrolled manner from 7-oxanorbornenic sulfones *via* S_N2' additions of organolithium reagents[3] (Scheme 1, path a) or by strain-directed oxa-ring opening of the saturated derivatives[4] (path b).



Scheme 1

Although these oxabicyclic sulfones can be usually prepared in homochiral fashion starting from the appropriate enantiomerically pure Diels-Alder adduct of furan,[5] in some cases this approach is impossible. In this context, we recently reported[6] the preparation of the racemic aminocyclitol **6** (Scheme 2) as a first goal towards the total synthesis of the *Amaryllidaceae* alkaloids pancratistatin **7** and 7-deoxypancratistatin **8**[7] (Figure 1). The unavailability in enantiomerically pure form of the starting disulfone **1**, the Diels-Alder adduct between furan and *trans*-1,2-*bis*-phenylsulfonylethylene[8] led us to the resolution of the intermediate alcohol **4** by treatment with a suitable resolving agent. In this report we describe this process and the determination of the absolute configuration of each enantiomer by developing a new synthesis of the naturally occurring *chiro*-inositol derivative (+)-pinitol **9**. It should be pointed out that only two syntheses of this compound in homochiral form have been previously reported starting from products derived from the microbial oxidation of aromatics.[9]



Scheme 2

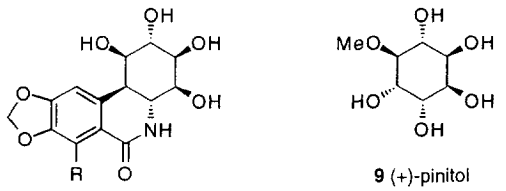
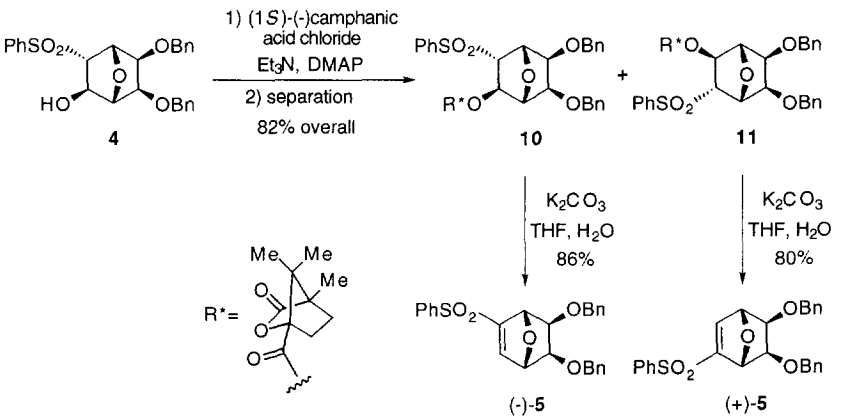


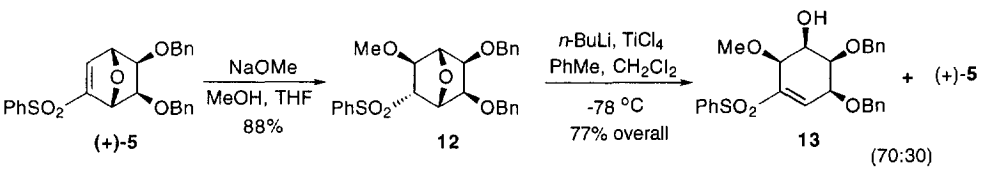
Figure 1

Alcohol **4** was prepared in four steps from disulfone **1** in 68% overall yield.[6] The reaction of **4** with 2 equivalents of (1*S*)-(-)-camphanic acid chloride gave a 1:1 mixture of diastereomeric esters **10** and **11** (Scheme 3) which were separated by column chromatography on silica gel (**10**, R_f= 0.32, hexane:EtOAc, 1:1; **11**, R_f= 0.29, hexane:EtOAc, 1:1). Removal of the chiral auxiliary was performed by treatment with K_2CO_3 in aqueous THF affording the enantiomerically pure vinyl sulfones (-)-**5** ([α]$_D$ -95.2, (c 1.0, $CHCl_3$)) and (+)-**5** ([α]$_D$ +95.4, (c 0.8, $CHCl_3$)) from **10** and **11**, respectively.



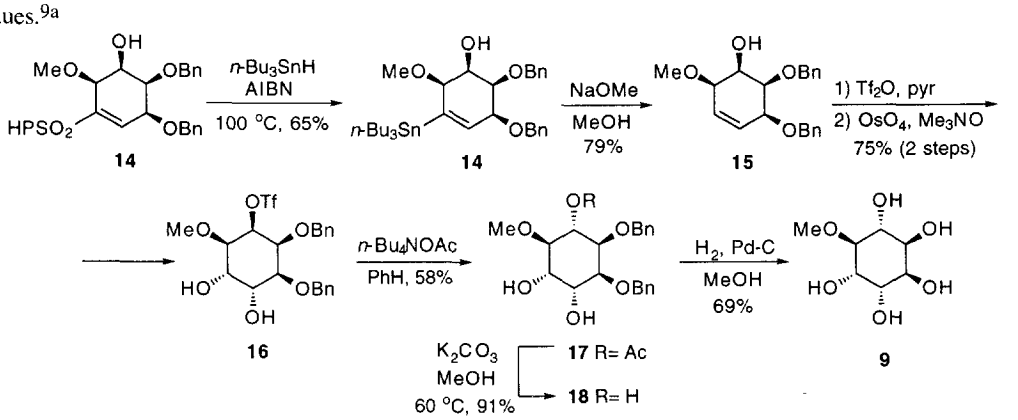
Scheme 3

At this stage, we chose (+)-**5** for the chemical correlation with pinitol. Addition of NaOMe to (+)-**5** gave methoxysulfone **12**[10] (Scheme 4). Next, according to the methodology developed by us,[4] the reaction of **12** with *n*-BuLi/$TiCl_4$[11] at -78 °C afforded the cyclohexenyl sulfone **13** in moderate yield (54%). In addition, a significant amount of (+)-**5** (23%) was recovered and recycled after separation. This unexpected lack of regioselectivity in the elimination process should be consequence of the *exo* orientation of the methoxy group, despite the strained character of the oxygen bridge.[4]



