Articles

Asymmetric Synthesis of (2R,5S,7R)-2,7-Dimethyl-1,6-dioxaspiro[4.4]nonane

Guy Solladié,*,† Nathalie Huser,† Jean Fischer,‡ and A. Decian‡

Laboratoire de Stéréochimie (EHICS) Associé au CNRS and Laboratoire de Cristallochimie et de Chimie Structurale (Institut Lebel) Associé au CNRS, Université Louis Pasteur, F-67008-Strasbourg, France

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A short enantioselective synthesis of (2R,5S,7R)-2,7-dimethyl-1,6-dioxaspiro[4.4]nonane is described via an enantioselective synthesis of (2S,8S,SR)-2,8-dihydroxy-5-(1,3-dioxolanyl)-1,9-(p-tolylsulfinyl)-nonane by stereoselective reduction of the corresponding diketo disulfoxide. The formation of the spiro carbon was stereocontrolled during a cyclization carried out under equilibrating conditions in the presence of $ZnBr_2$.

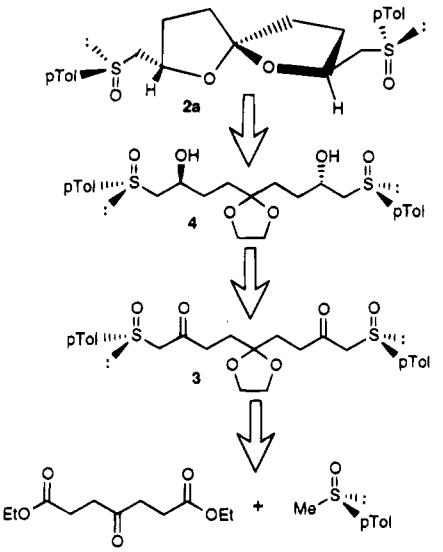
Spiroketals occur as substructures in many biologically active natural products from many sources including insects, microbes, plants, fungi, and marine organisms.[1] The increasing pharmacological importance of compounds containing spiroketal assemblies has led to the development of many new synthetic approaches[1,2] to these systems.

Spiroketals are often obtained by intramolecular cyclization of the corresponding dihydroxyketo precursors. In substituted 1,7-dioxaspiro[5.5]undecane, the formation of the spiro carbon is totally stereocontrolled by the anomeric effect occurring in six-membered rings.[3] Several stereoselective syntheses showing this stereoelectronic control have been already reported.[4]

In 1,6-dioxaspiro[4.4]nonane derivatives, such as **1**, the formation of the spiro carbon during the cyclization of the dihydroxyketo precursor, leading to five-membered spiro rings, cannot be stereocontrolled by any kind of anomeric effect. For this reason, all the syntheses reported in the literature[5] resulted in a mixture of diastereomers due to the formation of a *R,S*-spiro carbon. In a few cases, the diastereomeric mixture was partially resolved by chromatographic techniques.[6]

We report in this paper on the enantioselective synthesis of (2R,5S,7R)-2,7-dimethyl-1,6-dioxaspiro[4.4]-nonane (**1**). This molecule was already prepared as a mixture of all the possible racemic stereomers[7] or from optically active precursors as a mixture of two diastereomers resulting from a *R,S*-spiro center.[8]

Scheme 1



Our approach was to prepare the sulfinyl spiroketal **2a**, precursor of the target molecule **1**, from the protected keto dihydroxydisulfoxide **4**. Compound **4** was readily obtained by stereoselective reduction of the corresponding diketo disulfoxide **3** which was synthesized from the ketal of ethyl 4-oxopimelate and (+)-(*R*)-methyl *p*-tolylsulfoxide (Scheme 1).

Ethyl 4-oxopimelate was first transformed into the corresponding ketal with ethylene glycol in refluxing benzene in the presence of a catalytic amount of PPTS. Reaction with 4 equiv of the anion of (+)-(*R*)-methyl *p*-tolylsulfoxide gave the diketo disulfoxide **3** isolated in 57% yield by crystallization. DIBAL reduction of the diketo disulfoxide **3** should give, according to our previous results,[4d] the (*R,R*)-dihydroxy disulfoxide **4a** (Scheme 2).

