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# Asymmetric Synthesis of Chiral Spiroacetals from Chiral Diketodisulfoxides : 2,8-dimethyl-1,7-dioxaspiro [5,5] undecane.

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*Abstract : (2R,6S,8R) and (2S,6R,8S) 2,8-dimethyl-1,7-dioxaspiro [5,5] undecane have been prepared by asymmetric reduction of a diketodisulfoxide intermediate.*

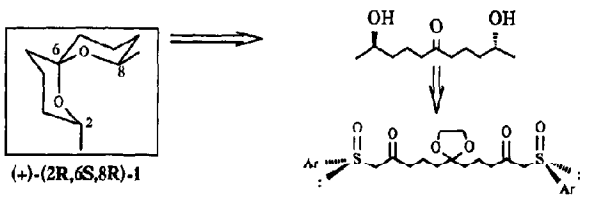
Spiroacetals are part of many natural products with a broad spectrum of biological activities [1]. Among them are, for instance, antiparasitic agents (avermectins and milbemycins), antibiotics (calcimycin) and many volatile spiroacetals with simple substituents used by insects as pheromones [1].

One important component of the mandibular secretion of bees *Andrena Wilkella* was identified [2] in 1980 as 2,8-dimethyl-1,7-dioxaspiro [5,5] undecane, 1. Later this spiroacetal has been demonstrated to be present in the rectal glandular secretion of certain species of fruit flies [3], while the (2S,6R,8S) enantiomer was the major glandular component in the Cucumber fly *B. Cucumis* [3].

We report in this paper the asymmetric synthesis of the 2 enantiomers (2R,6S,8R) and (2S,6R,8S) of 2,8-dimethyl-1,7-dioxaspiro [5,5] undecane, **1**.

Several syntheses of the stereoisomers of 2,8-dimethyl-1,7-dioxaspiro [5,5] undecane have been already published : from ethyl (S)-(+)-3-hydroxy-butanoate made by the reduction of ethyl acetoacetate with Baker's yeasts [4], from (S) malic acid [5] and from (S)(+) lactic acid [6,7]. Other reports described also different approaches to this molecule [8].

We have shown in a preceding work [9] that chiral methyl carbinols can be efficiently obtained in both enantiomeric forms by reduction of β-ketosulfoxides, followed by desulfurization of the resulting β-hydroxysulfoxides : DIBAL reduction of the (R)-β-ketosulfoxide gives the (S)-carbinol and $ZnCl_2$/DIBAL the (R)-carbinol as a result of an intramolecular hydride shift from an intermediate having either Dibal chelated on the sulfoxide oxygen or on a zinc chelate [9d].



