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Stereoselective Synthesis of 8-Aza-9,11-ethenoprostaglandin H_1

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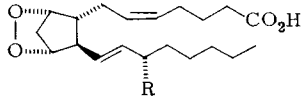
A stereoselective synthesis of the title compound [8-aza-9,11-etheno-PGH_1 (**3**)] starting from butyl 2-(*p*-tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-ene-*exo*-3-carboxylate (**5**) is described.

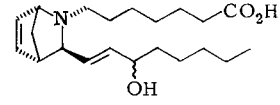
Stereoselektive Synthese von 8-Aza-9,11-ethenoprostaglandin H_1

Die stereoselektive Synthese der Titelverbindung [8-Aza-9,11-etheno-PGH_1 (**3**)] ausgehend von 2-(*p*-Tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-en-*exo*-3-carbonsäure-butylester (**5**) wird beschrieben.

The uncovering of the central role of the labile prostaglandin endoperoxides PGG_2 (**1**) and PGH_2 (**2**) in the cascade of events by which arachidonic acid is converted into prostaglandins, prostacyclin PGI_2, and thromboxanes, has been greeted with an enormous outpouring of efforts directed towards the preparation of more stable analogues[1].



1: R = OOH
2: R = OH



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These analogues have stimulated current studies concerning the complex interactions between the various physiological pathways and might permit to obtain more informations about their mechanism of action. Although some of them exhibit inhibitory action on endoperoxides, others showed agonist activity.

We report herein a stereoselective synthesis of a new analogue, 8-aza-9,11-etheno-PGH_1 (**3**), as a potential inhibitor of thromboxane synthetase and of platelet aggregation. The choice of the target compound **3** was based on the following considerations:

a) Our constant interest in the area of aza-analogues of prostaglandins[2].

b) The bicyclic moiety of PGH_2 was replaced by the stereoelectronic 2-azabicyclo-[2.2.1]hept-5-ene system.

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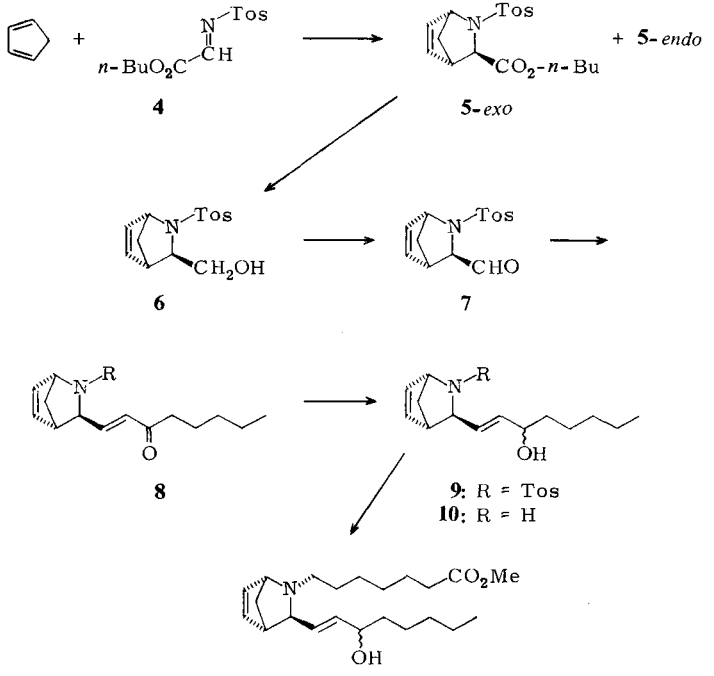
c) The peroxidic bridge was substituted for the more stable ethylene group as already experienced[3].

d) The displacement of the C-8 by a nitrogen atom was performed trying to produce an analogous response as for the similar replacement in 11-deoxy-PGE_1[4].

e) The selection of the carboxyhexyl side chain stems on the finding that a C-5 double bond seems to be the absolute requirement for aggregatory activity[5].

The starting material for our synthesis was obtained by the known[6] cycloaddition of cyclopentadiene and butyl (*p*-tolylsulfonylimino)acetate[7] (**4**) which produced a 41% yield of butyl 2-(*p*-tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**5**) as a liquid mixture of *exo* and *endo* isomers separable by column chromatography on silica gel.



