Non-selectivity in the reaction of levoglucosenone with the sulfinyl allyl carbanion

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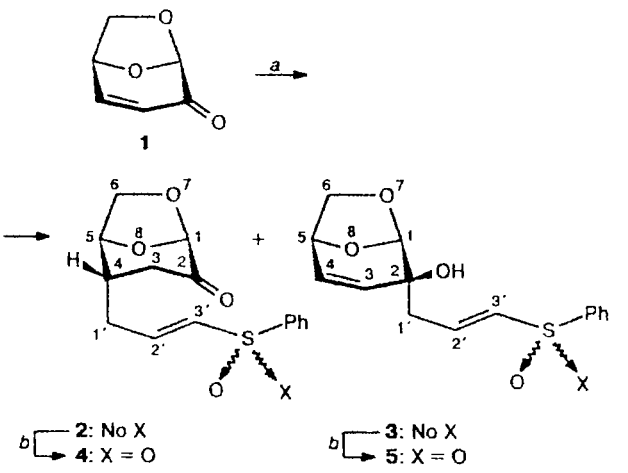
Condensation of levoglucosenone with the carbanion of *rac*-allyl phenyl sulfoxide, in contrast with reactions of this anion with the majority of other unsaturated ketones, proceeds without regio- or enantioselectivity to give a (1.0—1.8) : 1 mixture of products of both 1,2- and 1,4-γ-addition of the allylic residue. Each product is a (1.2—1.6) : 1 mixture of epimers at the asymmetric sulfur atom.

Key words: levoglucosenone; *rac*-allyl phenyl sulfoxide, carbanion; 1,2-γ-addition, 1,4-γ-addition; regioselectivity; enantioselectivity.

In recent years, levoglucosenone (**1**) has been successfully used as an easily available chiral starting material exhibiting high stereoselectivity in the majority of the reactions studied.[1,2] It is also known that condensation of sulfinyl allyl carbanions with cyclic conjugated unsaturated ketones is a remarkable reaction because of the high regio-, chemo-, stereo-, and enantioselectivity of the 1,4-γ-adduct formation.[3—5] Due to this feature, this reaction has been used repeatedly in the stereodirected total synthesis of natural products.[6—8] Therefore, special interest is aroused by the lack of regio- or enantioselectivity in the addition of this carbanion to levoglucosenone, which we discovered during the total synthesis of eicosanoids.

Condensation of a twofold excess of *rac*-$H_2C{=}CHCH_2SOPh$ with levoglucosenone **1** at −78 °C under standard conditions of generation of the sulfinyl allyl carbanion (Scheme 1) yielded both the normal 1,4-γ-adduct (**2**) and the corresponding 1,2-γ-adduct (**3**), which (unexpectedly) predominated (Table 1). Moreover, each of the adducts was a chromatographically unseparable mixture of epimers (below referred to as S-epimers) at the asymmetric sulfur atom (ratio of (1.2—1.6) : 1.0), as indicated by doubling of many signals in the ^1H NMR spectra. The addition of HMPA increased the proportion of 1,4-γ-addition but did not improve the enantioselectivity of the reaction.

Scheme 1



Reagents and conditions: *a*. *rac*-$H_2C{=}CHCH_2SOPh$, LDA, HMPA—THF, −78 °C; *b*. MCPBA, CH_2Cl_2, 0 °C.

The fact that adducts **2** and **3** are formed as mixtures of epimers at the sulfur atom was proved by oxidation into the corresponding sulfones (**4** and **5**), which were

Table 1. Results of condensation of the allyl phenyl sulfoxide anion with levoglucosenone (**1**)

1 : PhSOAll : HMPA ratio	Yield of 1,4- and 1,2-γ-adduct mixture 2 + 3 (%)	Ratio of regioisomeric adducts 2 : 3	Ratio of S-epimers in 2	Ratio of S-epimers in 3
1 : 2 : 0	76	1.0 : 1.8	1.5 : 1.0	1.6 : 1.0
1 : 1 : 0	77	1.0 : 1.3	1.2 : 1.0	1.3 : 1.0
1 : 1 : 1 or 1 : 1 : 2	65	1.0 : 1.0	1.2 : 1.0	1.4 : 1.0