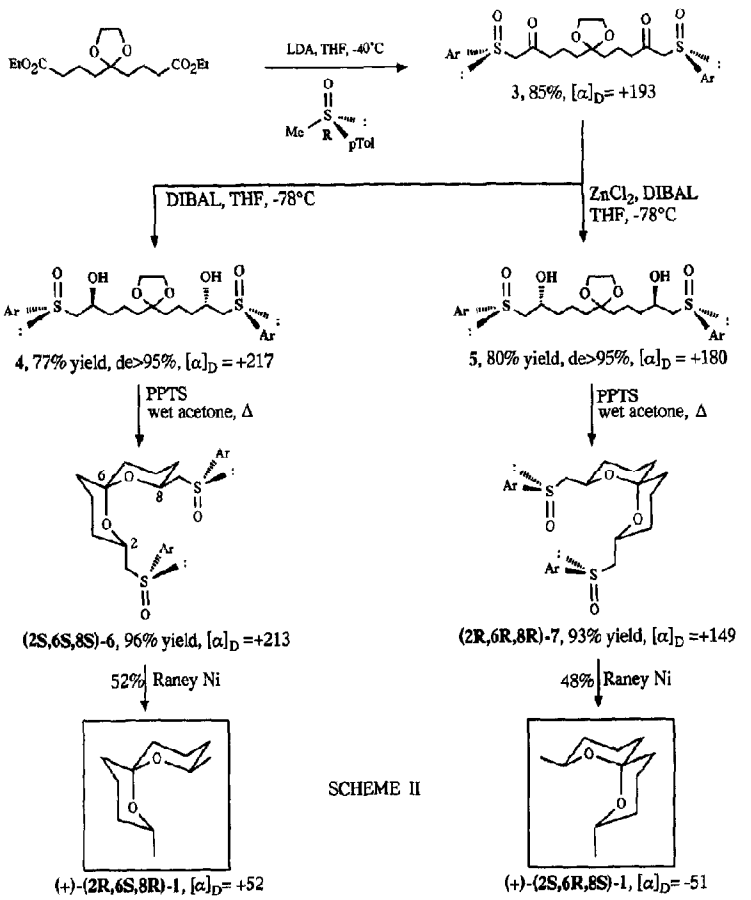

(+)-(2R,6S,8R)-1

SCHEME I

The retrosynthetic scheme I of the enantiomer (2R,6S,8R)-(+)-**1**, shows that the spiroacetal structure can be readily made by cyclization of (2R,10R)-6-keto-2,10-undecanediol. The $C_2$ symmetry of the desired diol allowed us to propose the diketodisulfoxide **3** as a very simple intermediate to create both chiral hydroxylic centers in the desired configurations.

The diketodisulfoxide **3** (Scheme II) was prepared in high yield by reaction of the carbanion of (R)-(+)-methyl p-tolylsulfoxide [10] with the acetal of diethyl 5-ketoazelate, **2**, obtained by esterification and carbonyl protection of 5-ketoazelaic acid [11].

DIBAL reduction yielded as expected the dihydroxydisulfoxide **4** with the S configuration at




SCHEME II

both hydroxylic centers. Because of the $C_2$ symmetry of the molecule, the $^1H$ NMR showed only one set of 7 signals and only one ABX pattern for the $CH_2$ $\alpha$ to the sulfoxide, indicating that the diastereoselectivity of the reduction was higher than 95%. The other diastereomer could not be detected as well as by $^{13}C$ NMR. The absolute configuration was deduced from our preceding results [9] and confirmed by the non-equivalence of the AB protons of the methylene $\alpha$ to sulfoxide [9b] ($\Delta\nu$ = 71 Hz at a concentration 0.04M for the diastereomer 4 and $\Delta\nu$ = 49Hz for the diastereomer 5) as well as by the correlation with the known final product (+) **1**.

Similarly, $ZnCl_2$/DIBAL reduction of 3 lead to the dihydroxydisulfoxide 5 with the R configuration at the new hydroxylic center in 80% yield and de>95%.

Deprotection of the acetal with PPTS in wet acetone allowed the immediate spiroacetalisation of the product in almost a quantitative yield. Compound 4 lead to the spiroacetal [2(S),6(S),8(S),S(R)] 6 and 5 to [2(R),6(R),8(R),S(R)] 7. The stereochemistry of the created chiral spirocarbon was totally controlled by the anomeric effect, a well documented process [12]. The $^1H$ and $^{13}C$ NMR spectra confirmed the absence of any other diastereomer.

Finally desulfurization with Raney Ni in methanol of compounds 6 and 7 afforded the corresponding enantiomeric spiroacetals (+) (2S,6S,8R) **1** and (-) (2S,6R,8S) **1**. The high volatility of these molecules explains the 50% yield observed for this reaction, the solvent separation being rather difficult.

The $^{13}C$ NMR spectrum of (+) 1 shows only six signals [4,5,8c] confirming the $C_2$ symmetry of the molecule with axial C-O bonds exclusively.

In conclusion, this short asymmetric synthesis of the enantiomers (+) and (-) 1 is an example of the interest of diketodisulfoxides reduction for the formation of optically active diols precursors of spiroacetals with a $C_2$ symmetry. The diastereoselectivity for the creation of the chiral centers is very high (95%, corresponding to the detection by $^1H$ and $^{13}C$ NMR of only one diastereomer). No racemization occuring in the final steps, the enantiomeric purity of the final spiroacetal must be of the same order. However the determination of the optical rotations of volatile compounds being always a difficult measurement, the value of 52 we reported is not accurate. The difficulties to determine the maximum optical rotation for synthetic samples of the spiroacetal 1 must be underlined : Mori [4] was the first to report a value of 52 for a pure synthetic enantiomer. But later [5] he published a very careful determination using synthetic material from different routes and ended up with values ranging from 57 to 60. A comparison of these last values to our measurement shows an ee around 90%.

