Chemistry of Natural Compounds, Bioorganic, and Biomolecular Chemistry

Synthesis of a C(9)—C(13) fragment of acutiphycin from levoglucosan

M. S. Miftakhov,[a]★ M. S. Ermolenko,[b]★ I. N. Gaisina,[a] O. M. Kuznetsov,[a] N. K. Selezneva,[a] Z. A. Yusupov,[a] and R. R. Muslukhov[a]

[a]*Institute of Orqanic Chemistry, Ufa Research Center of the Russian Academy of Sciences, 71 prosp. Oktyabrya, 450054 Ufa, Bashkortostan, Russian Federation. Fax: +7 (347 2) 35 6066. E-mail: bioreg@anrb.ru*
[b]*Institut de Chimie des Substances Naturelles du CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France. E-mail: Mikhail.Ermolenko@icsn.cnrs-gif.fr*

Alkylation of (1*R*,2*R*,5*R*)-2-benzenesulfonyl-6,8-dioxa-bicyclo[3.2.1]octan-3-one, which is accessible from levoglucosan, afforded (1*R*,2*R*,5*R*)-2-benzenesylfonyl-2,4,4-trimethyl-6,8-dioxabicyclo[3.2.1]octan-3-one. This was further converted into (1*S*,2*R*,3*S*,5*R*)-2,4,4-trimethyl-6,8-dioxabicyclo[3.2.1]octan-3-ol representing the C9—C13 fragment of acutiphycin molecule.

Key words: levoglucosan, hydride reduction, sulfonyl ketone, alkylation, acutiphycin.

A *gem*-dimethyl group in close vicinity of a chiral center is a fairly frequently encountered element of structures of natural products of the polyketide origin, for example, in epothilones,[1] acutiphycin,[2] *etc.* Stereochemical transformations near such a quaternized center are often characterized by low selectivity. Therefore, well-developed synthetic strategies can fail;[3] this stipulates the need for thorough investigation when planning a synthesis. Numerous methods for the construction of a polyketide chain have been developed; carbohydrate-based syntheses occupy a special place among them. The preparation of large polyketide fragments using stereoselective transformations of cyclic carbohydrate derivatives is well documented;[4] however, the introduction of a *gem*-dimethyl group for this series is limited to several studies dealing with the use of annelated cyclopropanes,[5—7] 1,4-addition to conjugated enones,[6] and stepwise alkylation of sugar keto-derivatives.[8—10]

In a study of approaches to the synthesis of acutiphycin, one aesthetically attractive strategy has led us, by means of retrosynthetic analysis, to polymethylated bicyclic derivative **1** as a precursor of the C(9)—C(13) fragment of the target molecule (Scheme 1). The purpose of the present study is to synthesize this compound using exhaustive methylation of sulfonyl ketone **2** as the key stage.

Results and Discussion

Sulfonyl ketone **2** was synthesized starting from the known phenylthio epoxide **3**, prepared from 2,4-di-*O*-tosyllevoglucosan **4** by the reaction with PhSH in the

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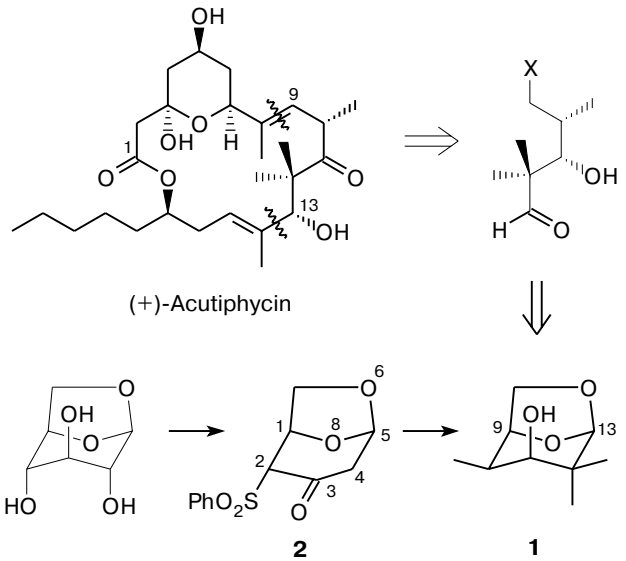
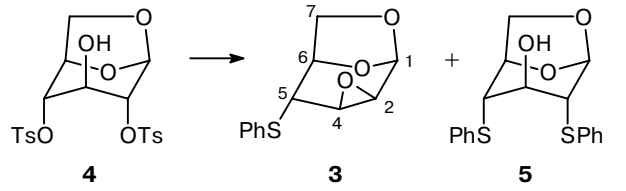
Scheme 1



presence of NaOH [11] (Scheme 2). Unfortunately, our attempts to reproduce the yield reported in the short communication failed. Due to the limited solubility of **4** in aqueous dioxane and to the reaction of rapidly formed reactive epoxide **3** with PhSNa, this reaction becomes non-selective; even with deficiency of the reagent, a substantial amount of bis(phenylthio) derivative **5** is always formed, together with the desired phenylthio epoxide **3**.