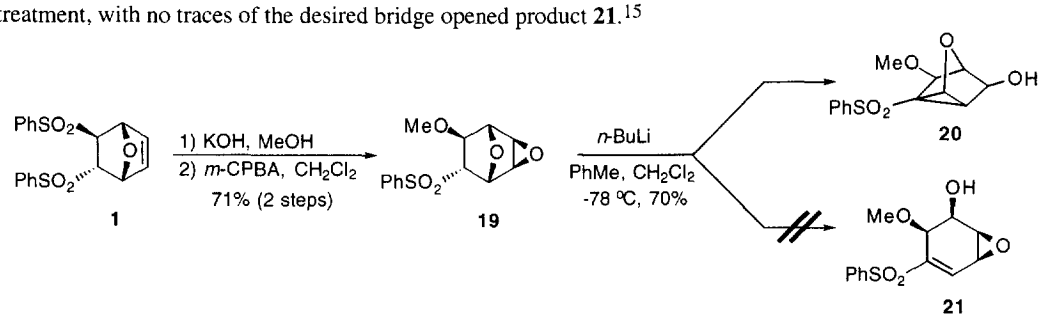
Scheme 4

Desulfonylation of **13** could not be carried out by reducing methods in a clean way due to competitive double bond migrations and allylic deoxygenations. However, this problem was circumvented using a two-step procedure, namely stannane **14** formation and subsequent NaOMe-mediated destannylation[12] (Scheme 5). In this way, the protected conduritol D **15** was obtained in 51% overall yield. At this point, we needed the inversion of configuration of the free hydroxyl group and the stereoselective dihydroxylation of the double bond. Thus, triflate formation[13] followed by osmylation gave **16**. Substitution of triflate **16** with *n*-Bu_4NOAc gave acetate **17** with small amounts (ca. 10%) of elimination products. The ^1H NMR spectra of **17** showed a triplet at 5.42 ppm for proton H-4 with two axial-axial coupling constants ($J_{3,4}= J_{4,5}= 9.8$ Hz), thus indicating the equatorial orientation of the acetoxy group. Finally, deprotection of **17** afforded (+)-pinitol **9**, ($[\alpha]_D$ +60.2 (c 0.5, H_2O); lit:[9a] $[\alpha]_D$ +61.5 (c 0.27, H_2O)), whose spectral data were in agreement to those reported values.[9a]



Scheme 5

We also tried to obtain precursors for other inositol diastereoisomers. The reaction of **1** with KOH/MeOH[14] followed by treatment of the derived methoxysulfone with *m*-CPBA afforded the epoxide **19** (Scheme 6). In this case, the increase of strain in the oxirane ring led to the cyclopropane **20** after base treatment, with no traces of the desired bridge opened product **21**.[15]



Scheme 6

In summary, the synthesis of (+)-pinitol **9** has been accomplished from disulfone **1** as a new example of the accesibility of inositols and their derivatives from oxabicyclic compounds.[16] The resolution of the racemic alcohol **4** resulted in the preparation of homochiral 7-oxanorbornenic sulfones, also intermediates for the synthesis of *Amaryllidaceae* alkaloids as pancratistatin.

Experimental section.

General Methods. All air-sensitive reactions were carried out under a positive pressure of dry argon using freshly distilled solvents under anhidrous conditions. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran (THF) was distilled from sodium and benzophenone; dichloromethane, benzene, toluene, triethylamine and pyridin from CaH_2. Flash chromatography was performed using Merck 230-400 mesh silica gel. Analytical TLC was carried out on 0.20 mm Merck precoated silica gel plates (60F-254), with detection by UV light, acidic vanillin solution and a 10% solution of phosphomolybdic acid in ethanol. Melting points were determined on a Büchi 512 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Brüker AM-250 or a Varian VXR-300S instruments using $CDCl_3$ or D_2O as solvents. The following abbreviations are used to describe peak patterns when appropriate: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed at the Universidad Complutense de Madrid.

(±)-5-*exo*-((*p*-Methoxy)-benzyloxy)-6-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]-heptane-2,3-*exo*-diol, 2. To a solution of 500 mg (1.33 mmol) of **1**[8] in 20 ml of MeCN, 500 mg (8.9 mmol) of KOH and 1.66 mL (13.3 mmol) of PMBOH were added. After stirring at room temperature for 24 h, H_2O was added. The crude was extracted with Et_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 12 mL of acetone and 1.5 mL of H_2O. Then, 304 mg (2.66 mmol) of $NMe_3O{\bullet}H_2O$ and 0.33 mL (0.03 mmol) of OsO_4 (2.5% wt. solution in *t*-BuOH) were added. After stirring for 48 h, a few drops of 10% aqueous solution of $NaHSO_3$ were added. The crude was concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 1:1) to give 450 mg of **2** as a white solid (83% yield). Data of **2**: Mp: 209-210 °C. R_f= 0.21 (hexane:EtOAc, 1:2). ^1H NMR (300 MHz) δ 2.80-3.00 (m, 2 H, 2 OH), 3.57 (dd, 1 H, *J*= 5.4, 3.4 Hz, H-6), 3.80 (s, 3 H, Me), 4.04-4.07 (m, 2 H, H-3, H-5), 4.22 (d, 1 H, *J*= 11.4 Hz, 1 C$\underline{H}_2$-Ar), 4.34 (d, 1 H, *J*= 11.4 Hz, 1 C$\underline{H}_2$-Ar), 4.44 (s, 1 H, H-4), 4.53 (d, 1 H, *J*= 5.7 Hz, H-1), 4.83 (d, 1 H, *J*= 5.7 Hz, H-2), 6.82 (d, 2 H, *J*= 8.4 Hz, 2 ar$\underline{H}$-CH$_2$), 7.00 (d, 2 H, *J*= 8.4 Hz, 2 ar$\underline{H}$-CH$_2$), 7.60 (t, 2 H, *J*= 7.7 Hz, 2 arH-SO$_2$), 7.72 (t, 1 H, *J*= 7.4 Hz, 1 arH-SO$_2$), 7.88 (d, 2 H, *J*= 7.7 Hz, 2 arH-SO$_2$). ^{13}C NMR (75 MHz) δ 55.3, 70.2, 70.7, 71.4, 71.5, 78.3, 81.5, 87.8, 113.8, 127.9, 129.6, 129.6, 129.7, 134.3, 139.2, 159.4. IR (KBr) 3350, 1600, 1520, 1450, 1310, 1250, 1150, 1120, 1080, 1000, 830 cm^{-1}. Anal. calcd for $C_{20}H_{22}O_7S$: C, 59.10; H, 5.46; found: C, 58.87; H, 5.45.

