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Synthesis and Structural Study of (+)-5-Acetyl-6-methyl-5ptolylsulfinyl-3a,4,5,6tetrahydro (3H)-Benzofuran-2one

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Synthesis and Structural Study of (+)-5-Acetyl-6-methyl-5<u>p</u>-tolylsulfinyl-3a,4,5,6-tetrahydro (3<u>H</u>)-benzofuran-2-one

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Abstract : an efficient synthesis of the title compound has been developed from 3-phenyl sulfonylpropanoic acid via the butenolide <u>2</u>. The key synthetic step is a Diels-Alder reaction. A mechanism is suggested.

In a previous paper (1), we have reported the Diels-Alder reaction between a dienic lactone and an ethylenic α -acylsulfoxide which appeared to be a pathway to intermediates with a skeleton close to a variety of sesquiterpenes (e.g. ivangulin (2) or igalane (3)), (Scheme 1). The very smooth conditions of this reaction which proceeded in aqueous medium at room temperature, without a catalyst, is possible in the presence of different functionnal groups. In all cases, essentially one isomer was formed and isolated with a yield of about 80 %, which agree with the known high regio- and diastereospecificity in these conditions (4). Furthermore it should be noted that the ethylenic sulfoxide which is used as a dienophile, has been widely utilized in several synthetic investigations (5).

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Scheme 1

In this communication, we wish to report a new and facile method to prepare the chiral cycloadduct <u>5</u>(Scheme 2). For this, we used (S)- α -acetylvinylsulfoxide <u>1</u> (6) derived in two steps from (R)-p-tolylvinylsulfoxide. The 5-prop-1-enyl(3H)-

-dihydrofuran-2-one $\underline{2}$ was easily obtained by a sequence corresponding to a modification of the procedure described (7). Condensation in basic medium of the 3-phenylsulfonylpropanoic acid upon crotonaldehyde gave after cyclization, the phenylsulfonylbutenolide $\underline{4}$ which, treated by one equivalent of DBU, led to the dienic lactone $\underline{2}$ (8). This new route was shorter and gave better yields (1).

At room temperature, in water, cycloaddition of $\underline{1}$ and $\underline{2}$ took place to afford after half an hour, in good yield, the adduct $\underline{5}$ which crystallized by adding ether to the reaction mixture. $\underline{5}$ showed a specific rotation of +664° in aceton.

The 'H NMR spectra of $\underline{5}$ confirmed the structure of this compound, which exhibited the expected characteristics as compared to spectroscopic data in the racemic serie. The X-ray diffraction of a single crystal fully supported the analytical data and allowed to assign the absolute configuration to the stereocenters of this molecule.

On the basis of our results, we consider the most acceptable mechanism to explain the stereochemistry of the [4+2] adduct is to involve the attack by the less conges-



Scheme 2

ted side of the dienophile <u>1</u>. this last one is stated in a conformation where bonds S=O and C=O are opposite and where system C=C-S=O adopts a <u>s</u>-cis geometry (Scheme 3, form i). On the other hand the opposite conformation in which this system adopts a <u>s</u>-trans geometry would led to lactone <u>5</u>, only by an attack on the most crowdy face of the dienophile, a supposition which is less consistent (Scheme 3, form ii).



Scheme 3

The present study develops a mild and convenient method for the enantioselective formation of a bicyclic lactone which has a potential utility in the synthesis of natural products. The stereoselectivity of this Diels-Alder reaction with other substituted dienic lactones are currently in progress.

Experimental section

General Methods. ¹H and ¹³C NMR were recorded with a Bruker AC400 (400 MHz) spectrometer. Chemical shifts were reported in ppm (δ) relative to tetramethylsilane as internal standard, for solutions in CDCl₃.; coupling constants (J) are given in Hz with the following abbreviations for splitting patterns: s = singlet, ps = pseudo-singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Flash chromatography was performed on 230-400 mesh Merck Silica gel 60. Elemental analyses were performed in the *Service de Microanalyses* (ICSN, Gif-sur-Yvette, France).