The stereochemical outcome of the reaction was determined from the relative resonance signals of the proton adjacent to the carboxylate group. The NMR spectrum showed a singlet at $\delta = 3.5$ in the 5-*exo* compound and a doublet at $\delta = 4.2$ ($J = 4$ Hz) in the 5-*endo* isomer, as already reported for similar structures[8].

In order to overcome tedious chromatographic operations we have explored the possibility of obtaining the desired adduct **5**-*exo* as the sole product and we were able to secure it in 84% yield by careful choice of experimental conditions (see Experimental). The isolation of **5** as a solid indicates that it deals with the product of kinetic stereochemical preference and of minor thermodynamic stability as well.

We can rationalize the observed stereo- and regiochemistry considering that the cycloaddition step takes place between cyclopentadiene and the (*E*)-imine **4** [a mixture

of (*E*)- and (*Z*)-imine cannot be taken into account owing to the low barrier to configurational inversion[9]], and the tosyl group lowers the energy of the transition state more than the butoxycarbonyl group through non-bonding interactions.

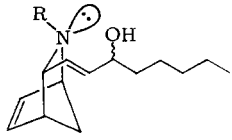
Reaction of **5**-*exo* with $LiAlH_4$ gave quantitatively the alcohol **6**, which was promptly oxidized to the formyl derivative **7** using the Moffatt reagent.

We tried unsuccessfully to effect reduction of the ester to the aldehyde group by means of diisobutylaluminium hydride, owing to the involvement of the double bond in the reductive process.

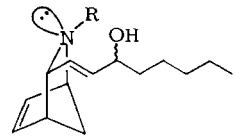
In a Wittig-Horner reaction **7** and dimethyl 2-oxoheptylphosphonate produced the enone **8** which was reduced with $NaBH_4$ to give an inseparable mixture of epimeric allylic alcohols **9**.

The attachment of the α-side chain was achieved by alkylation of **10**, in turn obtained by detosylation of **9** promoted by sodium in liquid ammonia[10], with methyl 7-iodoheptanoate, to afford **11**.

The stereochemical outcome of the alkylation step deserves some considerations, since two invertomers **A** and **B** of **11** are possible, the former being more desirable by analogy with the structures **1** and **2**.



A R = $[CH_2]_6$–CO_2Me



B

It is well known[11] that *N*-methyl-2-azabicyclo[2.2.1]hept-5-ene shows the overwhelming predominance of the invertomer having the *endo*-methyl group and the observed preference was accounted for a repulsive interaction between the *N*-methyl group and the hydrogen atom of the carbon bridge. Since such a repulsive interaction is enhanced in our model by the presence of a second alkyl substituent on the adjacent carbon, we think that the alkylation of **10** generates a product of type **A** possessing the correct stereochemistry of natural endoperoxides.

Hydrolysis of the ester group was accomplished by treatment with methanolic lithium hydroxide solution at room temperature producing **3** as a mixture of unresolved C-15 epimers.

The interesting biological profile of **3** will be published elsewhere.

Experimental

IR spectra were obtained with Perkin-Elmer 297 spectrometer. ^1H NMR spectra were recorded on Bruker WP80 spectrometer; the chemical shift values are reported with respect to internal TMS. Melting points and boiling points were uncorrected.

Butyl 2-(p-tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-ene-exo-3-carboxylate (**5**-*exo*): To an ice-cooled solution of **4**[7] (22.2 g, 78.4 mmol) in dry benzene (36 ml) was added freshly distilled and

dried ($CaCl_2$) cyclopentadiene (5.18 g, 78.5 mmol). When the exothermic reaction began to subside, the reaction mixture was left at room temperature for 12 h and was then concentrated in vacuo. The oily residue was taken up with ether (50 ml) and washed with 5% sodium hydrogen carbonate solution, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue, which solidified upon standing, was crystallized from ether/*n*-hexane (1:5) to yield 23.0 g of **5**-*exo* (84%) as a colourless solid, m. p. 53–55 °C. – IR (nujol): 1740, 1600 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.93 (3H, t, *J* = 5 Hz), 2.5 (3H, s), 3.33 (1H, m), 3.53 (1H, s), 4.13 (2H, t, *J* = 6 Hz), 6.23 (2H, m), 7.56 (4H, m).

