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Synthons for Syntheses of Spiro[2.4]heptane Analogues of Prostaglandins

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Methods for the preparation of synthons for syntheses of spiro[2.4]heptane analogues of prostaglandins are described. Two of them (**1a** and **1b**) enable the syntheses of 11-deoxy-type compounds and were prepared from spiro[2.4]heptan-4-one (**3**) which after transformation into the 5-phenylthio-α,β-unsaturated ketone **5** was subjected to conjugate addition of organocuprate reagent **6**. The third synthon (**2**)—a potential intermediate in syntheses of complete spiro[2.4]heptane analogues of prostaglandins—was prepared from the bicyclic ketone **10** by *Baeyer-Villiger* oxidation followed by epoxidation.

(Keywords: Prostaglandin analogues; Spiro[2.4]heptan-4-ones; 2H-Cyclopenta[b]furan-2-ones; Desulfurization; Conjugate addition of cuprate)

Ausgangsverbindungen für die Synthese von Prostaglandin-analogen Spiro[2.4]heptanen

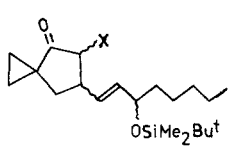
Es werden Synthesewege für Spiro[2.4]hepane als Analoge zu Prostaglandinen beschrieben. Zwei davon (**1a** und **1b**) ermöglichen die Synthese von Verbindungen des 11-Deoxy-Typs; sie wurden aus Spiro[2.4]heptan-4-on (**3**) dargestellt, das nach der Umwandlung zum 5-phenylthio-α,β-ungesättigten Keton **5** einer konjugierten Addition von Organocuprat-Reagens **6** unterworfen wurde. Das dritte (**2**), ein potentielles Zwischenprodukt in der Synthese von vollständigen Spiro[2.4]heptan-Analogen zu Prostaglandinen, wurde aus dem bicyclischen Keton **10** durch *Baeyer-Villiger*-Oxidation gefolgt von einer Epoxidierung dargestellt.

Introduction

Among many known prostaglandin analogues there are only few in which position 10 is blocked by two additional substituents such as methyl groups. This modification protects E-type prostaglandins against the well known ready dehydration of the β-hydroxy-ketone moiety[1,2].

Results and Discussion

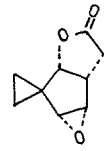
In our laboratory we undertook the preparation of new prostaglandin analogues bearing a spirocyclopropane ring in position 10. In this paper we would like to report the synthesis of three synthons: **1 a**, **1 b**, and **2**.



1a,b

a X=SPh

b X=CO2Me

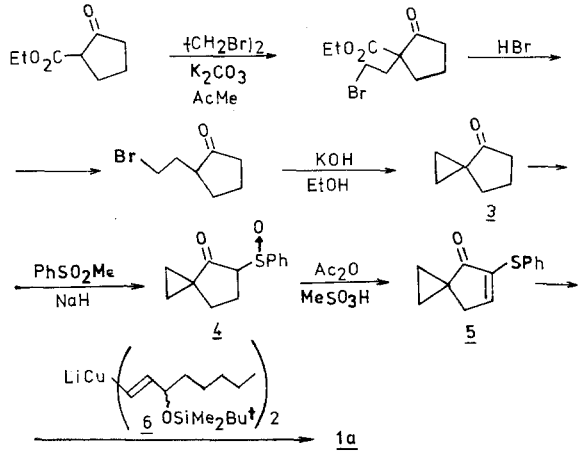


2

Compounds of that type are useful intermediates in the syntheses of prostaglandins and their analogues due to the possibility of alkylation at the acidic center C-8[3] (**1 a** and **1 b**) or nucleophilic opening of the oxirane ring[4] (compound **2**).

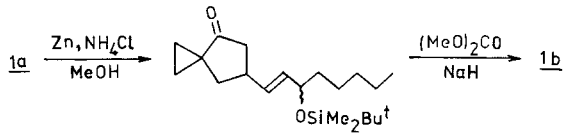
The substrate in the synthesis of **1 a** and **1 b** was spiro[2.4]heptan-4-one (**3**) which was prepared in 27% overall yield from 2-carboethoxycyclopentanone by simplifying the procedure described by *Crandall* and *Seidewand*[5] (alkylation of 2-carboethoxycyclopentanone in presence of K_2CO_3 instead of preparing the potassium salt).