4-Phenylsulfonyl-5-prop-1-enyl-tetrahydrofuran-2-one 4

To a solution of LDA (56 mmol) in THF (100 mL), cooled to -78°C under argon, dropwise (one hour), a solution in THF of 6 g of was added 3-phenylsulfonylpropanoic acid (28 mmol). The solution was stirred at -78°C for 30 min, then crotonaldehyde (42 mmol, or 3.5 mL), were added. After quenching with a saturated aqueous NH₄Cl, the reaction mixture was washed with ether, then acidified and extracted with chloroform. The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was heated to reflux for one hour in toluene (100 mL) containing a few mg of p-toluenesulfonic acid. The solution was washed with sodium hydrogenocarbonate and with brine followed by drying over MgSO₄. The solvent was removed by evaporation to give 4.47 g (17.6 mmol, 63 %) of the crude lactone which was used directly in the next step without further purification. IR film (selected data) v_{max} 1769 (C=O lactone), 1603 (C=C) cm^{-1} ; NMR ¹H 1.55 (3H, d, J = 6.5 Hz, Me), 2.95 (2H, m, CH₂), 4.00 (1H, m, HCSO₂), 5.15 to 5.90 (3H, m, H_{ethyl} and HCO), 7.70 to 8.15 (5H, m, H_{arom}).

5-Prop-1-enyl (5H)-dihydrofuran-2-one 2

A solution of the sulfone 4 (3.8 g) in dichloromethane (30 mL), cooled to 0°C,

was placed under argon in a round bottomed flask (100 mL). After addition of DBU (2.16 g) the mixture was stirred for 30 min before to be washed successively with diluted hydrochloric acid (5 %, 3*20 mL) and brine (30 mL). The organic layer was dried over MgSO₄. The solvent was removed *in vacuo* and the crude reaction product chromatographed on silica (cyclohexane/AcOEt, 95:5) to provide the title lactone (1.24 g, 67 %). IR film (selected data) v_{max} 1802 (C=O lactone), 1611 (C=C) cm⁻¹; NMR ¹H 1.85 (3H, d, J = 6.5 Hz, Me), 3.3 (2,Hm), 5.35 (1H, m, \underline{H}_{ethvl} ring), 5.80 to 6.45 (2H, m, \underline{H}_{ethvl} chain).

5-Acetyl-6-methyl-5-p-tolylsulfinyl-3a,4,5,6-tetrahydro(3H)benzofuran-2-one

A mixture of 0.7 g (3.2 mmol) of sulfoxide <u>1</u> and 0.4 g (3.2 mmol) of lactone <u>2</u> was stirred with 2 mL of water for 30 min. By addition of ether, the crude lactone which crystallized was filtered, washed with ether, then dried (MgSO₄). This yielded 0.9 g (2.6 mmol, 80 %) of a white solid ; m.p. 103-104°C (from CH₂Cl₂).

 $[\alpha_{D}]$ +664° (acetone, c = 0.48). IR (selected data) film v_{max} (cm⁻¹)1819 (C=O lactone), 1698 and 1032. NMR ¹H 0.94 (3H, d, J = 6.5 Hz, Me); 2.10 (1H, dd, J_{3α-3a} = 6.5 Hz, J_{3α-3β} = 13 Hz, H_{3α}), 2.30 (3H, s, MeCO), 2.45 (1H, dd, J_{4α-3a} = 12 Hz, J_{4α-4β} = 17 Hz, H_{4α}), 2.45 (3H, s, MeAr), 2.60 (1H, m, H₆), 2.93 (1H, dd, J_{4β-3a} = 8.5 Hz, J_{4α-4β} = 17 Hz, H_{4β}), 3.15 (1H, dd, J_{3β-3a} = 7.5 Hz, J_{3α-3β} = 13 Hz, H_{3β}), 3.70 (1H, m, H_{3a}), 5.32 (1H, dd, J₆₋₇ = 4.3 Hz, J_{7-3a} = 2.5 Hz, H₇), 7.45 (4H, m, H_{arom}). Elemental analysis, found : C, 65.06; H, 6.08; O, 19.34; S, 9.58 %. C₁₈H₂₀O₄S requires C, 65.03; H, 6.06; O, 19.25; S, 9.64 %.

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