(±)-2,3-*exo*-Bis-(benzyloxy)-5-*exo*-((*p*-methoxy)-benzyloxy)-6-*endo*-(phenyl-sulfonyl)-7-oxabicyclo[2.2.1]heptane, 3. To a cold (0 °C) solution of 305 mg (0.75 mmol) of **2** in 7.5 mL de THF, 60 mg (1.50 mmol) of HNa (60% wt. in mineral oil), 0.36 mL (3.00 mmol) of BnBr and 69 mg (0.19 mmol) of *n*-Bu_4NI were added. After stirring at room temperature for 24 h, H_2O was added. The crude was extracted with EtOAc, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 390 mg of **3** as a white solid (89% yield). Data of **3**: Mp: 158-159 °C. R_f= 0.38 (hexane:EtOAc, 1:1). ^1H NMR (300 MHz) δ 3.53 (dd, 1 H, *J*= 5.6, 3.2 Hz, H-6), 3.79 (s, 3 H, Me), 3.85 (d, 1 H, *J*= 5.9 Hz, H-3), 3.99 (d, 1 H, *J*= 3.2 Hz, H-5), 4.20 (d, 1 H, *J*= 11.4 Hz, 1 C$\underline{H}_2$-Ar), 4.27 (d, 1 H, *J*= 11.4 Hz, 1 C$\underline{H}_2$-Ar), 4.47 (s, 1 H, H-4), 4.49 (d, 1 H, *J*= 11.7 Hz, 1 C$\underline{H}_2$-Ar), 4.61 (d, 1 H, *J*= 11.8 Hz, 1 C$\underline{H}_2$-Ar), 4.62 (d, 1 H, *J*= 5.5 Hz, H-1), 4.67 (d, 1 H, *J*= 11.9 Hz, 1 C$\underline{H}_2$-Ar), 4.68 (d, 1 H, *J*= 11.8 Hz, 1 C$\underline{H}_2$-Ar), 4.69 (d, 1 H, *J*= 5.9 Hz, H-2), 6.81 (d, 2 H, *J*= 8.6 Hz, 2 ar$\underline{H}$-CH$_2$), 7.00 (d, 2 H, *J*= 8.7 Hz, 2 ar$\underline{H}$-CH$_2$), 7.27-7.38 (m, 10 H, 10 ar$\underline{H}$-CH$_2$), 7.53 (t, 2 H, *J*= 7.7 Hz, 2 arH-SO$_2$), 7.68 (t, 1 H, *J*= 7.7 Hz, 1 arH-SO$_2$), 7.74 (d, 1 H, *J*= 7.7 Hz, 2 arH-SO$_2$). ^{13}C NMR (75 MHz): 55.2,

71.2, 71.4, 73.0, 78.3, 78.8, 79.5, 85.5, 113.8, 127.5, 127.7, 127.8, 128.0, 128.4, 128.6, 129.6, 134.1, 137.5, 137.6, 139.3, 159.4. IR (KBr) 1600, 1515, 1310, 1155, 935, 675 cm^{-1}. Anal. calcd for $C_{34}H_{34}O_7S$: C, 69.61; H, 5.84; found: C, 69.25; H, 5.78.

(±)-5,6-*exo*-Bis-(benzyloxy)-3-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptan-2-*exo*-ol, 4. To a solution of 1.39 g (2.37 mmol) of **3** in 47 mL of CH_2Cl_2 and 2.5 mL of H_2O, 808 mg (3.56 mmol) of DDQ was added. After stirring at room temperature for 24 h, brine was added. The crude was extracted with CH_2Cl_2, washed with 5% aqueous solution of $NaHCO_3$, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 1.12 g of **4** as a white solid (92% yield). Data of **4**: Mp: 142-143 °C. R_f= 0.16 (hexane:EtOAc, 1:1). ^1H NMR (300 MHz) δ 2.02 (d, 1 H, *J*= 8.4 Hz, OH), 3.38 (dd, 1 H, *J*= 5.7, 3.0 Hz, H-3), 3.95 (d, 1 H, *J*= 5.9 Hz, H-6), 4.34 (dd, 1 H, *J*= 8.4, 3.0 Hz, H-2), 4.45 (s, 1 H, H-1), 4.55 (d, 1 H, *J*= 11.7 Hz, 1 C$\underline{H}_2$-Ph), 4.64 (d, 1 H, *J*= 11.8 Hz, 1 C$\underline{H}_2$-Ph), 4.67-4.70 (m, 3 H, H-4, 2 C$\underline{H}_2$-Ph), 4.72 (d, 1 H, *J*= 5.9 Hz, H-5), 7.29-7.40 (m, 10 H, 10 $\underline{\text{ar}}$H-CH_2), 7.58 (t, 2 H, *J*= 7.8 Hz, 2 arH-SO_2), 7.69 (t, 1 H, *J*= 7.4 Hz, 1 arH-SO_2), 7.82 (d, 2 H, *J*= 7.1 Hz, 2 arH-SO_2). ^{13}C NMR (75 MHz) δ 72.5, 72.7, 72.8, 77.9, 79.6, 88.5, 127.5, 127.7, 127.8, 127.9, 128.3, 129.4, 134.0, 137.3, 137.4, 139.2. IR (KBr) 3600-3300, 1455, 1300, 1155, 1085, 905, 735, 695. Anal. calcd for $C_{26}H_{26}O_6S$: C, 66.93; H, 5.62; found: C, 66.40; H, 5.64.