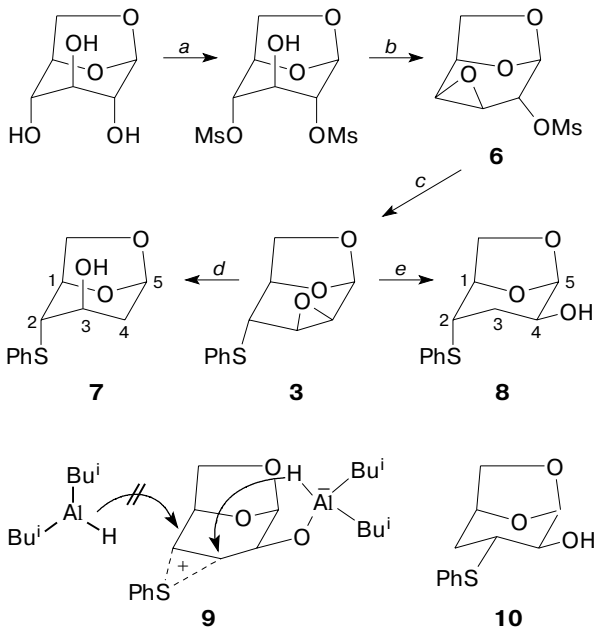
Scheme 2



After numerous experiments, a good yield of sulfide **3** was attained in the reaction of previously unknown mesyloxy epoxide **6** with nearly stoichiometric amounts of PhSH and NaOH in aqueous tetrahydrofuran. In this case, the yield of side bissulfide **5** did not exceed 3—5%. The reductive opening of the oxirane ring in sulfide **3** on treatment with $LiBHEt_3$ occurs with high yield and with the expected selectivity, giving rise to the C(3) alcohol **7** upon "*trans*-diaxial" opening (occurring *via* a chair-like transition state) (Scheme 3). Note that the reaction of epoxide **3** with Bu_2^iAlH affords selectively regioisomeric equatorial alcohol **8** in high yield. The change in the regio-direction is due to the fact that the latter reaction involves coordination of Bu_2^iAlH to the O atom of the oxirane ring, ring opening due to the anchimeric assistance of the neighboring phenylthio group, and subsequent intramolecular transfer of the hydride ion in the intermediate complex episulfonium aluminum hydride **9** to the spatially accessible carbenium center, C(3) (see Ref. 12). No product of the transformation of the episulfonium intermediate **9** induced by an external hydride, alcohol **10**, was detected. Other hydride reagents, including $LiAlH_4$, are of little use for reductive opening of the oxirane ring in **3** due to the low activity and/or selectivity.

The structures of regioisomeric alcohols **7** and **8** were established based on the data from the NMR spectra. In particular, the signals for the C(2) and C(5) are characteristic in the ^{13}C NMR spectra of **7** and **8**, respectively; they are located in a lower field due to the influence of the vicinal OH group (β-effect).[13]

Scheme 3

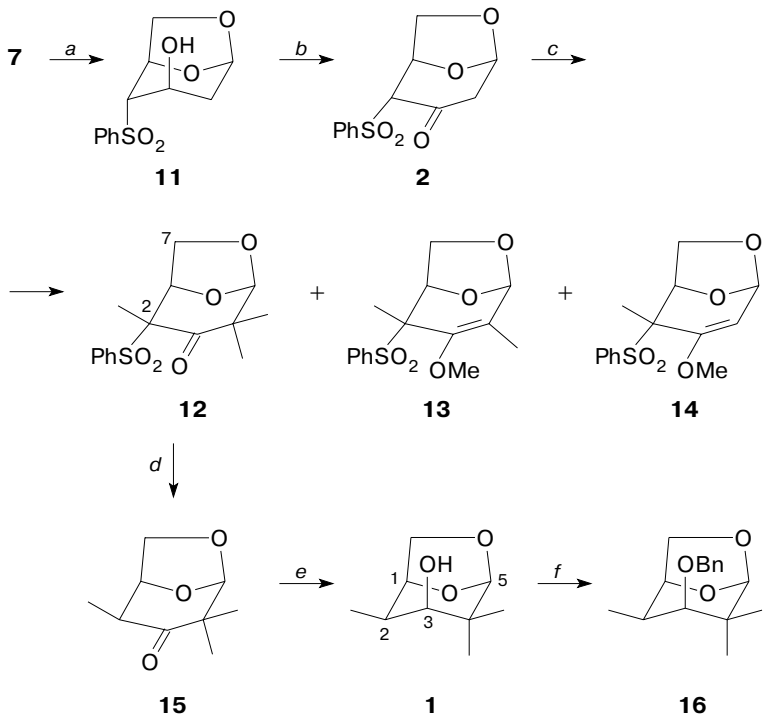


Reagents: *a*. MsCl/Py; *b*. MeONa/MeOH; *c*. 1 equiv. PhSH, NaOH/THF—H_2O; *d*. $LiBHEt_3$/THF; *e*. Bu_2^iAlH/THF.

The resulting phenylthio alcohol **7** was converted into hydroxy sulfone **11** by treatment with H_2O_2 in the presence of catalytic amounts of sodium tungstate[14] and then oxidized by pyridinium chlorochromate (PCC) to give sulfonyl ketone **2** (Scheme 4). Exhaustive methylation of sulfonyl ketone **2** with an excess of MeI in a THF—HMPA mixture (4 : 1) in the presence of NaH gave rise to trimethyl derivative **12** (yield ~65%), together with minor amounts of enol ethers **13** and **14** (ratio 2 : 1, overall yield 20%).