Ketone **3** was transformed into the α,β-unsaturated ketone **5** in 58% yield using a general procedure[6]—treatment with methyl benzenesulfinate and sodium hydride followed by reaction of the resulting sulfoxide **4** with acetic anhydride in presence of methanesulfonic acid.



The prostaglandin lower side-chain was introduced by conjugate addition of the organocuprate **6** to ketone **5** to give adduct **1a** in 86.5% yield.

1a could be allylated in position C-5 with allyl bromide using sodium hydride in *THF*[3a,7]. Under the same conditions alkylation with methyl 7-iodoheptanoate failed. Introduction of the methyl heptanoate moiety in the position C-5 was possible after replacing the phenylthio group by carbomethoxy group in two steps.

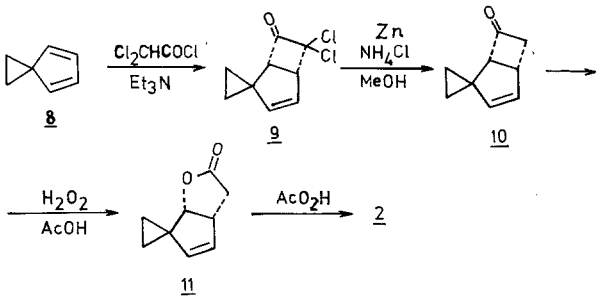


7

In the first step the phenylthio group was removed by a novel procedure—reduction with zinc dust and ammonium chloride in methanol to give ketone **7** in 76% yield. This method allows to carry out the reductive cleavage of the C—S bond under very mild conditions.

Treatment of **7** with dimethyl carbonate and sodium hydride gave β-ketoester **1b** in 93% yield. Alkylation of **1b** with methyl 7-iodoheptanoate (K_2CO_3, *AcMe*) proceeded without difficulty allowing the syntheses of prostaglandin analogues of the one series.

Lactone **2**—potential precursor for syntheses of complete spiro[2.4]heptane analogues of prostaglandins—was prepared in six steps from cyclopentadiene.



8 9 10 11

Spiro[2.4]heptan-4-one **8**, readily available from cyclopentadiene[8], was converted into the known bicyclic ketone **9** by modifying the procedure described by *Brook* and *Harrison*[9]. Reaction of the diene **8** with dichloroketene afforded adduct **9** in 78% yield which was reduced with zinc dust and ammonium chloride in methanol[10] to give **10** in 70%

yield. *Baeyer-Villiger* oxidation of **10** with hydrogen peroxide in acetic acid[11] furnished the lactone **11** in 54% yield. Finally **11** was converted into the oxirane **2** in 58% yield by treatment with peracetic acid according to the procedure described by *Corey* and *Noyori*[12]. A minor amount of the undesired (1 a β, 2 a α, 5 a α, 5 b β)-stereoisomer was also formed during this reaction but was easily separated by crystallization.

Work on syntheses of spiro[2.4]heptane analogues of prostaglandins from **1 a**, **1 b** and **2** is in progress and will be described later.

Experimental

The following instruments were used for the spectra: IR: SPECORD-5; ^{1}H-NMR: JEOL MH-100. Elemental analysis (C, H, S) are in agreement with the formulas given for **1 a**, **1 b**, **2**, **5**, **7**, **10**, and **11**.

Spiro[2.4]heptan-4-one (**3**)

In a 6-l flask equipped with mechanical stirrer and reflux condensor were placed 218 g (1.4 mol) of 2-carboethoxycyclopentanone, 1 579.2 g (8.4 mol) of 1,2-dibromoethane, 496 g (3.6 mol) of potassium carbonate and 3 200 ml of acetone. The mixture was stirred and heated under reflux for 9 h, cooled to room temperature and filtered with suction. The precipitate was washed twice with acetone and the filtrate concentrated under reduced pressure to give 347.8 g of crude 2-(β-bromoethyl)-2-carboethoxycyclopentanone as a brown oil. The crude product was placed in a 2-l flask and treated with 1 240 ml of 40% hydrobromic acid. The mixture was heated under reflux for 2 h, cooled, poured into 3 000 ml of water and extracted three times with 200 ml of ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give 185 g of crude 2-(β-bromoethyl)cyclopentanone. The crude product was added to a solution of 242 g of KOH in 700 ml of ethanol, the mixture heated under reflux for 1.5 h, cooled, and poured into 3 000 ml of water. The product was extracted three times with 150 ml of ether and the combined organic layers washed with aqueous sodium bicarbonate and water. The solution was dried over $MgSO_4$, the solvent removed under reduced pressure and the residue distilled to yield 42 g (27%) of **3** as a colourless oil, b. p. 58–59 °C (16 mm).