The highly stereoselective reduction (de > 95%) of β-keto sulfoxides was described in our previous studies.[9]

† Laboratoire de Stéréochimie.
‡ Laboratoire de Cristallochimie.
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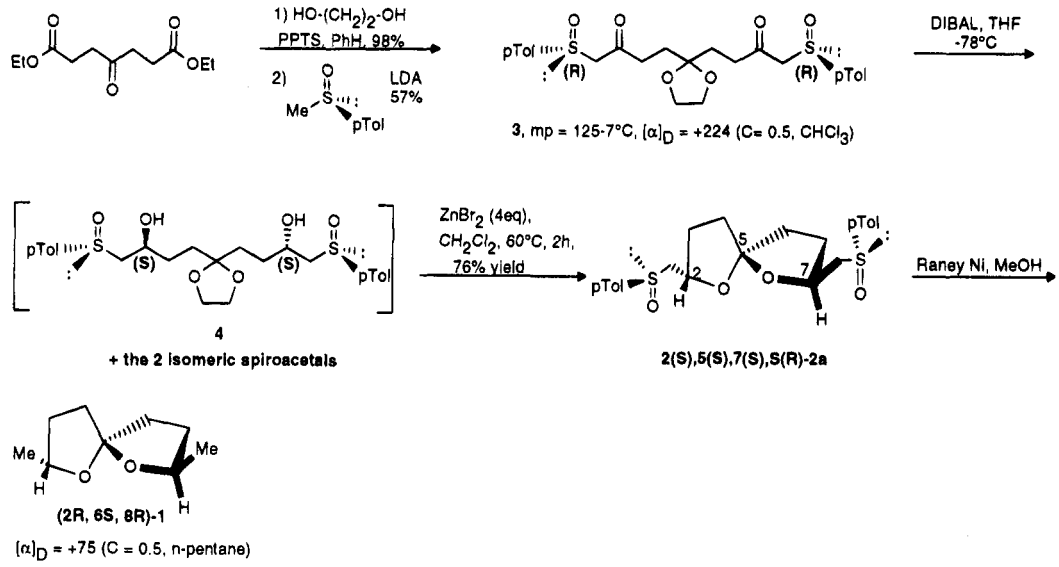
Scheme 2



We have shown indeed that enantiomerically pure β-hydroxy sulfoxides could be efficiently obtained in both diastereomeric forms by reduction of β-keto sulfoxides, DIBAL reduction of (*R*)-β-keto sulfoxide giving the (*R*,*S*)-β-hydroxy sulfoxide by an intramolecular hydride shift from an intermediate having aluminium chelated on the sulfoxide oxygen. $ZnCl_2$/DIBAL reduction afforded the *R*,*R*-β-hydroxy sulfoxide by hydride transfer from a zinc chelate between the sulfoxide and carbonyl oxygens.[9d] Similar results were obtained from diketo disulfoxides.[4d,10]

The reduction product was indeed a mixture of the expected diol **4** and the two spiroketals **2a** and **2b**. This crude product was then cyclized in refluxing acetone in the presence of PPTS, giving, in 81% yield, the two spiroketals **2a** and **2b** in a 1:1 ratio (determined by ^1H NMR from the signals of CH_2 α to the sulfoxides). As expected from the literature, the ketalization led to a 1:1 mixture of the diastereomers resulting from an *R*,*S*-spiro center.

We assumed that the Lewis character of $ZnBr_2$, with its possible chelation on the sulfoxide oxygens (clearly demonstrated by our previous work[11]) and on the ring oxygens, should allow the diastereomers **2a** and **2b** to equilibrate via an open intermediate and possibly should lead to only one stereomer resulting from the formation of the thermodynamically more stable chelate.

In heating the 1:1 mixture of **2a** and **2b** in the presence of 4 equiv of $ZnBr_2$ in CH_2Cl_2 at 60 °C for 2 h, we observed an equilibration of the two diastereomers in favor of diastereomer **2a** which was isolated by crystallization in an 80:20 CH_2Cl_2/ether solution. The formation of the stereogenic spiro carbon was controlled during the cyclization carried out under equilibrating conditions in the presence of $ZnBr_2$, giving the pure diastereomer **2a.**

Finally, we have shown also that the pure diastereomer **2a** could also be obtained directly in 76% yield from the crude reduction product **4**, using these equilibration conditions—4 equiv of $ZnBr_2$ in CH_2Cl_2 at 60 °C for 2 h—and avoiding the ketalization step with PPTS.