The attempts to increase the yield of sulfone **12** by changing the solvent were unsuccessful; however, it was found that the same result can be attained using DMF; thus, the use of expensive and carcinogenic HMPA can

Scheme 4



Reagents: *a*. H_2O_2, $Na_2WO_4 \cdot H_2O$/THF; *b*. PCC, MS 4A/CH_2Cl_2; *c*. MeI, NaH/THF—HMPA; *d*. Al—Hg/THF—H_2O or Na—Hg, Na_2HPO_4/MeOH; *e*. $LiBHEt_3$/THF; *f*. BnCl, NaH/DMF.

be avoided. It is noteworthy that no pronounced β-elimination of the anomeric alkoxyl is observed, which is surprising for such a strained system. Interesting and intriguing is the stereochemical outcome of the methylation of sulfonyl ketone **2** at the C(2) center, which is confirmed by the existence of a nuclear Overhauser effect between the methyl group at C(2) and the H-(7)$_{endo}$ proton in product **12**. Thorough monitoring of the reaction shows that it is this, more acidic C atom that undergoes primary alkylation (under controlled conditions, using 1 equiv. of $KN(SiMe_3)_2$ and MeI, the product of monoalkylation at C(2) can be obtained in high yield); therefore, the observed stereochemical outcome cannot be explained by any steric influence exerted by the C(4) center. It remains only to guess whether the *endo*-attack by the alkylating agent is due to stabilization of the transition state by the antiperiplanar C(1)—O(8) bond,[15] or the phenylsulfonyl group in the carbanion (which, apparently, exists in solution in the aggregated state) is rotated in such a way[16] that the approach of the reagent from the *exo*-side is impossible. A model study with a carba-analog of bicyclic sulfonyl ketone **2** would apparently provide the answer to this question.

Treatment of the methylation product **12** with sodium amalgam in methanol or with aluminum amalgam in aqueous THF[17] affords trimethyl ketone **15** in high yield and in a diastereomerically pure form. It should be noted that stereochemistry of this step is due to the kinetic protonation of the intermediate carbanion because, as has been shown by treatment of ketone **15** with sodium methoxide in methanol, at thermodynamic equilibrium, trimethyl ketone contains 14% axial isomer. The reduction of ketone **15** on treatment with $LiBHEt_3$ affords selectively axial alcohol **1**, which is then converted into benzyl ether **16**.

The structure of the last-mentioned product, in particular, the configuration of the C(2) center, is confirmed by the presence of a doublet for H(3) at δ 3.13 with $J_{2,3}$ = 4.5 Hz in its ^{1}H NMR spectrum.[18]

Thus, owing to the peculiar combination of activation and control, we were able to introduce three methyl groups in the molecule in one step and thus to prepare with a high selectivity a chiral unit (**16**), which can be used in the synthesis of acutiphycin.

Experimental

UV and IR spectra were recorded on Specord-400 and Specord M-80 spectrophotometers. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C); Me_4Si was used as the internal standard. Optical rotation was measured on a Perkin—Elmer 241 MC instrument at 22±2 °C. Mass spectra were recorded on an MKh-1320 instrument. The following commercial solvents and reagents were used: MsCl, PhSH, and Super-hydride®

($LiBHEt_3$) (Aldrich); THF was distilled under Ar over benzophenone-Na. The reactions were carried out under Ar. Preparative chromatography was performed using silica gel L (40—100 μm) (Chemapol, Czech Republic) and light petroleum with b.p. 40—70 °C. TLC analysis was carried out using Silufol plates (Czech Republic).

(1*R*,2*S*,3*S*,4*R*,5*R*)-2,4-Dimethylsulfonyloxy-6,8-dioxabicyclo[3.2.1]octan-3-ol. Mesyl chloride (5.90 mL, 76.24 mmol) was added at 5 °C to a solution of levoglucosan (5.03 g, 31.03 mmol) in 25 mL of Py. The mixture was stirred for 2 h at this temperature and for 24 h at 20 °C. Then the reaction mixture was diluted with 100 mL of water and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with water and brine, dried with $MgSO_4$, and concentrated. The residue was crystallized from an acetone—light petroleum mixture (1 : 1) to give 7.02 g (72%) of dimethanesulfonate, R_f 0.30 (EtOAc—heptane, 2 : 1). M.p. 111—112 °C, $[\alpha]_D$ −36.3 (*c* 1.0, Me_2CO). Found (%): C, 30.60; H, 4.42; S, 20.37. $C_8H_{14}O_9S_2$. Calculated (%): C, 30.18; H, 4.43; S, 20.15. IR, ν/cm^{-1}: 1200, 1320 (SO_2), 3520 (C—OH). ^{1}H NMR (DMF-d_6), δ: 3.32, 3.36 (both s, each 3 H, SO_2Me); 3.74 (dd, 1 H, $H(7)_{exo}$, J = 5.5, 7.5 Hz); 4.04 (s, 1 H, H(4)); 4.20 (d, 1 H, $H(7)_{endo}$, J = 7.5 Hz); 4.37 (s, 1 H, H(3)); 4.65 (s, 1 H, H(2)); 4.85 (d, 1 H, H(1), J = 5.5 Hz); 5.57 (s, 1 H, H(5)). ^{13}C NMR (DMF-d_6), δ: 38.01 (Me); 65.84 (C(7)); 70.08 (C(1)); 75.20 (C(4)); 78.43 (C(3)); 79.69 (C(2)); 100.47 (C(5)).

(1*R*,2*R*,4*S*,5*R*,6*R*)-5-Methylsulfonyloxy-3,7,9-trioxatricyclo[4.2.1.0^{2,4}]nonane (6). A 5 *M* solution of MeONa (15 mL) in MeOH was added to a solution of the dimethanesulfonate (7.10 g, 22.30 mmol) (see above) in 50 mL of CH_2Cl_2. The reaction mixture was stirred for 22 h at 20 °C, diluted with 300 mL of CH_2Cl_2, washed with water and brine, dried with $MgSO_4$, and concentrated. Crystallization from an acetone—light petroleum mixture (3 : 7) gave 2.97 g (59.8%) of mesyloxy epoxide **6**. The mother liquor was concentrated, the residue was chromatographed on a column with SiO_2 using a hexane—EtOAc (7 : 3) mixture as the eluent to give 1.28 g (25.8%) of mesyloxy epoxide **6**. The total yield was 4.25 g (85.6%). R_f 0.46 (EtOAc—benzene, 7 : 3). M.p. 148—150 °C, $[\alpha]_D$ −48.7 (*c* 1.1, $CHCl_3$). Found (%): C, 37.65; H, 4.27; S, 14.47. $C_7H_{10}O_6S$. Calculated (%): C, 37.83; H, 4.54; S, 14.43. IR, ν/cm^{-1}: 1190, 1370 (SO_2). ^{1}H NMR ($CDCl_3$), δ: 3.15 (s, 3 H, SO_2Me); 3.34 (dd, 1 H, H(4), J = 1.6, 4.2 Hz); 3.57 (dd, 1 H, $H(8)_{exo}$, J = 4.8, 6.7 Hz); 3.69 (dd, 1 H, H(1), J = 4.4, 4.8 Hz); 4.03 (d, 1 H, $H(8)_{endo}$, J = 5.5 Hz); 4.67 (br.s, 1 H, H(5)); 4.88 (t, 1 H, H(1), J = 4.8 Hz); 5.39 (s, 1 H, H(6)). ^{13}C NMR ($CDCl_3$), δ: 38.50 (Me); 47.75 (C(4)); 52.89 (C(2)); 64.88 (C(8)); 70.86 (C(5)); 71.75 (C(1)); 98.21 (C(6)).