(-)-(1*S*,2*S*,3*R*,4*R*,5*R*,6*R*)-2,3-*exo*-Bis-(benzyloxy)-5-*exo*-[(1*S*)-camphanoyloxy]-6-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane, 10; and (+)-(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2,3-*exo*-bis-(benzyloxy)-5-*exo*-[(1*S*)-camphanoyloxy]-6-*endo*-(phenylsulfonyl)-7-oxabicyclo-[2.2.1]heptane, 11. To a cold (0 °C) solution of 1.69 g (3.63 mmol) of **4** in 27 mL of CH_2Cl_2, 1 mL (7.25 mmol) of Et_3N, 1.57 g (7.25 mmol) of (1*S*)-(-)-camphanic acid chloride and a catalytic amount of DMAP were added. After stirring for 3 h at room temperature, HCl 0.5 N was added. The crude was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 972 mg of **10** and 960 mg of **11**, both as white solids (82% overall yield). Data of **10**: Mp: 74-75 °C. $[\alpha]_D$ -29.8 (c 1.0, $CHCl_3$). R_f= 0.32 (hexane:EtOAc, 1:1). ^1H NMR (300 MHz) δ 0.65 (s, 3 H, 1 Me), 0.89 (s, 3 H, 1 Me), 1.05 (s, 3 H, 1 Me), 1.55-1.65 (m, 1 H, 1 CH_2), 1.68-1.87 (m, 2 H, 2 CH_2), 2.00-2.10 (m, 1 H, 1 CH_2), 3.64 (t, 1 H, *J*= 4.5 Hz, H-6), 4.08 (d, 1 H, *J*= 5.9 Hz, H-3), 4.47 (s, 1 H, H-4), 4.59 (d, 1 H, *J*= 11.6 Hz, 1 C$\underline{H}_2$-Ph), 4.64-4.76 (m, 4 H, H-1, 3 C$\underline{H}_2$-Ph), 4.83 (d, 1 H, *J*= 5.5 Hz, H-2), 5.30 (d, 1 H, *J*= 3.7 Hz, H-5), 7.25-7.42 (m, 10 H, 10 $\underline{\text{ar}}$H-CH_2), 7.54 (t, 2 H, *J*= 7.8 Hz, 2 arH-SO_2), 7.67 (t, 1 H, *J*= 7.4 Hz, 1 arH-SO_2), 7.81 (d, 2 H, *J*= 7.1 Hz, 2 arH-SO_2). ^{13}C NMR (75 MHz) δ 9.6, 16.4, 16.6, 28.8, 30.4, 54.2, 54.7, 69.4, 69.5, 73.3, 73.3, 75.2, 77.4, 78.2, 86.6, 90.1, 127.9, 128.1, 128.3, 128.4, 129.7, 134.5, 137.4, 137.5, 139.2, 166.6, 177.4. IR ($CHCl_3$) 2980-2940, 1790, 1710, 1420, 1360, 1150, 1090, 1060 cm^{-1}. Anal. calcd for $C_{36}H_{38}O_9S$: C, 66.86; H, 5.92; found: C, 66.68; H, 5.90. Data of **11**: Mp: 165-166 °C. $[\alpha]_D$ +25.9 (c 1.0, $CHCl_3$). R_f= 0.29 (hexane:EtOAc, 1:1). ^1H NMR (300 MHz) δ 0.71 (s, 3 H, 1 Me), 0.78 (s, 3 H, 1 Me), 1.04 (s, 3 H, 1 Me), 1.55-1.65 (m, 1 H, 1 CH_2), 1.72-1.88 (m, 2 H, 2 CH_2), 2.16-2.28 (m, 1 H, 1 CH_2), 3.65 (dd, 1 H, *J*= 5.2, 3.7 Hz, H-6), 4.08 (d, 1 H, *J*= 5.9 Hz, H-3), 4.45 (s, 1 H, H-4), 4.59 (d, 1 H, *J*= 11.6 Hz, 1 C$\underline{H}_2$-Ph), 4.66-4.76 (m, 4 H, H-1, 3 C$\underline{H}_2$-Ph), 4.81 (d, 1 H, *J*= 6.5 Hz, H-2), 5.33 (d, 1 H, *J*= 3.5 Hz, H-5), 7.25-7.42 (m, 10 H, 10 $\underline{\text{ar}}$H-CH_2), 7.56 (t, 2 H, *J*= 7.8 Hz, 2 arH-SO_2), 7.67 (t, 1 H, *J*= 7.4 Hz, 1 arH-SO_2), 7.81 (d, 2 H, *J*= 7.1 Hz, 2 arH-SO_2). ^{13}C NMR (75 MHz) δ 9.6, 16.5, 28.7, 30.4, 54.2, 54.7, 69.3, 73.2, 74.9, 76.8, 78.0, 79.8, 86.6, 90.2, 127.9, 128.2, 128.4, 129.8, 134.5, 137.3, 139.0, 166.6, 177.5. IR ($CHCl_3$) 2980-2940, 1790, 1710, 1420, 1360, 1150, 1090, 1060 cm^{-1}.