## EXPERIMENTAL.

**Diethyl 5-Ketoazelate:** 5-Ketoazelaic acid[11] (205 mg, 1 mmol.) was dissolved in a mixture of benzene (10 mL) and ethanol (5 mL) containing a small amount of conc. HCl (0.2 mL) and refluxed with a Dean-Stark for 16h. After adding at room temp. sodium bicarbonate (1,5g), the mixture was stirred for 15 min. and filtered. After evaporation of the solvent, crude ketoester 1 was obtained in 94% yield and used in the next step with further purification. Rf : 0.34 (hexane/ether : 60/40), m.p.= 4°C. $^1H$ NMR (200MHz, $CDCl_3$) : $\delta$ : 1.08 (t, 6H, J=7Hz, $CH_3$) ; 1.72 (m, 4H, H-3, H-7) ; 2.16 (t, 4H, J=7Hz, H-2, H-8) ; 2.33 (t, 4H, J=7Hz, H-4, H-6) ; 3.95 (q, 4H, J=7Hz, $COOCH_2$). $^{13}C$ NMR ($CDCl_3$) : $\delta$ : 14.13 ($CH_3$), 18.82 (C-3, C-7), 33.17 (C-2, C-8), 41.43 (C-4, C-6), 60.19 ($OCH_2$),

172.98 ($CO_2$), 209.11 (CO). Anal. Calc. for $C_{13}H_{22}O_5$ ; C, 66.44 ; H, 8.58. Found : C, 66.62 ; H, 8.78.

**Diethyl 5-(1,3-dioxolane) azelate, 2:** A solution containing the preceding ketodiester (6g, 23,2 mmol), ethylene glycol (7.85 mL, 139.3 mmol, 6 eq.), PPTS (500 mg, 2.3 mmol, 0.1 eq) in benzene (170 mL) was refluxed with a Dean-stark apparatus for 19h. After evaporation of the solvent, water (50 mL) was added and the mixture extracted with ether (3x30 mL). The organic phase was dried ($Na_2SO_4$) and evaporated to yield a crude product which was purified by chromatography (silica gel, EtOAc/hexane 30/70). Yield : 88% ; Rf=0.5 (EtOAc/hexane : 30/70). $^1H$ NMR ($CDCl_3$, 200MHz) : δ : 1.17 (t, 6H, J=7Hz, $CH_3$), 1.57 (m, 8H, H-3, H-4, H-6, H-7), 2.23 (t, 4H, J=7Hz, H-2, H-8), 3.85 (s, 4H, dioxolane), 4.04 (q, 4H, J=7Hz, $CO_2CH_2$). $^{13}C$ NMR ($CDCl_3$) : δ : 14.26 ($CH_3$), 19.35 (C-3, C-7), 34.27 (C-4, C-6), 36.28 (C-2, C-8), 60.22 ($CO_2CH_2$), 64.96 (dioxolane), 111.04 (C-5), 173.44 (COO). Anal. calcd for $C_{15}H_{26}O_6$ : C, 59.58 ; H, 8.67. Found : C, 59.32 ; H, 8.71.

**1,11-bis-[(R,R)-p-tolylsulfinyl]-2,10-diketo-6-(1,3-dioxolane) undecane, 3:** To a solution of diisopropylamine (5.75 mL, 40.8 mmol., 4.3 eq.) in THF (50 mL) was added at -50°C a 1.47M solution of n-BuLi in hexane (26.46 mL, 38.9 mmol, 4.1 eq.). The mixture was stirred for 45 mn before adding (+)-(R)-methyl p-tolylsulfoxide [10] (6g, 38.9 mmol, 4.1 eq) in THF (30 mL). After stirring at -50°C for 30 min., the diester 2 (2.8g, 9.26 mmol., 1 eq.) dissolved in THF (10 mL) was added and the reaction mixture stirred for 4h (the reaction was controled by TLC, methanol/ether : 5/95). Sat. $NH_4Cl$ (50 mL) was then added and the solution extracted with ether (3x30 mL). The organic layers were washed with sat. NaCl (30 mL), dried ($Na_2SO_4$) and evaporated. The crude product was purified by chromatography (silica gel, MeOH/ether : 5/95) to yield pure β-diketodisulfoxide 3 in 85% yield.