$C_{18}H_{23}NO_4S$ (349.4) Calcd. C 61.88 H 6.64 N 4.01 Found C 61.97 H 6.59 N 3.83

2-(p-Tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-ene-3-methanol (**6**): To an ice-cooled slurry of $LiAlH_4$ (1.0 g, 2.0 mmol) in dry ether (40 ml) was added a solution of **5** (4.0 g, 11.46 mmol) in 15 ml of dry ether. After stirring for a additional 1.5 h at room temperature, the excess of reducing agent was decomposed by careful addition of water (10 ml). The organic phase was decanted and the inorganic salts were washed with ether (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallized from methanol/ether (1:3) to give 2.9 g (91%) of **6**, m. p. 113–114 °C. – IR (nujol): 3400, 1600 cm^{-1}. – ^1H-NMR ($CDCl_3$): δ = 1.6 (2H, m, *J* = 8 Hz), 2.33 (3H, s), 3.8 (2H, m), 4.53 (1H, m), 5.8 (2H, m), 7.4 (4H, m).

$C_{14}H_{17}NO_3S$ (279.3) Calcd. C 60.20 H 6.14 N 5.02 Found C 60.15 H 6.09 N 4.92

2-(p-Tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carbaldehyde (**7**): A mixture of **6** (2.9 g, 10.39 mmol), dicyclohexylcarbodiimide (6.44 g), trifluoroacetic acid (0.91 ml), pyridine (1.72 ml), DMSO (18.8 ml), and benzene (40 ml) was stirred for 3 h at room temperature. After addition of ether (67 ml), oxalic acid (2.7 g) in methanol (14 ml) was added carefully. The mixture was stirred for 15 min, filtered, and the filtrate was repeatedly washed with brine, dried ($MgSO_4$), and the solvent evaporated in vacuo to afford 2.68 g of **7** (93%), m. p. 125–126 °C (ether). – IR (nujol): 1720, 1600 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.6 (2H, m, *J* = 8 Hz), 2.33 (3H, s), 3.1 (1H, d, *J* = 3 Hz), 3.3 (1H, m), 4.66 (1H, m), 5.93 (2H, m), 7.4 (4H, m), 9.7 (1H, d, *J* = 3 Hz).

$C_{14}H_{15}NO_3S$ (277.3) Calcd. C 60.64 H 5.45 N 5.05 Found C 60.60 H 5.31 N 4.82

(1E)-1-[2-(p-Tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-en-3-yl]-1-octen-3-one (**8**): Dimethyl 2-oxoheptylphosphonate (2.68 g, 12 mmol) in dry THF (16 ml) was added to a suspension of sodium hydride (0.576 g, 50% dispersion in oil, 12 mmol) in dry THF (80 ml) at 0 °C. After the mixture was stirred for 15 min at 0 °C and 1.5 h at room temperature, aldehyde **7** (2.68 g, 9.65 mmol) in dry THF (10 ml) was added with cooling in an ice-bath, and stirring was continued for 2 h at room temperature. Water was then added to the mixture which was extracted with ether (3 × 40 ml). The ethereal solution was dried ($MgSO_4$) and concentrated in vacuo. The crude product, which slowly solidifies, was crystallized from ether/*n*-hexane (1:10) to give **8** (3.2 g, 89%), m. p. 53–55 °C. – IR (nujol): 1660, 1630, 1600 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.9 (3H, t, *J* = 5 Hz), 2.5 (3H, s), 3.06 (1H, m), 3.56 (1H, d, *J* = 6 Hz), 4.76 (1H, m), 6.0 (2H, m), 6.2 (1H, d, *J* = 16 Hz), 6.73 (1H, dd, *J* = 17 and 6 Hz), 7.56 (4H, m).