(-)-(1*S*,4*S*,5*R*,6*S*)-5,6-*exo*-Bis-(benzyloxy)-2-(phenylsulfonyl)-7-oxabicyclo[2.2.1]-hept-2-ene, (-)-5. To a solution of 601 mg (0.93 mmol) of **10** in 9.5 mL of THF, 643 mg (4.65 mmol) of K_2CO_3 and 0.5 mL of H_2O were added. The reaction was stirred at 60 °C for 6 h. Next, the mixture was cooled and H_2O was added. The crude was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 360 mg of (-)-**5** as a white solid (86% yield). Data of (-)-**5**: Mp: 153-154 °C. $[\alpha]_D$ -95.2 (c 1.0, $CHCl_3$). R_f= 0.36 (hexane:EtOAc, 1:1). ^{1}H NMR (300 MHz) δ 3.78 (d, 1 H, *J*= 5.6 Hz, H-5 or H-6), 3.94 (d, 1 H, *J*= 5.6 Hz, H-5 or H-6), 4.55 (d, 1 H, *J*= 11.9 Hz, 1 C$\underline{H}_2$-Ph), 4.66 (d, 1 H, *J*= 11.6 Hz, 1 C$\underline{H}_2$-Ph), 4.73 (d, 1 H, *J*= 11.9 Hz, 1 C$\underline{H}_2$-Ph), 4.73 (d, 1 H, *J*= 11.6 Hz, 1 C$\underline{H}_2$-Ph), 4.80 (d, 1 H, *J*= 1.2 Hz, H-1), 5.00 (t, 1 H, *J*= 1.5 Hz, H-4), 6.98 (d, 1 H, *J*= 1.7 Hz, H-3), 7.28-7.44 (m, 10 H, 10 $\underline{ar}H$-CH_2), 7.54 (t, 2 H, *J*= 7.8 Hz, 2 arH-SO_2), 7.66 (t, 1 H, *J*= 7.4 Hz, 1 arH-SO_2), 7.82 (d, 2 H, *J*= 7.2 Hz, 2 arH-SO_2). ^{13}C NMR (75 MHz) δ 72.9, 73.2, 74.7, 75.6, 81.5, 84.0, 127.8, 127.9, 128.1, 128.3, 128.4, 129.5, 134.1, 137.4, 137.4, 138.5, 143.4, 149.7. IR (KBr) 1500, 1370, 1330, 1165, 1100, 1035, 925 cm^{-1}. Anal. calcd for $C_{26}H_{24}O_5S$: C, 69.62; H, 5.39; found: C, 69.36; H, 5.42.

(+)-(1*R*,4*R*,5*S*,6*R*)-5,6-*exo*-Bis-(benzyloxy)-2-(phenylsulfonyl)-7-oxabicyclo[2.2.1]-hept-2-ene, (+)-5. According to the procedure described for the preparation of (-)-**3**, from 800 mg (1.24 mmol) of **11**, 444 mg of (+)-**5** was obtained as a white solid (80% yield). Mp: 154-155 °C. $[\alpha]_D$ +95.4 (c 0.8, $CHCl_3$).

(+)-(1*R*,2*R*,3*S*,4*R*,5*S*,6*R*)-2,3-*exo*-Bis-(benzyloxy)-5-*exo*-(methoxy)-6-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane, 12. To a solution of 147 mg (0.33 mmol) of (+)-**5** in 4 mL of THF, a solution of 15 mg (0.66 mmol) of Na in 4 mL of MeOH was added. After stirring at room temperature for 4 h, H_2O was added. The crude was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 1:1) to give 139 mg of **12** as a white solid (88% yield). Data of **12**: Mp: 146-147 °C. $[\alpha]_D$ +45.8 (c 1.0, $CHCl_3$). R_f= 0.29 (hexane:EtOAc, 1:1). ^{1}H NMR (300 MHz) δ 3.10 (s, 3 H, Me), 3.44 (dd, 1 H, *J*= 5.7, 3.0 Hz, H-6), 3.85 (d, 1 H, *J*= 3.0 Hz, H-5), 3.91 (d, 1 H, *J*= 5.8 Hz, H-3), 4.51 (d, 1 H, *J*= 1.8 Hz, H-4), 4.54 (d, 1 H, *J*= 11.7 Hz, 1 C$\underline{H}_2$-Ph), 4.59 (dd, 1 H, *J*= 5.6, 2.0 Hz, H-1), 4.61 (d, 1 H, *J*= 11.4 Hz, 1 C$\underline{H}_2$-Ph), 4.67 (d, 1 H, *J*= 11.8 Hz, 1 C$\underline{H}_2$-Ph), 4.69 (d, 1 H, *J*= 5.9 Hz, H-2), 4.74 (d, 1 H, *J*= 11.6 Hz, 1 C$\underline{H}_2$-Ph), 7.29-7.38 (m, 10 H, 10 $\underline{ar}H$-CH_2), 7.55 (t, 2 H, *J*= 7.7 Hz, 2 arH-SO_2), 7.68 (t, 1 H, *J*= 7.6 Hz, 1 arH-SO_2), 7.79 (d, 2 H, *J*= 7.2 Hz, 2 arH-SO_2). ^{13}C NMR (75 MHz) δ 57.2, 70.8, 72.9, 73.0, 78.3, 79.4, 81.2, 85.4, 127.6, 127.8, 128.0, 128.3, 129.5, 134.2, 137.4, 137.5, 139.1. IR (KBr) 2950, 1500, 1450, 1365, 1310, 1155, 1100, 700, 670 cm^{-1}. Anal. calcd for $C_{27}H_{28}O_6S$: C, 67.48; H, 5.87; found: C, 67.25; H, 5.82.

1D-(1,2,3,4)-1,2-Di-*O*-benzyl-4-*O*-methyl-5-*C*-(phenylsulfonyl)-cyclohex-5-ene-1,2,3,4-tetraol, 13. To a cold (-78 °C) solution of 175 mg (0.36 mmol) of **12** in 0.5 mL of CH_2Cl_2 and 2 mL of PhMe, 0.68 mL (1.09 mmol) of *n*-BuLi (1.6 M solution in hexane) and 1.09 mL (1.09 mmol) of $TiCl_4$ (1 M solution in PhMe). After stirring for 30 min at -78 °C, the reaction was quenched with brine. The crude was extracted with EtOAc, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 1:1) to give 95 mg of **13** as a colorless oil (54% yield), and 40 mg of (+)-**5** (23% yield). Data of **13**: $[\alpha]_D$ +116.6 (c 0.7, $CHCl_3$). R_f= 0.25 (hexane:EtOAc, 1:1). ^{1}H NMR (300 MHz) δ 3.25 (d, 1 H, *J*= 9.7 Hz, OH), 3.35 (s, 3 H, Me), 3.74 (dd, 1 H, *J*= 3.4, 2.5 Hz, H-2), 4.06 (ddd, 1 H, *J*= 9.7, 5.4, 2.2 Hz, H-3), 4.17 (dt, 1 H, *J*= 5.4, 1.5 Hz, H-4), 4.21 (td, 1 H, *J*= 3.7, 1.5 Hz, H-1), 4.68 (d, 1 H, *J*= 12.3 Hz, 1 C$\underline{H}_2$-Ph), 4.74 (d, 1 H, *J*= 12.1 Hz, 1 C$\underline{H}_2$-Ph), 4.81 (d, 1 H, *J*= 12.1 Hz, 1