Reaction of mesyloxy epoxide 6 with PhSNa. PhSH (0.97 g, 8.82 mmol) and NaOH (0.38 g, 9.62 mmol) were added to a solution of mesyloxy epoxide **6** (1.78 g, 8.02 mmol) in 20 mL of a THF—H_2O (9 : 1) mixture. The reaction mixture was stirred for 3 h at 55 °C, diluted with 200 mL of EtOAc, and washed successively with 1 *M* HCl, a saturated solution of $NaHCO_3$, and brine. The organic layer was dried with Na_2SO_4 and concentrated, and the residue was chromatographed on SiO_2 using a light petroleum—EtOAc mixture (9 : 1, then 7 : 3) as the eluent to give 1.66 g (87.8%) of phenylthio epoxide **3** and 0.1 g of bis(phenylthio) derivative **5**.

(1*R*,2*S*,4*R*,5*S*,6*R*)-5-Phenylthio-3,8,9-trioxatricyclo[4.2.1.0^{2,4}]nonane (3). R_f 0.63 (benzene—EtOAc, 7 : 3). M.p. 112.5—114 °C, $[\alpha]_D$ +8.4 (*c* 1.0, $CHCl_3$). Found (%): C, 60.84; H, 5.13; S, 13.37. $C_{12}H_{12}O_3S$. Calculated (%): C, 61.00; H, 5.12; S, 13.57. IR, ν/cm^{-1}: 1256 (epoxide), 1460, 1580 (SPh). ^{1}H NMR (acetone-d_6), δ: 3.13 (dd, 1 H, H(4), J = 0.9, 3.8 Hz); 3.44 (dd, 1 H, H(2), J = 3.1, 3.8 Hz); 3.65 (dd, 1 H, $H(7)_{exo}$, J = 6.8, 7.2 Hz); 3.70 (dd, 1 H, H(5), J = 0.9, 1.1 Hz); 3.73 (dd, 1 H, $H(7)_{endo}$, J = 1.8, 7.2 Hz); 4.53 (dd, 1 H, H(6), J = 1.8, 6.8 Hz); 5.68 (d, 1 H, H(1), J = 3.1 Hz); 7.25—7.55 (m, 5 H, SPh). ^{13}C NMR ($CDCl_3$), δ: 47.40 (C(2)); 49.31 (C(4)); 54.11 (C(5)); 68.49 (C(7)); 71.92 (C(6)); 98.18 (C(1)); 127.87, 129.37, 131.95, 133.30 (SPh).

(1*R*,2*S*,3*S*,4*R*,5*R*)-2,4-Bis(phenylthio)-6,8-dioxabicyclo[3.2.1]octan-3-ol (5). R_f 0.45 (benzene—EtOAc, 7 : 3). M.p. 106—108 °C, $[\alpha]_D$ −51.4 (*c* 1.0, $CHCl_3$) (*cf.* Ref. 11: m.p. 93—94 °C, $[\alpha]_D^{20}$ −51 (*c* 1.6, $CHCl_3$)). Found (%): C, 62.48; H, 5.15; S, 14.06. $C_{18}H_{18}O_3S_2$. Calculated (%): C, 62.40; H, 5.24; S, 18.51. IR, ν/cm^{-1}: 3490 (C—OH). ^{1}H NMR ($CDCl_3$), δ: 3.20 (d, 1 H, OH, J = 6.3 Hz); 3.31 (s, 1 H, H(4)), 3.36 (s, 1 H, H(2)); 3.77 (dd, 1 H, $H(7)_{exo}$, J = 5.0, 7.4 Hz); 4.15 (br.s, 1 H, H(3)); 4.18 (d, 1 H, $H(7)_{endo}$, J = 7.4 Hz); 4.69 (d, 1 H, H(1)); 5.71 (s, 1 H, H(5)); 7.20—7.55 (m, 10 H, 2 SPh). ^{13}C NMR ($CDCl_3$), δ: 52.44 (C(4)); 52.99 (C(2)); 68.38 (C(7)); 71.47 (C(1)); 75.50 (C(3)); 102.53 (C(5)); 127.26, 127.54, 129.22, 129.27, 131.04, 131.87, 134.47, 134.84 (2 SPh).