Rf=0.36 (EtOAc/MeOH : 95/5) ; $[\alpha]_D$ = +193 (c=0.58, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$, 200 MHz) : δ : 1.35 (m, 8H, H-4, H-5, H-7, H-8), 2.22 (s, 6H, $CH_3$), 2.32 (m, 4H, H-3, H-9), 3.66 (AB, 4H, $J_{AB}$=13.5Hz, Δν=14Hz, H-1, H-11), 3.69 (s, 4H, dioxolane), 7.25 (AB, 8H, $J_{AB}$=8Hz, Δν=41Hz, arom.). $^{13}C$ NMR ($CDCl_3$) : δ : 17.62 (C-4, C-8), 21.46 ($CH_3$), 35.74 (C-5, C-7), 44.84 (C-3, C-9), 64.87 (dioxolane), 68.10 (C-1, C-11), 110.95 (C-6), 124.06 and 130.14 (arom. CH), 139.73 and 142.19 (arom. C), 201.37 (C=O). Anal. Calcd. for $C_{27}H_{34}O_6S_2$ : C, 65.52 ; H, 6.61. Found : C, 62.62 ; H, 6.82.

**1,11-bis[(R,R)-p-tolylsulfinyl]-2S, 10S-dihydroxy-6-(1,3-dioxolane) undecane, 4:** To the β-diketodisulfoxide, 3, (2.5g, 4.8 mmol., 1 eq.) in THF solution (150 mL), cooled at -78°C, was added a 1M solution of DIBAL in toluene (10.6 mL, 10.6 mmol., 2.2 eq.) over 45 min.. Ten min. after, the reaction mixture was hydrolyzed with methanol (10 mL), EtOAc (40 mL) and sat. sodium tartrate (20 mL). After stirring for 30 min., the solvent was evaporated and the resulting white solid dissolved in water and EtOAc, acidified with 10% HCl till pH=3 and extracted with EtOAc (3x50 mL). The organic phases were washed with sat. NaCl, dried ($MgSO_4$) and evaporated. The crude product (95% yield) was shown by $^1H$ NMR to contain a diastereomers mixture in the ratio 91/9. One recrystallization in acetone at 0°C yielded the pure [S(R),2(S),10(S),S(R)] diastereoisomer in 77% yield (de > 95%, only one ABX system can be seen on the 200 MHz $^1H$ NMR for the protons α to the sulfoxides groups). Rf=0.2 (EtOAc/MeOH : 95/5) ; $[\alpha]_D$ = +217 (c=0.44, $CH_2Cl_2$) ; m.p. 78-81°C. $^1H$ NMR (200MHz, $CDCl_3$) : δ : 1.5 (m, 12H, H-3, H-4, H-5, H-7, H-8, H-9), 2.42 (s, 6H, $CH_3$), 2.9 (AB

of ABX, 4H, $J_{AB}$=13.5Hz, $J_{AX}$=1.5Hz, $J_{BX}$=10Hz, Δν=71Hz, H-1-H-11), 3.86 (s, 4H, dioxolane), 3.87 (bs, 2H, OH), 4.14 (X of ABX, m, 2H, H-2, H-10), 7.40 (AB, 8H, $J_{AB}$=8Hz, Δν=33Hz, arom.). $^{13}$C NMR ($CDCl_3$) : δ : 19.52 (C-4, C-8), 21.49 ($CH_3$), 36.59 and 37.19 (C-3, C-5, C-7, C-9), 62.45 (dioxolane), 64.91 (C-1, C-11), 66.14 (C-2, C-10), 111.46 (C-6), 124.05 and 130.14 (arom. CH), 139.80 and 141.56 (arom. C). Anal. Calcd for $C_{27}H_{38}O_6S_2$ : C, 62.04 ; H, 7.33. Found : C, 62.06 ; H, 7.20.