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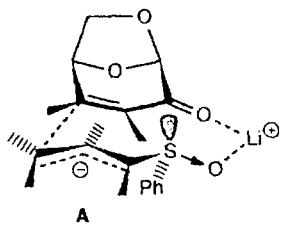
individual compounds as shown by all the available criteria. The *exo*-configuration of the allyl sulfoxide residue in adduct **2** was derived from the typical[9,10] values of the vicinal spin-spin coupling constants of the H(4) proton, *viz.*, the small constants (J < 1 Hz) with the $H(3)_{eq}$ and H(5) protons and the large constant (J = 7.8 Hz) with the $H(3)_{ax}$ proton, in the ^{1}H NMR spectra of compounds **2** and **4**; for adduct **3**, this configuration was assumed by analogy and based on the well known[1,2] *exo*-selectivity of addition to levoglucosenone.

A nontrivial property of the S-epimers of adducts **2** and **3** is the large difference between the chemical shifts of the protons remote from the asymmetric sulfur atom; this difference reaches 0.06—0.09 ppm for $H(3)_{eq}$ and H(5) in adduct **2** and 0.04—0.05 ppm for H(1) and H(3) in **3**, while the spin-spin coupling constants in the pairs of epimers are identical (see Experimental). Conformation analysis (by the PM3 semiempirical method) showed that both epimers of the adduct **2** are characterized by "folded" conformations of the side chains (the H—C(3)—C(1′)—C(2′) dihedral angle is +/−176°), whose inner energy differs slightly (by 0.30—0.58 kcal mol^{-1}) from that of "stretched" conformations (the same dihedral angle is −53 to −55°). Similar "folded" conformations were found for adduct **3**. In these "folded" conformations, the benzene ring is located close to the $H(3)_{eq}$ and H(5) or H(1) and H(3) protons (the distances are 3.8—4.8 Å), whose chemical shifts in the ^{1}H NMR spectra of the S-epimers differ to the greatest extent. This difference is apparently due to the different orientations of the phenyl ring in the epimers.

According to published data, the highest 1,4-γ-selectivity and enantioselectivity are observed in the addition of allyl sulfoxide anions to cyclopentenones. For unsubstituted cyclopent-2-enone these selectivities are greater than 20 : 1.[8,11,12] However, when the ring in the unsaturated ketone expands to a six- and then to a seven-membered ring, both types of selectivity sharply decrease down to a ratio of the 1,4- to 1,2-γ-addition products of 1.0 : 2.3 and to an enantioselectivity of 1 : 3 in the case of cyclohept-2-enone.[11]

The selectivity of the addition of the sulfinyl allyl carbanions of unsaturated ketones has been explained by postulating a 10-centered transition state,[13] which is responsible for the 1,4-γ-selectivity and predicts the configuration of the asymmetric sulfur atom in the adducts. For levoglucosenone, this transition state can be depicted as **A**. Conformational analysis did not show substantial energetic or other distinctions between this transition state (which should lead to the 1,4-γ-(S_S)-adduct) and the corresponding transition state in the case of cyclopent-2-enone, for which all the types of selectivity are observed.[3] In our opinion, the lack of 1,4-selectivity or stereoselectivity at the sulfur atom in the case of levoglucosenone is due to the high reactivity of this unsaturated ketone, which was repeatedly demonstrated (and which is equivalent to performing of the reaction at a high temperature); this levels off the energy difference between the highly organized transition state (**A**) and other transition states.



A

Irrespective of the reasons for the absence of selectivity, this possibility should be taken into account when planning syntheses based on levoglucosenone **1** and related compounds.

Experimental

IR spectra were recorded on a Specord-751R instrument. NMR spectra were measured using Tesla BS-587A, Bruker AC-200, WM-250 (80, 200, and 250 MHz for ^{1}H), and AM-300 (75.4 MHz for ^{13}C) spectrometers using Me_4Si as the internal standard. Mass spectra (EI, 22.5 eV) were run on an LKB-2091 GC/MS instrument with direct inlet into the ion source at a given temperature of the sampler or in the course of chromatograpy. Optical rotations were measured on a Polamat A polarimeter. TLC analysis was carried out on Silufol UV-254 plates.