(1*R*,2*S*,3*R*,5*R*)-2-Phenylthio-6,8-dioxabicyclo[3.2.1]octan-3-ol (7). A 1.0 *M* solution of $LiBHEt_3$ (25 mL) was added at 20 °C to a solution of epoxide **3** (2.53 g, 10.71 mmol) in 20 mL of THF. The reaction mixture was stirred for 6 h, $NaHCO_3$ (6.30 g, 75.00 mmol) was added, and 30% H_2O_2 (7.60 mL, 75.00 mmol) was carefully added dropwise. The mixture was stirred for 1 h at 40—50 °C. The reaction mixture was diluted with 200 mL of EtOAc and washed successively with a saturated solution of $Na_2S_2O_3$, H_2O, and brine, dried with $MgSO_4$, and concentrated. The residue was chromatographed on SiO_2, using a benzene—EtOAc mixture (9 : 1, then 7 : 3) as the eluent to give 2.17 g (85%) of alcohol **9**. R_f 0.30 (benzene—EtOAc, 7 : 3). M.p. 125.5—127 °C, $[\alpha]_D$ −39.6 (*c* 1.0, $CHCl_3$). Found (%): C, 60.20; H, 5.94; S, 13.52. $C_{12}H_{14}O_3S$. Calculated (%): C, 60.48; H, 5.92; S, 13.46. IR, ν/cm^{-1}: 1450, 1580, 1630 (SPh), 3450 (C—OH). ^{1}H NMR ($CDCl_3$), δ: 1.86 (dd, 1 H, $H(4)_{ax}$, J = 0.8, 15.0 Hz); 2.33 (ddd, 1 H, $H(4)_{eq}$, J = 1.2, 4.9, 15.0 Hz); 3.25 (br.s, 1 H, OH); 3.43 (s, 1 H, H(2)); 3.77 (dd, 1 H, $H(7)_{exo}$, J = 5.0, 7.4 Hz); 3.98 (m, 1 H, H(3)); 4.36 (d, 1 H, $H(7)_{endo}$, J = 7.4 Hz); 4.69 (d, 1 H, H(1), J = 5.0 Hz); 5.67 (d, 1 H, H(5), J = 1.2 Hz); 7.20—7.50 (m, 5 H, SPh). ^{13}C NMR ($CDCl_3$), δ: 35.33 (C(4)); 52.40 (C(2)); 67.79 (C(7)); 68.26 (C(3)); 75.28 (C(1)); 101.45 (C(5)); 127.00, 129.23, 130.81, 134.63 (SPh).

(1*R*,2*S*,4*S*,5*R*)-2-Phenylthio-6,8-dioxabicyclo[3.2.1]octan-4-ol (8). A 4.0 *M* solution of Bu_2^iAlH (6.30 mL) in THF was slowly added dropwise to a solution of epoxide **3** (2.00 g, 8.47 mmol) in 15 mL of THF cooled to −20 °C. The reaction mixture was stirred for 1 h, and 2 mL of a saturated solution of NH_4Cl and 100 mL of EtOAc were added. The organic layer was separated, washed successively with 1 *M* HCl, a saturated solution of $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated. The residue was chromatographed on SiO_2, using a light petroleum—EtOAc mixture (9 : 1, then 7 : 3) as the eluent to give 1.65 g (82%) of alcohol **8**. R_f 0.20 (light petroleum—EtOAc, 1 : 1). M.p. 107—109 °C, $[\alpha]_D$ −70.8 (*c* 0.85, $CHCl_3$). Found (%): C, 60.61; H, 6.02; S, 13.50. $C_{12}H_{14}O_3S$. Calculated (%): C, 60.48; H, 5.92; S, 13.46. IR, ν/cm^{-1}: 1376, 1464, 1580 (SPh), 3424 (C—OH). ^{1}H NMR ($CDCl_3$), δ: 1.77 (m, 1 H, $H(3)_{ax}$); 2.12 (dd, 1 H, $H(3)_{eq}$, J = 5.7, 14.0 Hz); 2.33 (d, 1 H, OH, J = 9.3 Hz); 3.25 (d, 1 H, H(2), J = 5.4 Hz); 3.70—3.80 (m, 3 H, H(4), $H(7)_{endo}$, $H(7)_{exo}$); 4.46 (d, 1 H, H(1), J = 4.5 Hz); 5.32 (s, 1 H, H(5)); 7.05—7.45 (m, 5 H, SPh). ^{13}C NMR ($CDCl_3$), δ: 31.34 (C(3)); 47.57 (C(2)); 66.46 (C(7)); 68.52 (C(4)); 74.99 (C(1)); 103.26 (C(5)); 127.56, 129.20, 132.18, 134.34 (SPh).

(1*R*,2*S*,3*R*,5*R*)-2-Phenylsulfonyl-6,8-dioxabicyclo[3.2.1]octan-3-ol (11). $Na_2WO_4 \cdot 2\ H_2O$ (1.72 g, 5.93 mmol) was added at 0 °C to a mixture of alcohol **7** (14.00 g, 59.32 mmol) and 30% H_2O_2 (24.00 mL, 237 mmol) in 70 mL of THF and the temperature was brought to ~20 °C. The reaction mixture was stirred for 2 h at 55 °C, diluted with 300 mL of EtOAc, washed successively with a saturated solution of $Na_2S_2O_3$ and brine, dried with Na_2SO_4, and concentrated. The residue was chromatographed on SiO_2 using a light petroleum—EtOAc mixture (5 : 1) as the eluent to give 14.26 g (90%) of product **11**. R_f 0.20 (benzene—EtOAc, 7 : 3). M.p. 125.5—127 °C, $[\alpha]_D$ −77.1 (*c* 1.0, $CHCl_3$). Found (%): C, 53.59; H, 5.25; S, 11.69. $C_{12}H_{14}O_5S$. Calculated (%): C, 53.32; H, 5.22; S, 11.86. IR, ν/cm^{-1}: 1276, 1376, 1456 (SO_2Ph), 3448 (C—OH). ^{1}H NMR ($CDCl_3$), δ: 1.73 (d, 1 H, $H(4)_{ax}$, J = 14.7 Hz); 1.82 (ddd, 1 H, $H(4)_{eq}$, J = 2.1, 5.5, 14.7 Hz); 3.43 (s, 1 H, H(2)); 3.73 (dd, 1 H, $H(7)_{exo}$, J = 5.7, 7.2 Hz); 4.27 (d, 1 H, $H(7)_{endo}$, J = 7.2 Hz); 4.33 (d, 1 H, H(3), J = 5.5 Hz); 4.40 (br.s, 1 H, OH); 5.09 (d, 1 H, H(1), J = 5.7 Hz); 5.45 (d, 1 H, H(5), J = 2.1 Hz); 7.55—8.00 (m, 5 H, SO_2Ph). ^{13}C NMR ($CDCl_3$), δ: 36.44 (C(4)); 61.21 (C(2)); 66.72 (C(7)); 68.65 (C(3)); 69.69 (C(1)); 100.22 (C(5)); 127.99, 129.25, 133.87, 138.50 (SO_2Ph).