**1,11-bis [(R,R)-p-tolylsulfinyl]-2R, 10R-dihydroxy-6- (1,3-dioxolane) undecane, 5:** The β-diketodisulfoxide **3** (1.5g, 2.89 mmol., 1 eq.) was added to dry zinc chloride (1,3g, 5.78 mmol., 2 eq.) in THF (140 mL). After stirring at RT for 30 min., the mixture was cooled and a 1M DIBAL solution in toluene (6.4 mL, 6.4 mmol., 2.2 eq.) was dropwise added over 1h. Ten min. after the end of the addition, MeOH (10 mL) was added, the mixture was stirred for 30 min. at RT and the solvant evaporated. The crude white solid was dissolved in water and $CH_2Cl_2$, acidified with 5% $H_2SO_4$ (60 mL), extracted with $CH_2Cl_2$ (3x40 mL), dried ($MgSO_4$) and evaporated. The crude product was then purified by chromatography (silica gel, EtOAc/MeOH : 95/5) to yield 5 in 80% yield and a d.e.>95%. Rf=0.2 (EtOAc/MeOH : 95/5) ; $[\alpha]_D$ = +180 (c=0.39, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$) : δ : 1.5 (mm, 12H, H-3, H-4, H-5, H-7, H-8, H-9), 2.37 (s, 6H, $CH_3$), 2.85 (AB of ABX, 4H, $J_{AB}$=13Hz, $J_{AX}$=2.5Hz, $J_{BX}$=9Hz, Δν=49Hz, H-1, H-11), 3.84 (s, 4H, dioxolane), 4.04 (bs, 2H, OH), 4.13 (X of ABX, m, 2H, H-2, H-10), 7.40 (AB, 8H, $J_{AB}$=8Hz, Δν=43Hz, arom.). $^{13}$C NMR ($CDCl_3$) : δ : 19.56 (C-4, C-8), 21.48 ($CH_3$), 36.65 and 37.18 (C-3, C-5, C-7, C-9), 63.90 and 64.82 (dioxolane and C-1, C-11), 67.59 (C-2, C-10), 111.34 (C-6), 124.24 and 130.08 (arom. CH), 140.29 and 141.82 (arom. C). Anal. calcd for $C_{27}H_{38}O_6S_2$ : C , 62.04 ; H, 7.33. Found : C, 61.82 ; H, 7.45.

**(2S,6S,8S) bis [(R,R)-p-tolylsulfinylmethyl]-6-(1.7-dioxaspiro-[5,5]) undecane, 6:** A solution of the dihydroxysulfoxide **4** (800 mg, 1,5 mmol., 1 eq.) in acetone (25 mL) and water (15 drops) in presence of PPTS (114 mg, 0.46 mmol., 0.3 eq.) was refluxed for 48h. After evaporation of the solvent, the crude product was diluted with water and extracted with $CH_2Cl_2$ (3x30 mL). Washed with sat. NaCl (30 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc : 30/70 with 2% of $Et_3N$). Yield : 96%, Rf=0.5 (EtOAc), $[\alpha]_D$ = +213 (c=0.43, $CCl_4$), m.p. 25-26°C. $^1$H NMR ($CDCl_3$, 200MHz) : δ : 1.2-2.03 (m, 12H, H-3, H-4, H-5, H-9, H-10, H-11), 2.40 (s, 6H, $CH_3$), 2.88 [AB of ABX, 4H, $J_{AB}$=13HZ, $J_{AX}$=9Hz, $J_{BX}$=4.5Hz, Δν=31Hz, $CH_2$ α to S(O)], 4.42 (X of ABX, m, 2H, H-2, H-8), 7.45 (AB, 8H, $J_{AB}$=8Hz, Δν=57Hz, arom.). $^{13}$C NMR ($CDCl_3$) : δ : 18.39 (C-4, C-10), 21.35 ($CH_3$), 30.72 and 35.00 (C-3, C-5, C-9, C-11), 64.64 (C-2, C-8), 65.07 [$CH_2$-S(O)], 96.77 (C-6), 124.00 and 129.80 (arom. CH), 140.97 and 142.18 (arom. C). Anal. calcd for $C_{25}H_{32}O_4S_2$ : C, 65.18 ; H, 7.00. Found : C, 64.96 ; H, 6.90.