$C\underline{H}_2$-Ph), 4.83 (d, 1 H, *J*= 12.3 Hz, 1 $C\underline{H}_2$-Ph), 7.13 (d, 1 H, *J*= 3.7 Hz, H-6), 7.24-7.39 (m, 10 H, 10 arH-CH_2), 7.47 (t, 2 H, *J*= 7.5 Hz, 2 arH-SO_2), 7.58 (t, 1 H, *J*= 7.4 Hz, 1 arH-SO_2), 7.85 (d, 2 H, *J*= 7.2 Hz, 2 arH-SO_2). ^{13}C NMR (75 MHz) δ 59.9, 67.9, 72.7, 72.8, 74.3, 75.4, 75.6, 127.3, 127.4, 127.6, 127.9, 128.2, 128.4, 128.7, 132.9, 137.3, 138.4, 141.7, 141.7. IR ($CHCl_3$) 3500, 2920, 1505, 1365, 1310, 1155, 1095, 700 cm^{-1}. Anal. calcd for $C_{27}H_{28}O_6S$: C, 67.48; H, 5.87; found: C, 67.12; H, 5.75.

1D-(1,2,3,4)-1,2-Di-*O*-benzyl-4-*O*-methyl-5-*C*-(tri-*n*-butylstannyl)-cyclohex-5-ene-1,2,3,4-tetraol, 14. To a solution of 148 mg (0.31 mmol) of **13** in 1.5 mL of PhMe, 0.25 mL (0.92 mmol) of *n*-Bu_3SnH and a catalytic amount of AIBN were added. The reaction was stirred at 100 °C for 8 h. Next, the mixture was cooled and a 10% aqueous solution of KF was added. After stirring for 12 h, the crude was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 126 mg of **14** as a colorless oil (65% yield). Data of **14**: $[\alpha]_D$ +50.6 (c 1.4, $CHCl_3$). R_f= 0.29 (hexane:EtOAc, 5:1). ^1H NMR (300 MHz) δ 0.81 (t, 9 H, *J*= 7.1 Hz, 3 $\underline{Me}$-CH_2), 1.17-1.29 (m, 12 H, 12 CH_2), 1.35-1.45 (m, 6 H, 6 CH_2), 3.36 (dd, 1 H, *J*= 4.2, 1.8 Hz, H-2), 3.38 (s, 3 H, Me-O), 3.41-3.51 (m, 1 H, H-4), 3.66 (d, 1 H, *J*= 8.6 Hz, OH), 4.02 (t, 1 H, *J*= 4.4 Hz, H-1), 4.43 (dt, 1 H, *J*= 8.6, 1.9 Hz, H-3), 4.60 (d, 1 H, *J*= 12.4 Hz, 1 $C\underline{H}_2$-Ph), 4.66 (d, 1 H, *J*= 11.9 Hz, 1 $C\underline{H}_2$-Ph), 4.69 (d, 1 H, *J*= 12.3 Hz, 1 $C\underline{H}_2$-Ph), 4.81 (d, 1 H, *J*= 12.1 Hz, 1 $C\underline{H}_2$-Ph), 5.89 (dd, 1 H, *J*= 4.9, 2.5 Hz, H-6), 7.21-7.34 (m, 10 H, 10 $\underline{arH}$). ^{13}C NMR (62.5 MHz) δ 9.9, 13.7, 27.3, 29.1, 56.1, 66.6, 70.1, 72.1, 72.8, 75.9, 83.4, 127.6, 127.7, 127.7, 127.9, 128.3, 128.4, 132.5, 138.2, 138.3, 149.3. IR ($CHCl_3$) 3600-3400, 2960, 2930, 2880, 1410, 1120, 1090, 1040, 1030, 700 cm^{-1}. Anal. calcd for $C_{33}H_{50}O_4Sn$: C, 62.97; H, 8.01; found: C, 62.51; H, 8.10.

1D-(1,2,3,4)-1,2-Di-*O*-benzyl-4-*O*-methylcyclohex-5-ene-1,2,3,4-tetraol, 15. To a solution of 70 mg (0.11 mmol) of **14** in 1 mL of MeOH, 1 mL of a solution of NaOMe in MeOH 1 M was added. The reaction was stirred at 60 °C for 4 h. Next, the mixture was cooled and H_2O was added. The crude was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 1:1) to give 30 mg of **15** as a colorless oil (79% yield). Data of **15**: $[\alpha]_D$ +33.0 (c 1.0, $CHCl_3$). R_f= 0.20 (hexane:EtOAc, 1:1). ^1H NMR (250 MHz) δ 3.43 (s, 3 H, Me), 3.46 (dd, 1 H, *J*= 3.9, 1.9 Hz, H-2), 3.59-3.63 (m, 1 H, H-4), 3.81 (d, 1 H, *J*= 8.4 Hz, OH), 4.07 (t, 1 H, *J*= 4.1 Hz, H-1), 4.31-4.36 (m, 1 H, H-3), 4.62 (d, 1 H, *J*= 12.3 Hz, 1 $C\underline{H}_2$-Ph), 4.65 (d, 1 H, *J*= 11.9 Hz, 1 $C\underline{H}_2$-Ph), 4.70 (d, 1 H, *J*= 12.2 Hz, 1 $C\underline{H}_2$-Ph), 4.76 (d, 1 H, *J*= 12.0 Hz, 1 $C\underline{H}_2$-Ph), 5.77 (dt, 1 H, *J*= 10.3, 1.5 Hz, H-5), 5.88 (ddd, 1 H, *J*= 10.3, 4.5, 2.0 Hz, H-6), 7.20-7.34 (m, 10 H, 10 $\underline{arH}$). ^{13}C NMR (62.5 MHz) δ 56.7, 67.4, 70.7, 72.2, 72.6, 75.6, 78.1, 126.0, 127.6, 127.7, 127.8, 127.8, 128.4, 128.4, 129.2, 137.9, 138.1. IR ($CHCl_3$) 3600-3300, 2950, 1460, 1270, 1100, 680 cm^{-1}. Anal. calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11; found: C, 73.88; H, 7.07.