5-Phenylthiospiro[2.4]hept-5-en-4-one (**5**)

In a 2-l two-necked flask, equipped with magnetic stirrer, nitrogen-inlet tube and reflux condensor was placed 8.7 g (55–60% in oil, about 0.18 mol) of sodium hydride and, under a nitrogen atmosphere, was washed several times by decantation with pentane. The flask was then charged with a solution of 28.2 g (0.18 mol) of freshly-distilled methyl benzenesulfinate and 18.2 g (0.17 mol) of **3** in 800 ml of anhydrous ether. The mixture was stirred at room temperature for 4 days and poured into 600 ml of 10% sulfuric acid. The separated aqueous layer was extracted with 100 ml of ether and the combined organic layers washed with saturated aqueous sodium bicarbonate and dried over $MgSO_4$. Evaporation under reduced pressure provided 40.1 g of crude 5-phenylsulfinylspiro[2.4]heptan-4-one (**4**). The crude product was placed in 2-l round-bottomed flask and a solution of 17.5 ml of acetic anhydride and 1.5 ml of methanesulfonic acid in

800 ml of methylene chloride was added. The mixture was stirred at room temperature for 16 h, concentrated under reduced pressure to a volume of about 300 ml and washed several times with diluted aqueous sodium carbonate (until the evolution of CO_2 ceased). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and solid residue twice crystallized from hexane. Concentration of the mother liquors and crystallization yielded an additional crop of product. Overall yield of almost colourless crystals of **5** was 20.4 g (57.5%), m.p. 80.5–82 °C.

IR (CCl_4): 1 700 and 1 720 cm^{-1}.

NMR (CCl_4): 0.87–1.30 (m, 4 H), 2.63 (d, $J = 3.0$ Hz, 2 H), 6.82 (t, $J = 3.0$ Hz, 1 H), 7.10–7.65 (m, 5 H).

5-Phenylthio-6-[3-tert-butyldimethylsilyloxy-(E)-1-octenyl]-spiro[2.4]heptan-4-one (**1a**)

A 500 ml flask was equipped with thermometer, magnetic stirrer, and inlet for dry argon (a weak stream of which was maintained through all the reaction). The flask was charged with a solution of 9.14 g (0.024 mol) of (*E*)-1-iodo-3-*tert*-butyldimethylsilyloxy-1-octene in 150 ml of ether and immersed in an acetone-dry ice bath. When the temperature reached −78 °C a solution of *tert*-butyllithium (24.9 ml, 1.5 *N* in pentane, 0.0373 mol) was added with a syringe. After stirring at −78 °C for 2 h the mixture of 1.74 g of tributylphosphine and 1.6 g of copper(I) iodide in 100 ml of ether (stirred for 15 min at room temperature beforehand) was added. The reaction mixture was stirred at −78 °C for 50 min and a solution of 1.78 g (0.008 mol) of **5** in 100 ml of ether was added. The stirring was continued at −78 °C for 15 min, at −18 to −23 °C for 30 min and 150 ml of cold, saturated aqueous ammonium sulfate was added. The reaction mixture was poured into a separatory funnel and shaken until the colour of the organic layer disappeared. A blue aqueous layer was separated and the organic layer shaken with an additional 100 ml portion of saturated aqueous ammonium sulfate. The combined aqueous layers were extracted with ether and the combined organic extracts washed with saturated aqueous sodium chloride, dried over Na_2SO_4 and concentrated under reduced pressure to yield a light-brown oil. The product was purified by column chromatography (silica gel). The column was eluted first with hexane and then hexane-ether (50 : 1). The combined eluates were concentrated under reduced pressure to give 3.26 g (86.5%) of **1a** as a pale yellow oil.

IR (film): 1 730 cm^{-1}.