(1*R*,2*R*,5*R*)-2-Phenylsulfonyl-6,8-dioxabicyclo[3.2.1]octan-3-one (2). PCC (11.70 g, 54.29 mmol) was added to a mixture of hydroxy sulfone **11** (5.87 g, 21.72 mmol) and 15 g of molecular sieves (4 Å) in 50 mL of CH_2Cl_2, and the mixture was stirred for 1 h at 20 °C. The reaction mixture was filtered through a layer of SiO_2 (~5 cm), this was washed with an Et_2O—CH_2Cl_2 mixture (1 : 1, 300 mL), the filtrate was concentrated, and the residue was chromatographed on SiO_2 using a light petroleum—EtOAc system (7 : 3) as the eluent to give 4.90 g (84%) of sulfonyl ketone **2**. R_f 0.37 (benzene—EtOAc, 7 : 3). M.p. 110—111 °C, $[\alpha]_D$ −202.6 (*c* 1.0, $CHCl_3$). Found (%): C, 53.61; H, 4.41; S, 11.64. $C_{12}H_{12}O_5S$. Calculated (%): C, 53.72; H, 4.51; S, 11.95. IR, ν/cm^{-1}: 1160, 1340, 1470 (SO_2Ph), 1720 (C=O). ^{1}H NMR ($CDCl_3$), δ: 2.63 (d, 1 H, $H(4)_{ax}$, J = 16.6 Hz); 2.77 (dd, 1 H, $H(4)_{eq}$, J = 2.1, 16.6 Hz); 3.79 (d, 1 H, $H(7)_{endo}$, J = 8.1 Hz); 3.84 (s, 1 H, H(2)); 3.93 (dd, 1 H, $H(7)_{exo}$, J = 5.6, 8.1 Hz); 5.53 (d, 1 H, H(1), J = 5.6 Hz); 5.83 (d, 1 H, H(5), J = 2.1 Hz); 7.55—7.72 (m, 5 H, SO_2Ph). ^{13}C NMR ($CDCl_3$), δ: 48.32 (C(4)); 68.28 (C(7)); 72.01 (C(2)); 76.74 (C(1)); 101.21 (C(5)); 128.36, 129.38, 134.64, 138.10 (SO_2Ph); 195.81 (C=O).

Alkylation of sulfonyl ketone 2. 60% NaH (4.16 g, 104.09 mmol) and MeI (14.77 mL, 104.09 mmol) were added at 20 °C to a solution of sulfonyl ketone **2** (3.99 g, 12.85 mmol) in 40 mL of a THF—HMPA mixture (4 : 1), and the mixture was stirred for 6 h. A saturated aqueous solution of NH_4Cl (5 mL) was added, the reaction mixture was diluted with 200 mL of EtOAc, and the organic phase was washed successively with a saturated solution of $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated. The residue was chromatographed on SiO_2 using a light petroleum—EtOAc mixture (9 : 1) as the eluent to give 2.57 g (64.6%) of trimethyl derivative **12**, 0.47 g (11.8%) of enol ether **13**, and 0.23 g (6%) of enol ether **14**.

(1*R*,2*R*,5*R*)-2,4,4-Trimethyl-2-phenylsulfonyl-6,8-dioxabicyclo[3.2.1]octan-3-one (12). R_f 0.54 (light petroleum—EtOAc, 1 : 1). M.p. 133—135 °C, $[\alpha]_D$ −51.7 (*c* 1.1, $CHCl_3$). Found (%): C, 58.15; H, 5.87; S, 10.45. $C_{15}H_{18}O_5S$. Calculated (%): C, 58.05; H, 5.85; S, 10.33. UV (EtOH), λ_{max}/nm (ε): 221 (12400), 260 (1500), 267 (2100), 274 (1800). IR, ν/cm^{-1}: 1165, 1320, 1475 (SO_2Ph), 1720 (C=O). ^{1}H NMR ($CDCl_3$), δ: 1.09, 1.16, 1.51 (all s, each 3 H, 2 C(4)Me, C(2)Me); 3.99 (dd, 1 H, $H(7)_{exo}$, J = 5.0, 8.8 Hz); 4.83 (d, 1 H, H(1), J = 5.0 Hz); 5.02 (d, 1 H, $H(7)_{endo}$, J = 8.8 Hz); 5.19 (s, 1 H, H(5)); 7.52—8.07 (m, 5 H, SO_2Ph). ^{13}C NMR ($CDCl_3$), δ: 20.05, 24.03, 25.16 (3 Me); 52.32 (C(4)); 67.19 (C(7)); 74.24 (C(2)); 77.64 (C(1)); 106.96 (C(5)); 128.57, 131.05, 134.17, 137.18 (SO_2Ph); 209.10 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 310 $[M]^+$ (1), 295 $[M - Me]^+$ (1), 281 $[M - Et]^+$ (1), 169 $[M - PhSO_2]^+$ (100), 141 $[PhSO_2]^+$ (7), 123 $[M - PhSO_2 - Et - OH]^+$ (89), 95 (32), 77 (53), 70 (23).