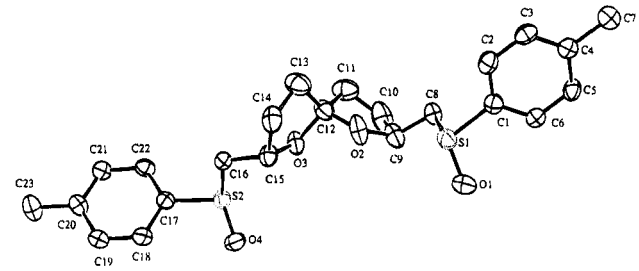


Figure 1. ORTEP plot of spiroacetal **2a**. Ellipsoids are scaled to enclose 50% of the electronic density. Selected mean bond lengths (Å): S1–O1, 1.494(5); S1–C1, 1.787(6); S1–C8, 1.795-(6); C8–C9, 1.521(8); C12–O2, 1.408(8); C12–C11, 1.51(1); C12–O3, 1.425(7); C15–C14, 1.522(8); C15–C16, 1.511(8); C16–S2, 1.803(5); S2–O4, 1.495(4); S2–C17, 1.798(5). Selected mean bond angles (deg): O1–S1–C1, 107.6(3); O1–S1–C8, 105.9(3); C1–S1–C8, 95.6(2); C11–C12–O2, 109.8(5); C13–C12–O3, 104.2(5); C16–S2–O4, 107.0(2); C17–S2–O4, 107.2-(2); C16–S2–C17, 96.2(2).

Table 1. Important Dihedral Angles in 2a

angle	deg	angle	deg
C6–C1–S1–C8	95	C18–C17–S2–C16	107
C1–S1–C8–C9	181	C17–S2–C16–C15	172
S1–C8–C9–O2	61	S2–C16–C15–O3	57

An X-ray analysis[12] (Figure 1) of a single crystal of **2a**, obtained by crystallization in an 80:20 CH_2Cl_2/ether mixture, revealed that (i) the configuration of the spiro carbon was S, (ii) the configurations of carbons C2 and C7 (atoms 9 and 15 on Figure 1) were R as expected from our model,[9d] and (iii) in both chains the sulfoxide oxygen was anti to the oxygen of the rings. Selected mean bond lenghts and mean bond angles are given in the caption of Figure 1. Important dihedral angles are listed in Table 1.

A reasonable explanation of this equilibration is the formation of a dichelate. With $ZnBr_2$ being chelated with

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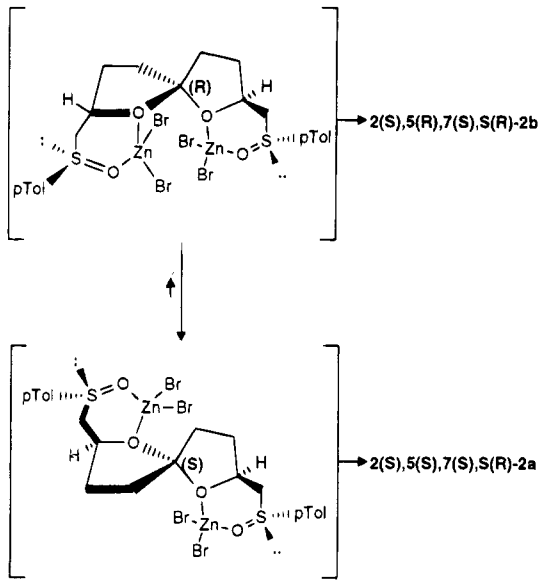
(11) Solladié, G.; Dominguez, C. *J. Org. Chem.* **1994**, *59*, 3898 and references cited therein.

(12) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Scheme 3



both the sulfoxide oxygen and the nearest ring oxygen, the chelate corresponding to the diastereomer **2a**, the main diastereomer at the equilibrium, is less hindered than the chelate of **2b** (Scheme 3).

In conclusion, these results showed that the pure enantiomer **1** could be prepared in a very short asymmetric synthesis by the following four steps (Scheme 2): protected ethyl 4-oxopimelate was first transformed into the diketo disulfoxide **3** which was reduced with DIBAL into the dihydroxy diketo sulfoxide **4** and cyclized under equilibrating conditions in the presence of $ZnBr_2$, giving only one diastereomer of the spiroacetal **2a**, which was desulfurized with Raney nickel into pure (2*R*,6*S*,8*R*)-**1**.

Experimental Section

(+)-(*R*,*R*)-2,8-Dioxo-5-(1,3-dioxolanyl)-1,9-bis(*p*-tolylsulfinyl)nonane (3). (1) Ketal of Ethyl 4-Oxopimelate. Ethyl 4-oxopimelate (15 g, 65.1 mmol) in benzene (200 mL), ethylene glycol (22 mL), and PPTS (500 mg, 2.3 mmol) were heated under reflux for 19 h in a Dean–Stark apparatus. After the solvent was evaporated, the residue was diluted with water (100 mL) and extracted with ether (3 × 50 mL). After drying (Na_2SO_4), the solvents were evaporated, and the crude product (17.5 g, 63.7 mmol, 98%) was used in the next step without further purification.