NMR (CCl_4): −0.03–0.15 (m, 6 H), 0.57–1.60 (m, 24 H), 1.93 (d, 2 H), 2.52–2.84 (m, 1 H), 3.23 (dd, 1 H), 3.91–4.12 (m, 1 H), 5.45–5.60 (m, 2 H), 7.05–7.52 (m, 5 H).

6-[3-tert-Butyldimethylsilyloxy-(E)-1-octenyl]-spiro[2.4]heptan-4-one (**7**)

A mixture of 0.772 g (1.67 mmol) of **1a**, 1.82 g (34 mmol) of ammonium chloride, 2.22 g (34 mmol) of zinc dust and 25 ml of methanol was stirred at room temperature for 17 h and then decanted. The precipitate was washed several times with methanol and the combined extracts concentrated under reduced pressure. The residue was treated with 50 ml of water and extracted twice with 50 ml of ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel). The column was eluted first with hexane and then

with hexane : ether (100 : 1). The combined eluates were concentrated under reduced pressure to give 0.433 g (73%) of **7** as a colourless oil.

IR (film): 2 930, 2 860, 1 730 cm^{-1}.

NMR (CCl_4): −0.02 and 0.01 (d, 6 H), 0.68–1.65 (m, 24 H), 1.89–2.60 (m, 4 H), 2.71–3.09 (m, 1 H), 3.92–4.16 (m, 1 H), 5.28–5.75 (m, 2 H).

5-Carbomethoxy-6-[3-tert-butyldimethylsilyloxy-(E)-1-octenyl]-spiro[2.4]heptan-4-one (**1 b**)

In a 25 ml flask equipped with magnetic stirrer and reflux condensor was placed 0.2 g of sodium hydride (55–60% in oil, about 4 mmol) and was washed several times by decantation with pentane. The flask was then charged with a solution of 0.384 g (1.1 mmol) of **7**, 1.07 g (12 mmol) of dimethyl carbonate and 1 drop of methanol in 10 ml of benzene. The mixture was stirred and heated under reflux for 4 h, cooled to room temperature and poured into diluted aqueous acetic acid. The mixture was extracted twice with 25 ml of ether and the combined oganic extracts washed with saturated aqueous sodium bicarbonate, brine and dried over Na_2SO_4. Evaporation under reduced pressure provided 0.416 g (93%) of **1 b** as a light-brown oil. TLC analysis (silica gel plates, hexan : ether 2 : 1 as a developing system) revealed only one sport.

IR (film): 1 725, 1 750 cm^{-1}.

NMR (CCl_4): −0.04 and 0.01 (d, 6 H), 0.43–1.60 (m, 24 H), 1.81–2.08 (m, 2 H), 2.95–3.43 (m, 2 H), 3.67 (s, 3 H), 3.88–4.13 (m, 1 H), 5.46–5.61 (m, 2 H).

6,6-Dichlorospiro[bicyclo[3.2.0]hept-3-ene-2,1'-cyclopropan]-7-one (**9**)

This compound was prepared in 78% yield from spiro[2.4]hepta-4,6-diene (**8**), dichloroacetyl chloride and triethylamine according to the procedure described by *Brook* and *Harrison*[9]. Compared with the original procedure we used a smaller excess of spiro[2.4]hepta-4,6-diene (0.1 mol in relation to 1 mol of dichloroacetyl chloride) than the authors (3- to 5-fold excess).

Spiro[bicyclo[3.2.0]hept-3-ene-2,1'-cyclopropan]-7-one (**10**)

In a 2-l flask equipped with mechanical stirrer, thermometer and dropping funnel with a pressure equalizing side tube were placed 350 g (5.3 mol) of zinc dust, 129 g (2.4 mol) of ammonium chloride and 1 000 ml of methanol. The stirrer was started and 117 g (0.57 mol) of **9** was added dropwise at such a rate that the temperature of the mixture did not exceed 40 °C cooling occasionally the flask in a water-ice bath. After the addition the mixture was stirred at room temperature until GLC (OV-17, 122 °C) showed that neither substrate nor monochlorderivative (intermediate in the reaction) was present (16 h). The mixture was then decanted and the precipitate washed several times with methanol. The combined extracts were concentrated under reduced pressure to a volume of about 100 ml and poured into 150 ml of water. The mixture was extrated three times with ether, the combined organic layers dried over $MgSO_4$ and evaporated. The residue was distilled under reduced pressure to give 54 g (70%) of **10** as a colourless oil, b. p. 86–90 °C (16 mm).