(1*R*,2*R*,5*R*)-3-Methoxy-2,4-dimethyl-2-phenylsulfonyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (13). R_f 0.42 (light petroleum—EtOAc, 1 : 1). M.p. 158—160 °C, $[\alpha]_D$ −23.3 (*c* 1.0, $CHCl_3$). Found (%): C, 58.09; H, 5.90; S, 10.20. $C_{15}H_{18}O_5S$. Calculated (%): C, 58.05; H, 5.85; S, 10.33. UV (EtOH), λ_{max}/nm (ε): 204 (28200), 217 (29900), 259 (2700), 266 (2900), 273 (2400). IR, ν/cm^{-1}: 1292, 1376, 1456 (SO_2Ph), 1668 (C=CH), 2856 (OMe). ^{1}H NMR ($CDCl_3$), δ: 1.43, 1.81 (both s, each 3 H, C(4)Me, C(2)Me); 3.61 (s, 3 H, OMe); 4.03 (dd, 1 H, $H(7)_{exo}$, J = 6.2, 8.7 Hz); 4.62 (dd, 1 H, H(1), J = 1.8, 6.2 Hz); 4.88 (dd, 1 H, $H(7)_{endo}$, J = 1.8, 8.7 Hz); 5.38 (s, 1 H, H(5)); 7.55—8.10 (m, 5 H, SO_2Ph). ^{13}C NMR ($CDCl_3$), δ: 13.34 (C(4)Me); 21.29 (C(2)Me); 61.43 (OMe); 64.94 (C(7)); 72.57 (C(2)); 77.76 (C(1)); 101.76 (C(5)); 119.20 (C(4)); 127.77, 130.37, 133.75, 138.69 (SO_2Ph); 148.68 (C(3)).

(1*R*,2*R*,5*R*)-3-Methoxy-2-methyl-2-phenylsulfonyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (14). R_f 0.37 (light petroleum—EtOAc, 1 : 1). M.p. 39—41 °C. $[\alpha]_D$ −92.0 (*c* 1.15, $CHCl_3$). Found (%): C, 56.86; H, 5.42; S, 10.90. $C_{14}H_{16}O_5S$. Calculated (%): C, 56.74; H, 5.44; S, 10.82. UV (EtOH), λ_{max}/nm (ε): 203 (16100), 208 (16600), 259 (1300), 266 (1400), 273 (1300). IR, ν/cm^{-1}: 1296,1376, 1460 (SO_2Ph), 1648 (C=CH), 2856 (OMe). ^{1}H NMR ($CDCl_3$), δ: 1.44 (s, 3 H, C(2)Me); 3.51 (s, 3 H, OMe); 4.02 (dd, 1 H, $H(7)_{exo}$, J = 6.0, 8.8 Hz); 4.65 (dd, 1 H, H(1), J = 1.8, 6.2 Hz); 4.93 (dd, 1 H, $H(7)_{endo}$, J = 1.8, 8.8 Hz); 4.96 (d, 1 H, H(4), J = 4.1 Hz); 5.66 (d, 1 H, H(5), J = 4.1 Hz); 7.40—7.90 (m, 5 H, SO_2Ph). ^{13}C NMR ($CDCl_3$), δ: 21.41 (Me); 54.86 (OMe); 64.79 (C(7)); 71.43 (C(2)); 77.59 (C(1)); 97.86 (C(5)); 97.98 (C(4)); 128.54, 130.60, 133.94, 138.85 (SO_2Ph), 155.14 (C(3)).

(1*S*,2*S*,5*R*)-2,4,4-Trimethyl-6,8-dioxabicyclo[3.2.1]octan-3-one (15). ***A.*** Aluminum amalgam (0.36 g, 13.5 mmol), prepared according to a previously published procedure,[17] was added to a solution of sulfonyl ketone **12** (0.42 g, 1.35 mmol) in 10 mL of a THF—H_2O mixture (9 : 1). The mixture was stirred for 12 h at 55 °C. The reaction mixture was filtered through a layer of *Celite*®, this was washed with EtOAc, the organic phase was washed successively with 1 *M* HCl, a saturated solution of $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated. The residue was chromatographed on SiO_2 using a petroleum ether—EtOAc mixture (9 : 1) as the eluent to give 0.17 g (74%) of ketone **15**.

B. Finely dispersed Na_2HPO_4 (1.66 g, 11.7 mmol) and 6% Na amalgam (8.8 g) was added with vigorous stirring to a solution of sulfonyl ketone **12** (0.91 g, 2.93 mmol) in 30 mL of MeOH cooled to 0 °C. After completion of the reaction (~1 h, TLC monitoring), the methanolic layer was decanted, the residue was washed with (2×100) mL of EtOAc, the combined organic phase was washed successively with water, 1 *M* HCl, a saturated solution of $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated. The residue was chromatographed on SiO_2 using a light petroleum—EtOAc mixture (9 : 1) to give 0.46 g (92%) of ketone **15**. R_f 0.52 (light petroleum—EtOAc, 7 : 3). M.p. 57—59 °C, $[\alpha]_D$ +27.6 (*c* 1.0, $CHCl_3$). Found (%): C, 63.55; H, 8.18. $C_9H_{14}O_3$. Calculated (%): C, 63.51; H, 8.29. IR, ν/cm^{-1}: 1708 (C=O). ^{1}H NMR ($CDCl_3$), δ: 1.01 (d, 3 H, C(2)Me, J = 7.0 Hz); 1.07, 1.17 (both s, each 3 H, 2 C(4)Me);