(2) Reaction of the Ketal of Ethyl 4-Oxopimelate with (+)-(*R*)-Methyl *p*-Tolylsulfoxide. (+)-(*R*)-Methyl *p*-tolylsulfoxide[13] (6 g, 39 mmol) in THF (40 mL) was added at −40 °C to a solution of LDA (made from diisopropylamine (4.4 equiv, 5.75 mL, 40.8 mmol) in THF (50 mL) and *n*-BuLi (4.1 equiv, 26.5 mL of a 1.47 M solution in hexane) at −40 °C). The reaction mixture was stirred at −40 °C for 30 min, and the preceding protected ester (2.8 g, 9.26 mmol) in THF (10 mL) was added. Thirty minutes later, the reaction mixture was hydrolyzed with saturated NH_4Cl (50 mL) and extracted with ether (3 x 30 mL). The organic phases were washed with saturated NaCl (30 mL), dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2:ether, 80:20) to yield the diketo disulfoxide **3** (2.59 g, 5.27 mmol, 57%): mp 125–127 °C; $[\alpha]_D$ +224 (c = 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.88 (m, 4H), 2.41 (s, 6H), 2.48 (m, 4H), 3.81 (AB, 4H, J_{AB} = 13.5 Hz, $\Delta\nu$ = 27 Hz), 3.83 (s, 4H), 7.43 (2 AB, 8H, J_{AB} = 8.0 Hz, $\Delta\nu$ = 40 Hz); ^{13}C NMR ($CDCl_3$) δ 21.3, 30.7, 39.3, 65.0, 68.3, 109.7, 124.2, 130.2, 139.9, 142.3, 201.2. Anal. Calcd for $C_{25}H_{30}O_6S_2$: C, 61.20; H, 6.16. Found: C, 61.12; H, 6.05.

(+)-(2*S*,5*S*,7*S*,S*R*)-2,7-Bis(methyl-*p*-tolylsulfinyl)-1,6-dioxospiro[4.4]nonane (2a). To the diketodisulfoxide **3** (1 g, 2.03 mmol) in THF (50 mL) at −78 °C, was added dropwise over a period of 15 min DIBAL (2.2 equiv, 4.48 mL of a 1 M solution in toluene). After 10 min, methanol (10 mL) was added and the solvent evaporated. The resulting solid was dissolved in water, acidified with 5% HCl to pH = 3, and extracted with CH_2Cl_2 (3 × 40 mL). The organic phases were washed with saturated NaCl (40 mL), dried ($MgSO_4$), and evaporated. The crude solid was immediately dissolved in CH_2Cl_2 (30 mL), $ZnBr_2$ (4 equiv, 1.83 g, 8.12 mmol) was added, the mixture was refluxed for 2 h, and the reaction was quenched with water (15 mL). After extraction with CH_2Cl_2 (3 × 30 mL), the organic phases were washed with saturated NaCl (30 mL), dried ($MgSO_4$), and evaporated. The spiroacetal **2a** was obtained by crystallization from a mixture of 80:20 CH_2Cl_2/ether at rt (667 mg, 1.54 mmol, 76%), mp: 169–171 °C; $[\alpha]_D$ +226 (c = 1.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) (only one set of signals was observed showing a de > 95%) δ 1.60–2.33 (m, 8H), 2.41 (s, 6H), 2.90 (AB from ABX, 4H, J_{AB} = 13.0 Hz, J_{AX} = 7.5 Hz, J_{BX} = 5.0 Hz, $\Delta\nu$ = 13 Hz), 4.55 (m, X from ABX, 2H), 7.43 (2 AB, 8H, J_{AB} = 8.0 Hz, $\Delta\nu$ = 45 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 30.4, 34.6, 64.4, 72.5, 115.2, 124.0, 130.0, 141.5, 141.6. Anal. Calcd for $C_{23}H_{28}O_4S_2$: C, 63.86; H, 6.52. Found: C, 63.76; H, 6.44.

(+)-(2*R*,6*S*,8*R*)-2,7-Dimethyl-1,6-dioxospiro[4.4]-nonane (1). The spiroacetal **2a** (338 mg, 0.78 mmol) in methanol (20 mL) was disulfurized with Raney nickel at rt. The reaction monitored by TLC (ether/hexane, 10:90) was complete in 90 min. The mixture was filtered through Celite and evaporated, and the residue was distilled, Eb(19 mm) = 32 °C. The separation of the solvent by distillation was difficult, and only one fraction (43 mg, 35% yield) was free of methanol: $[\alpha]_D$ +75 (c = 0.55, *n*-pentane); ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, 6H, J = 6 Hz), 1.38–1.55 and 1.99–2.17 (m, 6H), 4.17 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 32.1, 35.8, 74.1, 114.9.

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