Bu^nLi, MCPBA, Pr^i_2NH, THF and europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate) (Eu(fod)$_3$) produced by Aldrich were used. THF was distilled from sodium benzophenone ketyl. Allyl phenyl *rac*-sulfoxide was synthesized by a previously described procedure.[3] Levoglucosenone (**1**), b.p. 57—58 °C (0.1 Torr), n_D^{25} 1.5080, $[\alpha]_D^{25}$ −527° (*c* 1.002, $CHCl_3$), was prepared in 6.4% yield by pyrolysis of laboratory filter paper according to a known procedure.[14]

(1*R*,4*S*,5*R*,R_S+S_S)-4-[3-(Phenylsulfinyl)prop-2(*E*)-enyl]-7,8-dioxabicyclo[3.2.1]octan-2-one (2) and (1*R*,2*S*,5*R*,R_S+S_S)-2-hydroxy-2-[3-(phenylsulfinyl)prop-2(*E*)-enyl]-7,8-dioxabicyclo[3.2.1]oct-3-ene (3).* A 1.6 *M* solution of Bu^nLi (1.3 mL, 2.1 mmol) in hexane was added at −78 °C in an argon atmosphere to a solution of Pr^i_2NH (202 mg, 2 mmol) in 1.5 mL of anhydrous THF. The mixture was stirred for 20 min, and *rac*-PhSOAll (332 mg, 2 mmol) was added. The resulting solution was kept for 25 min at the same temperature for the formation of the carbanion (a yellow solution), and a solution of levoglucosenone **1** (126 mg, 1 mmol) in 1.5 mL of THF was added. After 5 min, the reaction mixture was poured into a mixture of 40 mL of a phosphate buffer (pH 7) and 40 mL of EtOAc. The layers were separated, the aqueous layer was additionally extracted with EtOAc, and the extract was dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to dryness to give 446 mg of a yellow oil, which was subjected to high-performance flash chromatography (silica gel 5—40 μm, EtOAc—$CHCl_3$, 2 : 3) to give sulfoxides **2** and **3**, each as an unseparable mixture of S-epimers.[15]

Similar procedures were employed to carry out the condensation at a different component ratio and in the presence of HMPA, which was added to the reaction mixture immediately before levoglucosenone. The results are summarized in Table 1.

* For all the compounds synthesized, the "carbohydrate" numbering of carbon atoms, according to which the anomeric carbon is denoted by C(1), is retained (see Scheme 1).

Sulfoxide 2, a viscous colorless oil, R_f 0.08 (EtOAc—$CHCl_3$, 2 : 3), $[\alpha]_D^{25}$ −113° (*c* 1.396, $CHCl_3$). IR (thin film), ν/cm^{-1}: 1045 (S=O); 1740 (C=O). ^1H NMR (250 MHz, C_6D_6), δ for S-epimers **a** and **b**: 1.23 (**a**+**b**) (q, 1 H, H(4)); 1.63—2.10 (**a**+**b**) (m, 2 H, 2 H(1′)); 1.72 (**b**), 1.81 (**a**) (both d, 1 H, $H(3)_{eq}$); 2.20 (**a**+**b**) (dd, 1 H, $H(3)_{ax}$); 3.28 (**a**+**b**) (d, 1 H, $H(6)_{endo}$); 3.40 (**b**), 3.43 (**a**) (both t, 1 H, $H(6)_{exo}$); 3.70 (**a**), 3.76 (**b**) (both d, 1 H, H(5)); 5.13 (**a**), 5.15 (**b**) (both s, 1 H, H(1)); 5.90 (**a**+**b**, doubles after the addition of $Eu(fod)_3$) (d, 1 H, H(3′)); 6.30 (**a**), 6.33 (**b**) (both dt, 1 H, H(2′)); 7.00—7.20, 7.53 (**a**+**b**) (both m, 5 H, Ph); $^2J_{H(3)_{eq},H(3)_{ax}}$ = 15.6 Hz, $^3J_{H(3)_{eq},H(4)} \approx 0$ Hz, $^3J_{H(3)_{ax},H(4)}$ = 7.8 Hz, $^3J_{H(4),2H(1')}$ = 7.8 Hz, $^3J_{H(4),H(5)} \approx 0$ Hz, $^3J_{H(5),H(6)_{exo}}$ = 7.8 Hz, $^3J_{H(5),H(6)_{endo}} \approx 0$ Hz, $^2J_{H(6)_{exo},H(6)_{endo}}$ = 7.8 Hz, $^3J_{2H(1'),H(2')}$ = 7.8 Hz, $^3J_{H(2'),H(3')}$ = 15.6 Hz (the signals of S-epimers **a** and **b** were assigned by comparison of the spectra of mixtures with various ratios of the epimers, the spectra recorded at 80, 200 and 250 MHz, and those recorded in $CDCl_3$). MS (GLC), *m/z* (I_{rel} (%)): 93 (100), 149 $[PhS{=}CHCH{=}CH_2]^+$ (53), 170 (40), 247 (14), 264 $[M - CO]^+$ (57), 276 $[M - O]^+$ (6), 292 $[M]^+$ (5).