**(2R,6R,8R) bis [(R,R)-p-tolylsulfinylmethyl]-6-(1.7-dioxaspiro-[5,5]) undecane, 7:** A solution of the dihydroxydiketosulfoxide **5** (390 mg, 0.75 mmol., 1 eq.) in acetone (20 mL) and water (10 drops) in presence of PPTS (77 mg, 0.27 mmol., 0.3 eq.) was refluxed for 15h. After concentration, the crude product was diluted with water and extracted with EtOAc (3x30 mL). The organic phases were washed with sat. NaCl (30 mL) dried ($MgSO_4$) and evaporated to yield white crystals which were purified by column chromatography (silica gel, hexane/EtOAc : 30/70 with 2% $Et_3N$). Yield : 93%, Rf : 0.5 (EtOAc), $[\alpha]_D$ = +149 (c=0.8, $CCl_4$), m.p. 110-112°C. $^1$H NMR ($CDCl_3$, 200MHz) : δ : 1.25-

1.80 (m, 12H, H-3, H-4, H-5, H-9, H-10, H-11), 2.40 (s, 6H, $CH_3$), 2.88 (AB of ABX, 4H, $J_{AB}$=13.5Hz, $J_{AX}$=5.5Hz, $J_{BX}$=6.0Hz, $\Delta\nu$=40Hz, [$CH_2$-S(O)], 4.00 (X of ABX, m, 2H, H-2, H-8), 7.45 (AB, 8H, $J_{AB}$=8.5Hz, $\Delta\nu$=51Hz, arom.). $^{13}C$ NMR ($CDCl_3$) : $\delta$ : 18.25 (C-4, C-10), 21.40 ($CH_3$), 30.45 and 34.78 (C-3, C-5, C-9, C-11), 64.41 [$CH_2$-S(O)], 65.45 (C-2, C-8), 97.01 (C-6), 124.26 and 129.96 (arom. CH), 141.31 and 141.70 (arom. C). Anal. calcd. for $C_{25}H_{32}O_4S_2$ : C, 65.18 ; H, 7. Found : C, 65.47 ; H, 6.93.

**(2R,6S,8R)-dimethyl-6-(1,7-dioxaspiro-[5,5]) undecane, (+)-1:** The spiroacetal **6** (245 mg, 0.53 mmol.) in methanol (30 mL) was desulfurized with Raney Nickel at room temperature in 4h (TLC monitoring, ether/hexane) : 1/9. After filtration on celite, the solvent was evaporated and the crude product purified by chromatography (silica gel, pentane). The solvent separation was difficult due to the high volatility of the spiroacetal. Yield : 52%, Rf=0.5(ether/hexane : 1/9), $[\alpha]_D$ = +52 (c=0.96, pentane). $^1H$ NMR ($CDCl_3$, 200MHz) : $\delta$ : 1.13 (d, 6H, J=6.5Hz, $CH_3$), 1.05-2.00 (m, 12H, $CH_2$), 3.67 (m, 2H, H-2, H-8). $^{13}C$ NMR ($CDCl_3$): $\delta$ :19.01 (C-4), 21.96 (C-7), 32.86 (C-3), 35.28 (C-5), 65.09 (C-2), 96.24 (C-6).

**(2S,6R,8S)-dimethyl-6-(1,7-dioxaspiro-[5,5]) undecane, (-) 1:** The spiroacetal **7** (200 mg, 0.43 mmol.) was desulfurized and purified following the same procedure. Yield : 48%, Rf=0.5(ether/hexane : 1/9), $[\alpha]_D$ = -51 (c=0.96, pentane). $^1H$ NMR ($CDCl_3$, 200MHz) : $\delta$ : 1.13 (d, 6H, J=6.5Hz, $CH_3$), 1.05-2.00 (m, 12H, $CH_2$), 3.67 (m, 2H, H-2, H-8).

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