1D-1,2-Di-*O*-benzyl-4-*O*-methyl-3-*O*-(trifluoromethylsulfonyl)-*allo*-inositol, 16. To a cold (0 °C) solution of 51 mg (0.15 mmol) of **15** in 1.5 mL of CH_2Cl_2, 0.024 mL (0.30 mmol) of pyridin and 0.038 mL (0.225 mmol) of Tf_2O were added. After 30 min, the reaction was quenched with 5% aqueous solution of $NaHCO_3$. The crude was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 1.3 mL of acetone and 0.2 mL of H_2O. Then, 34 mg (0.30 mmol) of $NMe_3O{\bullet}H_2O$ and 0.188 mL (0.015 mmol) of OsO_4 (2.5% wt. solution in *t*-BuOH) were added. After stirring for 48 h, a few drops of 10% aqueous solution of $NaHSO_3$ were added. The crude was concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 1:1) to give 57 mg of **16** as a colorless oil (75% yield). Data of **16**: $[\alpha]_D$ -4.8 (c 1.0, $CHCl_3$). R_f= 0.18 (hexane:EtOAc, 1:2).

^{1}H NMR (250 MHz) δ 2.45 (br s, 2 H, 2 OH), 3.39 (dd, 1 H, *J*= 9.4, 2.8 Hz, H-4), 3.43 (s, 3 H, Me), 3.77 (t, 1 H, *J*= 2.7 Hz, H-2), 3.92 (t, 1 H, *J*= 2.9 Hz, H-1), 4.04 (dd, 1 H, *J*= 9.4, 2.9 Hz, H-5), 4.10 (t, 1 H, *J*= 3.2 Hz, H-6), 4.49 (d, 1 H, *J*= 11.9 Hz, 1 C$\underline{H}_2$-Ph), 4.55 (d, 1 H, *J*= 12.1 Hz, 1 C$\underline{H}_2$-Ph), 4.66 (d, 1 H, *J*= 11.9 Hz, 1 C$\underline{H}_2$-Ph), 4.77 (d, 1 H, *J*= 12.1 Hz, 1 C$\underline{H}_2$-Ph), 5.39 (br s, 1 H, H-3), 7.20-7.30 (m, 10 H, 10 arH). ^{13}C NMR (62.5 MHz) δ 58.3, 67.8, 69.9, 71.9, 73.5, 73.7, 76.3, 77.2, 77.7, 82.2, 127.5, 127.5, 127.6, 127.9, 128.2, 128.5, 137.2, 138.3. IR ($CHCl_3$) 3600-3200, 2930, 1450, 1410, 1140, 1100, 1030, 930, 700 cm^{-1}.

1D-4-*O*-Acetyl-5,6-di-*O*-benzyl-3-*O*-methyl-*chiro*-inositol, 17. To a solution of 57 mg (0.113 mmol) of **16** in 1.5 mL of benzene, 85 mg (0.28 mmol) of *n*-Bu_4NOAc was added. After stirring at room temperature for 1 h, the crude was concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 1:2) to give 27 mg of **17** as a colorless oil (58% yield). Data of **17**: $[\alpha]_D$ +16.8 (c 0.25, $CHCl_3$). R_f= 0.19 (hexane:EtOAc, 1:2). ^{1}H NMR (250 MHz) δ 2.00 (s, 3 H, Me-CO), 2.38-2.64 (m, 2 H, 2 OH), 3.37 (t, 1 H, *J*= 9.6 Hz, H-3), 3.41 (s, 3 H, Me-O), 3.73 (dd, 1 H, *J*= 10.0, 2.8 Hz, H-5), 3.87 (t, 1 H, *J*= 3.4 Hz, H-6), 3.88 (dd, 1 H, *J*= 9.6, 3.2 Hz, H-2), 4.02 (t, 1 H, *J*= 3.5 Hz, H-1), 4.43 (d, 1 H, *J*= 12.1 Hz, 1 C$\underline{H}_2$-Ph), 4.52 (d, 1 H, *J*= 12.0 Hz, 1 C$\underline{H}_2$-Ph), 4.53 (d, 1 H, *J*= 12.0 Hz, 1 C$\underline{H}_2$-Ph), 4.74 (d, 1 H, *J*= 12.1 Hz, 1 C$\underline{H}_2$-Ph), 5.42 (t, 1 H, *J*= 9.8 Hz, H-4), 7.20-7.29 (m, 10 H, 10 arH). ^{13}C NMR (62.5 MHz) δ 21.2, 59.6, 69.8, 70.6, 72.5, 73.0, 73.5, 74.9, 77.8, 81.3, 127.4, 127.6, 127.6, 127.7, 128.3, 128.3, 138.2, 138.2, 170.1. IR ($CHCl_3$) 3600-3300, 2950, 1750, 1430, 1110, 910 cm^{-1}. Anal. calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; found: C, 66.28; H, 6.76.