Sulfoxide 3, a viscous colorless oil, R_f 0.05 (EtOAc—$CHCl_3$, 2 : 3), $[\alpha]_D^{25}$ −91° (*c* 1.024, $CHCl_3$). IR (CCl_4), ν/cm^{-1}: 1045 (S=O); 3400, 3567 (OH). ^1H NMR (250 MHz, $CDCl_3$), δ for S-epimers **a** and **b**: 2.53 (**a**+**b**) (br.d, 2 H, 2 H(1′)); 2.72 (**a**+**b**) (br.s, 1 H, OH); 3.71 (**a**+**b**) (dd, 1 H, $H(6)_{exo}$); 3.78 (**a**+**b**) (d, 1 H, $H(6)_{endo}$); 4.66 (**a**+**b**) (t, 1 H, H(5)); 5.18 (**b**), 5.22 (**a**) (both d, 1 H, H(1)); 5.54 (**a**), 5.59 (**b**) (both dd, 1 H, H(3)); 6.03 (**b**), 6.04 (**a**) (both dd, 1 H, H(4)); 6.34 (**a**+**b**) (dt, 1 H, H(3′)); 6.70 (**a**), 6.71 (**b**) (both dt, 1 H, H(2′)); 7.46—7.67 (**a**+**b**) (m, 5 H, Ph); $^4J_{H(1),H(3)}$ = 2.2 Hz, $^3J_{H(3),H(4)}$ = 9.8 Hz, $^3J_{H(4),H(5)}$ = 4.1 Hz, $^3J_{H(5),H(6)_{exo}}$ = 4.1 Hz, $^3J_{H(5),H(6)_{endo}} \approx 0$ Hz, $^2J_{H(6)_{exo},H(6)_{endo}}$ = 6.4 Hz, $^3J_{2H(1'),H(2')}$ = 7.2 Hz, $^4J_{2H(1'),H(3')}$ = 0.8 Hz, $^3J_{H(2'),H(3')}$ = 15.2 Hz (the signals of S-epimers **a** and **b** were assigned by comparison of the spectra of mixtures with various ratios of the epimers and the spectra recorded at 80 and 200 MHz). ^{13}C NMR ($CDCl_3$), δ: 39.4, 39.5 (both t, S-epimers); 69.7 (t); 71.5 (d); 72.4 (s); 103.7 (d); 124.5 (d); 129.3 (d); 130.9 (d); 131.3 (d); 135.1 (d); 138.0 (d); 144.0 (s). MS (GLC), *m/z* (I_{rel} (%)): 81 (24), 149 $[PhS{=}CHCH{=}CH_2]^+$ (100), 166 $[PhS(OH){=}CHCH{=}CH_2]^+$ (20), 229 (26), 247 (20), 275 $[M - OH]^+$ (2), 292 $[M]^+$ (6).