$C_{21}H_{27}NO_3S$ (373.4) Calcd. C 67.54 H 7.29 N 3.75 Found C 67.72 H 7.03 N 3.61

(1E)-1-[2-(p-Tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-en-3-yl]-1-octen-3-ol (**9**): Sodium borohydride (0.96 g, 25.3 mmol) was added in portions to an ice-cooled solution of **8** (3.2 g, 8.58 mmol) in methanol (80 ml). The mixture was stirred for 1 h, then acetone was added and most of the solvent was evaporated in vacuo. The residue was diluted with water (50 ml) and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated at reduced pressure, yielding 3.2 g of **9** as an oil mixture of inseparable epimeric alcohols. – IR (film): 3440, 1600 cm^{-1}. –

^{1}H NMR ($CDCl_3$): δ = 0.9 (3H, t, J = 5 Hz), 2.33 (3H, s), 2.86 (2H, m), 3.33 (1H, m), 4.0 (1H, m), 4.57 (1H, m), 5.63 (2H, m), 6.0 (2H, m), 7.4 (4H, m).

$C_{21}H_{29}NO_3S$ (375.45) Calcd. C 67.18 H 7.79 N 3.73 Found C 66.89 H 7.99 N 3.56

(1E)-1-(2-Azabicyclo[2.2.1]hept-5-en-3-yl)-1-octen-3-ol (**10**): To a solution of **9** (3.2 g, 8.53 mmol) in dry THF (15 ml) and liquid ammonia (300 ml) sodium (1.35 g, 58.7 mmol) was added in portions until a blue color persisted. After 30 min the mixture turned green and was maintained for 1 h at −78 °C. Solid anhydrous sodium acetate was added until the colour disappeared and the ammonia was left to evaporate at room temperature. Water (50 ml) was added and the mixture extracted with ethanol/chloroform (1 : 2.5) (3 × 35 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed to give **10** (1.62 g, 80%) as an oil. – IR (film): 3300 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.9 (3H, t, J = 4 Hz), 2.83 (2H, m), 3.1 (2H, m), 4.01 (2H, m), 5.7 (2H, m), 6.25 (2H, m).

$C_{14}H_{23}NO$ (221.3) Calcd. C 75.97 H 10.47 N 6.33 Found C 76.09 H 10.39 N 6.22

8-Aza-9,11-etheno-PGH$_1$ methyl ester (**11**): The crude alcohol **10** (1.62 g, 7.33 mmol) in methanol (10 ml) was treated with $KHCO_3$ (dry and finely powdered) (1 g) and methyl 7-iodoheptanoate (2.6 g, 9.75 mmol) and heated at 50 °C for 24 h. The solvent was evaporated, then water was added and the mixture extracted with ether. Removal of the solvent in vacuo left an oil, which was purified by treatment with 5% hydrochloric acid and subsequent precipitation with 5% sodium carbonate until pH 8. The residue, after extraction and solvent elimination, was column chromatographed (silica gel). Elution with ether/pyridine (99 : 1) afforded **11** (0.77 g, 29%). – IR (film): 3400, 1740 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 0.87 (3H, t, J = 4 Hz), 2.6 (1H, m), 3.66 (3H, s), 3.85 (1H, m), 4.08 (1H, m), 5.67 (2H, m), 6.05 (1H, m), 6.4 (1H, m).

$C_{22}H_{37}NO_3$ (363.5) Calcd. C 72.68 H 10.26 N 3.85 Found C 72.55 H 10.40 N 3.70

8-Aza-9,11-etheno-PGH$_1$ (**3**): The methyl ester **11** (0.72 g, 2.06 mmol) in methanol (100 ml) was treated at room temperature with lithium hydroxide solution (0.70 g in 30 ml of water). After 12 h stirring at ambient temperature (complete reaction by TLC: chloroform/methanol/AcOH 20 : 5 : 1, R_f = 0.4) the methanol was removed in vacuo and the residue was extracted with AcOEt. The aqueous solution, acidified to pH 5 with dilute sulfuric acid and saturated with solid NaCl, was extracted twice with chloroform. The elimination at reduced pressure of the solvent afforded a quantitative yield of **3** as an oil (0.69 g). – IR (film): 3250, 1710 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.87 (3H, t, J = 4 Hz), 2.6 (1H, m), 3.85 (1H, m), 4.08 (1H, m), 5.67 (2H, m), 6.08 (1H, m), 6.45 (1H, m), 7.7 (2H, bs).

$C_{21}H_{35}NO_3$ (349.5) Calcd. C 72.16 H 10.09 N 4.01 Found C 71.95 H 10.21 N 3.88

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