1D-5,6-Di-*O*-benzyl-3-*O*-methyl-*chiro*-inositol, 18. To a solution of 22 mg (0.053 mmol) of **17** in 0.8 mL of MeOH, 110 mg (0.79 mmol) of K_2CO_3 was added. After stirring at 60 °C for 2 h, the reaction was cooled and H_2O was added. The crude was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 1:2) to give 18 mg of **18** as a colorless oil (91% yield). Data of **18**: $[\alpha]_D$ +26.5 (c 0.3, $CHCl_3$). R_f= 0.14 (hexane:EtOAc, 1:5). ^{1}H NMR (300 MHz) δ 2.60-2.75 (m, 3 H, 3 OH), 3.27 (t, 1 H, *J*= 9.3 Hz, H-3), 3.58 (s, 3 H, Me), 3.62 (dd, 1 H, *J*= 9.7, 2.8 Hz, H-5), 3.78 (dd, 1 H, *J*= 9.4, 2.2 Hz, H-2), 3.89 (t, 1 H, *J*= 3.7 Hz, H-6), 3.93 (t, 1 H, *J*= 9.4 Hz, H-4), 4.08 (t, 1 H, *J*= 3.3 Hz, H-1), 4.45 (d, 1 H, *J*= 11.6 Hz, 1 C$\underline{H}_2$-Ph), 4.52 (d, 1 H, *J*= 11.9 Hz, 1 C$\underline{H}_2$-Ph), 4.55 (d, 1 H, *J*= 11.6 Hz, 1 C$\underline{H}_2$-Ph), 4.62 (d, 1 H, *J*= 11.9 Hz, 1 C$\underline{H}_2$-Ph), 7.19-7.29 (m, 10 H, 10 arH). ^{13}C NMR (62.5 MHz) δ 60.5, 69.5, 70.8, 72.3, 72.5, 73.1, 74.3, 79.9, 82.6, 127.6, 127.7, 127.9, 127.9, 128.4, 128.5, 137.9, 138.1. IR ($CHCl_3$) 3600-3300, 2950, 1460, 1050, 910 cm^{-1}. Anal. calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 6.00; found: C, 67.18; H, 5.90.

(+)-Pinitol, 9. To a solution of 28 mg (0.075 mmol) of **18** in 3 mL of MeOH, 80 mg of 10% Pd-C was added. The mixture was stirred in a Parr hydrogenator for 24 h. Next, the crude was filtered through a sort pad of silica gel with MeOH and concentrated under reduced pressure to give 10 mg of **9** as a colorless oil (69% yield). $[\alpha]_D$ +60.2 (c 0.5, H_2O), (lit:[9a] $[\alpha]_D$ +61.5 (c 0.27, H_2O)). Its spectral features were identical to those reported in the literature.[9a]

(±)-5-*exo*-(Methoxy)-6-*endo*-(phenylsulfonyl)-7,8-dioxatricyclo-[2.2.1.0^{2,3}]octane, 19. To a solution of 500 mg (1.80 mmol) of (±)-5-*exo*-(methoxy)-6-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-2-ene[14] in 19 mL of CH_2Cl_2, 1.18 g (3.76 mmol) of *m*-CPBA was added. After stirring at room temperature for 14 h, a 5% aqueous solution of $NaHCO_3$ was added. The crude was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 400 mg of **19** as a white solid (75% yield). Data of **19**: Mp: 163-164 °C.

R_f= 0.19 (hexane:EtOAc, 1:1). ^{1}H NMR (300 MHz) δ 3.12 (s, 3 H, Me), 3.44 (d, 1 H, *J*= 3.2 Hz, H-5), 3.58 (dd, 1 H, *J*= 4.5, 3.4 Hz, H-6), 3.97 (d, 1 H, *J*= 3.0 Hz, H-2 or H-3), 3.98 (d, 1 H, *J*= 3.0 Hz, H-2 or H-3), 4.53 (s, 1 H, H-4), 4.59 (d, 1 H, *J*= 4.7 Hz, H-1), 7.59 (t, 2 H, *J*= 7.2 Hz, 2 arH), 7.68 (t, 1 H, *J*= 7.1 Hz, 1 arH), 7.90 (d, 2 H, *J*= 7.2 Hz, 2 arH). ^{13}C NMR (75 MHz) δ 46.8, 48.8, 57.7, 74.8, 75.5, 79.0, 81.9, 127.6, 129.6, 134.3, 139.3. IR (KBr) 2950, 2840, 1450, 1320, 1160, 1120, 860 cm^{-1}. Anal. calcd for $C_{13}H_{14}O_5S$: C, 55.31; H, 5.00; found: C, 55.08; H, 5.03.

(±)-5-*exo*-(Methoxy)-6-(phenylsulfonyl)-7-oxatricyclo[2.2.1.0^{2,6}]heptan-3-*exo*-ol, 20. To a cold (-78 °C) solution of 50 mg (0.18 mmol) of **19** in 0.4 mL of CH_2Cl_2 and 1.4 mL of PhMe, 0.33 mL (0.53 mmol) of *n*-BuLi (1.6 M solution in hexane) was added. After stirring at -78 °C for 2 h, the reaction was quenched with brine. The crude was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane:EtOAc, 1:1) to give 35 mg of **20** as a white solid (70% yield). Data of **20**: Mp: 180-181 °C. R_f= 0.17 (hexane:EtOAc, 1:5). ^{1}H NMR (300 MHz) δ 2.68 (d, 1 H, *J*= 4.0 Hz, H-2), 3.19 (s, 3 H, Me), 3.66 (s, 1 H, H-5), 3.96 (br s, 1 H, H-3), 4.24 (s, 1 H, H-4), 4.73 (d, 1 H, *J*= 4.0 Hz, H-1), 7.51 (t, 2 H, *J*= 7.5 Hz, 2 arH), 7.62 (t, 1 H, *J*= 7.4 Hz, 1 arH), 7.88 (d, 2 H, *J*= 7.7 Hz, 2 arH). ^{13}C NMR (62.5 MHz) δ 29.1, 49.5, 57.7, 58.0, 69.2, 77.6, 78.9, 128.2, 129.0, 133.8, 140.1. IR (KBr) 3500-3300, 1530, 1440, 1100, 1050, 890 cm^{-1}. Anal. calcd for $C_{13}H_{14}O_5S$: C, 55.31; H, 5.00; found: C, 55.19; H, 4.79.

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