(1*R*,4*S*,5*R*)-4-[3-(Phenylsulfonyl)prop-2(*E*)-enyl]-7,8-dioxabicyclo[3.2.1]octan-2-one (4). A solution of sulfoxide **2** (50 mg, 0.17 mmol) and 85% MCPBA (87 mg, 0.43 mmol) in 5 mL of CH_2Cl_2 was stirred for 1 h at −10 to 0 °C and then poured into a 10% aqueous solution of Na_2SO_3. The product was extracted with EtOAc, the extract was washed with a 1 *M* solution of NaOH and water to neutral reaction, dried ($MgSO_4$), and concentrated to dryness to give 52 mg (99%) of sulfone **4** as a viscous colorless oil, R_f 0.32 (EtOAc—$CHCl_3$, 2 : 3), $[\alpha]_D^{25}$ −108° (*c* 1.021, $CHCl_3$). IR (CCl_4), ν/cm^{-1}: 1150 (SO_2); 1740 (C=O). ^1H NMR (250 MHz, C_6D_6), δ: 1.23 (q, 1 H, H(4)); 1.63—1.75 (m, 1 H, $H(1')_A$); 1.70 (d, 1 H, $H(3)_{eq}$); 1.93 (dt, 1 H, $H(1')_B$); 2.22 (dd, 1 H, $H(3)_{ax}$); 3.30 (**a**+**b**) (d, 1 H, $H(6)_{endo}$); 3.42 (t, 1 H, $H(6)_{exo}$); 3.73 (d, 1 H, H(5)); 5.12 (s, 1 H, H(1)); 6.05 (d, 1 H, H(3′)); 6.75 (dt, 1 H, H(2′)); 7.03—7.11, 7.87—7.93 (both m, 5 H, Ph); $^2J_{H(3)_{eq},H(3)_{ax}}$ = 16.6 Hz, $^3J_{H(3)_{eq},H(4)} \approx 0$ Hz, $^3J_{H(3)_{ax},H(4)}$ = 7.8 Hz, $^3J_{H(4),2H(1')}$ = 7.8 Hz, $^3J_{H(4),H(5)} \approx 0$ Hz, $^3J_{H(5),H(6)_{exo}}$ = 7.1 Hz, $^3J_{H(5),H(6)_{endo}} \approx 0$ Hz, $^2J_{H(3)_{exo},H(6)_{endo}}$ = 7.8 Hz, $^2J_{H(1')_A,H(1')_B}$ = 15.5 Hz, $^3J_{H(1')_A,H(2')} = {}^3J_{H(1')_B,H(2')}$ = 7.8 Hz, $^3J_{H(2'),H(3')}$ = 15.6 Hz. MS (GLC), *m/z* (I_{rel} (%)): 93 (100), 125 (20), 139 (23), 235 (10), 280 $[M - CO]^+$ (14), 293 $[M - O + H]^+$ (0.4), 309 $[M + H]^+$ (0.5).

(1*R*,2*S*,5*R*)-2-Hydroxy-2-[3-(phenylsulfonyl)prop-2(*E*)-enyl]-7,8-dioxabicyclo[3.2.1]oct-3-ene (5) was prepared from sulfoxide **3** by a procedure similar to that described above, yield 99%, colorless crystals, m.p. 84—85 °C (from a $CHCl_3$—hexane mixture, 7 : 3), R_f 0.23 (EtOAc—$CHCl_3$, 2 : 3), $[\alpha]_D^{25}$ −64° (*c* 1.194, $CHCl_3$). IR (KBr), ν/cm^{-1}: 1150 (SO_2); 3470 (OH). ^1H NMR (250 MHz, $CDCl_3$), δ: 2.53 (d, 2 H, 2 H(1′)); 3.71 (dd, 1 H, $H(6)_{exo}$); 3.78 (m, 2 H, $H(6)_{endo}$); 4.65 (t, 1 H, H(5)); 5.16 (d, 1 H, H(1)); 5.54 (dd, 1 H, H(3)); 6.05 (dd, 1 H, H(4)); 6.40 (d, 1 H, H(3′)); 7.06 (dt, 1 H, H(2′)); 7.50—7.65 (m, 3 H, *m*- and *p*-ArH); 7.90 (d, 2 H, *o*-ArH); $^4J_{H(1),H(3)}$ = 2.2 Hz, $^3J_{H(3),H(4)}$ = 9.8 Hz, $^3J_{H(4),H(5)}$ = 4.0 Hz, $^3J_{H(5),H(6)_{exo}}$ = 4.0 Hz, $^3J_{H(5),H(6)_{endo}} \approx 0$ Hz, $^2J_{H(6)_{exo},H(6)_{endo}}$ = 7.2 Hz, $^3J_{2H(1'),H(2')}$ = 8.0 Hz, $^4J_{2H(1'),H(3')} \approx 0$ Hz, $^3J_{H(2'),H(3')}$ = 15.2 Hz, $^3J_{o\text{-}ArH,m\text{-}ArH}$ = 8.0 Hz. MS (110 °C), *m/z* (I_{rel} (%)): 81 (100), 192 $[PhSO_2CH{=}CHCH_3]^+$ (9), 245 (1), 262 (4), 278 (1), 291 $[M - OH]^+$ (0.1), $[M]^+$ is missing.

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