3.00 (m, 1 H, H(2), J = 1.3, 4.8, 7.0 Hz); 3.70 (dddd, 1 H, $H(7)_{exo}$, J = 0.9, 1.3, 4.5, 7.7 Hz); 3.75 (dd, 1 H, $H(7)_{endo}$, J = 1.0, 7.7 Hz); 4.61 (td, 1 H, H(1), J = 1.0, 4.6 Hz); 5.18 (s, 1 H, H(5)). ^{13}C NMR ($CDCl_3$), δ: 9.54, 18.95, 23.57 (3 Me); 45.32 (C(2)); 51.82 (C(4)); 64.96 (C(7)); 78.17 (C(1)); 108.27 (C(5)); 211.78 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 170 $[M]^+$ (2), 155 $[M - Me]^+$ (1), 124 $[M - Et - OH]^+$ (59), 109 $[M - Et - Me - H_2O]^+$ (91), 81 (11), 70 (100), 55 (23).

(1*S*,2*R*,3*S*,5*R*)-2,4,4-Trimethyl-6,8-dioxabicyclo[3.2.1]octan-3-ol (1). A 1.0 *M* solution of $LiBHEt_3$ (2.20 mL, 0.22 mmol) was slowly added dropwise at 20 °C to a solution of ketone **15** (0.17 g, 0.10 mmol) in 4 mL of THF. The reaction mixture was stirred for 6 h, $NaHCO_3$ (0.06 g, 0.72 mmol) was added, 30% H_2O_2 (0.08 mL, 0.80 mmol) was carefully added dropwise, and the mixture was stirred for 1 h at 40—50 °C. The reaction mixture was diluted with 50 mL of EtOAc, washed successively with a saturated solution of $Na_2S_2O_3$, H_2O, and brine, dried with $MgSO_4$, and evaporated. The residue was chromatographed on SiO_2 using a benzene—EtOAc mixture (9 : 1, then 7 : 3) as the eluent to give 0.14 g (82%) of alcohol **1**. R_f 0.20 (light petroleum—EtOAc, 7 : 3). M.p. 70—72 °C, $[\alpha]_D$ −18.6 (c 0.9, $CHCl_3$). Found (%): C, 62.60; H, 9.54. $C_9H_{16}O_3$. Calculated (%): C, 62.77; H, 9.36. IR, ν/cm^{-1}: 3408 (C—OH). ^{1}H NMR ($CDCl_3$), δ: 0.99 (s, 3 H, C(4)Me); 1.01 (d, 3 H, C(2)Me, J = 7.3 Hz)); 1.07 (s, 3 H, C(4)Me); 2.15 (s, 1 H, OH); 2.32 (m, 1 H, H(2)); 3.29 (d, 1 H, H(3), J = 3.8 Hz); 3.55 (ddd, 1 H, $H(7)_{exo}$, J = 0.8, 5.4, 7.3 Hz); 4.14 (d, 1 H, $H(7)_{endo}$, J = 7.3 Hz); 4.24 (dd, 1 H, H(1), J = 3.8, 5.4 Hz); 5.17 (d, 1 H, H(5), J = 1.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 12.79, 21.28, 24.11 (3 Me); 33.73 (C(2)); 39.74 (C(4)); 64.21 (C(7)); 76.10 (C(5)); 77.32 (C(1)); 107.34 (C(5)).

(1*S*,2*R*,3*R*,5*R*)-3-Benzyloxy-2,4,4-trimethyl-6,8-dioxabicyclo[3.2.1]octane (16). 60% NaH (0.13 g, 3.24 mmol) and BnCl (0.19 mL, 1.65 mmol) were added to a solution of alcohol **1** (0.14 g, 0.81 mmol) in 3 mL of DMF. The resulting suspension was stirred for 12 h at 20 °C. Water (20 mL) was added, and the product was extracted with EtOAc (3×25 mL). The combined extracts were washed successively with 1 *M* HCl, a saturated solution of $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated. The residue was chromatographed on SiO_2 using a light petroleum—EtOAc mixture (9 : 1) as the eluent to give 0.19 g (89.6%) of ether **16**. R_f 0.56 (light petroleum—EtOAc, 7 : 3). $[\alpha]_D$ −21.2 (c 0.6, $CHCl_3$). Found (%): C, 73.43; H, 8.50. $C_{16}H_{22}O_3$. Calculated (%): C, 73.25; H, 8.45. IR, ν/cm^{-1}: 1528, 3016, 3048 and 3064 (Ph). ^{1}H NMR ($CDCl_3$), δ: 0.93 (s, 3 H, C(4)Me); 1.00 (d, 3 H, C(2)Me, J = 7.3 Hz)); 1.07 (s, 3 H, C(4)Me); 2.40 (m, 1 H, H(2)); 3.13 (d, 1 H, H(3), J = 4.5 Hz); 3.55 (ddd, 1 H, $H(7)_{exo}$), J = 1.0, 5.4, 6.6 Hz); 4.14 (dddd, H(1), J = 1.0, 1.0, 4.2, 5.3 Hz); 4.29 (dd, 1 H, $H(7)_{endo}$, J = 1.0, 6.6 Hz); 4.48 (d, 1 H, CH_2Ph, J_{AB} = 11.4 Hz); 4.56 (d, 1 H, CH_2Ph, J_{AB} = 11.4 Hz); 4.89 (d, 1 H, H(5), J = 1.0 Hz); 7.20—7.40 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 12.71, 21.34, 24.77 (3 Me); 33.43 (C(2)); 40.66 (C(4)); 64.00 (C(7)); 75.95 (CH_2Ph); 76.81 (C(1)); 83.91 (C(3)); 106.82(C(5)); 127.0, 127.2, 128.1, 138.76 (Ph).

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