IR (film): 1 780, 1 600 cm^{-1}.

NMR (CCl_4): 0.6–1.2 (m, 4 H), 2.52–2.82 (m, 1 H), 3.10–3.40 (m, 2 H), 3.44–3.70 (m, 1 H), 5.27 (d, $J = 5.4$ Hz, 1 H), 5.75 (dd, $J = 5.4$ Hz and 2.6 Hz, 1 H).

Spiro[3,3 a,6,6 a-tetrahydro-2H-cyclopenta[b]furan-6,1'-cyclopropan]-2-one (**11**)

In a 1-l three-neck flask equipped with magnetic stirrer and thermometer was placed a solution of 20 g **10** in 424 ml of 90% aqueous acetic acid. The flask was immersed in a ice-salt bath and a solution of 41 g of 30% hydrogen peroxide in 350 ml of 90% aqueous acetic acid was added dropwise over 1.5 h keeping the reaction temperature between -2 and $+2$ °C. After the addition the flask was kept in an refrigerator and the progress of the reaction was followed by TLC using silica gel plates and hexan : ether (1 : 1) to develop the chromatograms. When the starting material was essentially gone (about 35 h) the solution was diluted with water to a volume of 2 l and extracted with three 150 ml portions of chloroform. The combined organic layers were washed with 10% aqueous sodium bisulfite and several times with saturated aqueous sodium bicarbonate (till the evolution of CO_2 ceased). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and the solid residue crystallized from hexane: CCl_4 (4 : 1) to give 12 g (54%) of colourless **11**; m.p. 64–65 °C.

IR (CCl_4): 1 770, 1 605 cm^{-1}.

NMR (CCl_4): 0.64–1.36 (m, 4 H), 2.33 (dd, J = 17.2 Hz and 3.2 Hz, 1 H), 2.68 (dd, J = 17.2 Hz and 10.8 Hz, 1 H), 3.52–3.82 (m, 1 H), 4.47 (d, J = 6.3 Hz, 1 H), 5.29 (dd, J = 5.7 Hz and 1.8 Hz, 1 H), 5.51 (dd, J = 5.7 Hz and 1.6 Hz, 1 H).

(±)-(1 a α,2 a α,5 a α,5 b α)-Spiro[hexahydro-4H-oxireno[3,4]cyclopent[1,2—b]furan-2,1'-cyclopropan]-4-one (**2**)

Used in the reaction peracetic acid was obtained according to the literature[13] replacing ethyl acetate with CH_2Cl_2.

In a 250 ml three-necked flask equipped with magnetic stirrer, thermometer and dropping funnel was placed a solution of 3.0 g (0.02 mol) of **11** in 70 ml of hexane and 15 ml of CH_2Cl_2. The flask was immersed in an acetone-dry ice bath and 130 ml of 8% peracetic acid in CH_2Cl_2 was added dropwise over 40 min keeping the reaction temperature at -10 °C. After the addition the flask was kept in the refrigerator (at -10 °C) and the progress of the reaction was followed by TLC using silica gel plates and ethyl acetate : hexane (5 : 1). When the starting material was essentially gone (about 3 days) the mixture was poured into water and extracted 3 times with $CHCl_3$. The combined organic extracts were washed with aqueous sodium bisulfite, saturated aqueous sodium carbonate and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave 2.1 g of white crystalline product. TLC examination of the product revealed the presence of a major, more polar component (R_f = 0.36 in ethyl acetate : hexan 5 : 1) to which structure **2** was assigned, and a small amount of a less polar (R_f = 0.51) component to which the structure of the (1 a β,2 a α,5 a α,5 b β)-isomer of **2** was assigned. Crystallization of the crude product from benzene : $CHCl_3$ 4 : 1 afforded 1.9 g (58%) of pure **2**; m. p. 133–134 °C.

IR ($CHCl_3$): 1 780 cm^{-1}.

NMR ($CHCl_3$): 0.6–1.2 (m, 4 H), 2.71 (d, J = 5.9 Hz, 2 H), 3.01–3.30 (m, 2 H), 3.70 (m, 1 H), 4.37 (d, J = 7.1 Hz, 1 H).

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