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SYNTHESES OF NEW METABOLICALLY STABILIZED TXA_2/PGH_2-RECEPTOR ANTAGONISTS AND THEIR BIOLOGICAL PROPERTIES

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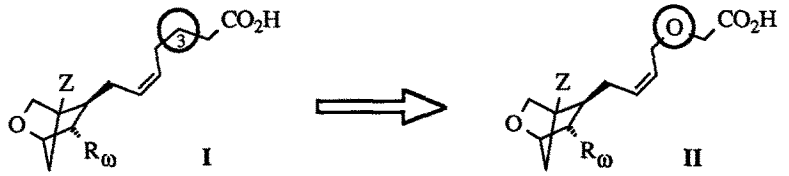
SUMMARY: To enhance the metabolic stability of our TXA_2/PGH_2-receptor antagonists derived from the 2-oxabicyclo[2.2.1]heptane skeleton of the standard agonist U 46619, a synthesis was developed to introduce a 3-oxa moiety into the α-chain. The consequence of this structural modification on receptor binding and antiaggregatory activity is discussed.

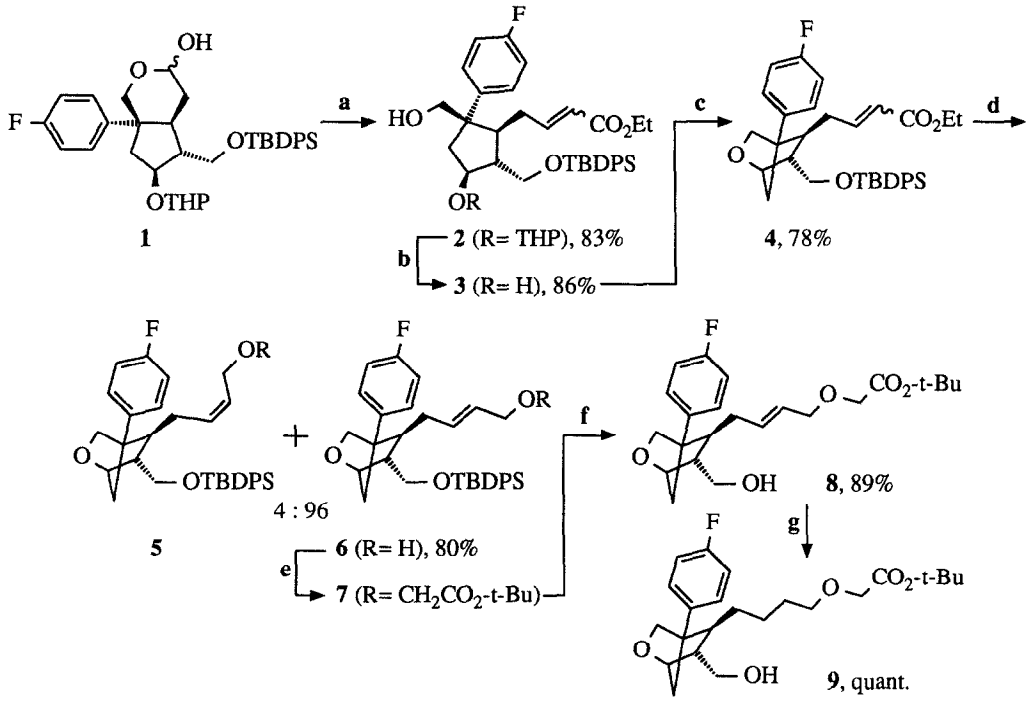
INTRODUCTION: As part of our program to evaluate metabolically stable TXA_2/PGH_2-receptor antagonists we found that the introduction of a suitable substituent Z (e.g. substituted phenyl) to the 2-oxabicyclo[2.2.1]heptane ring system of the standard TXA_2/PGH_2-agonist U 46619 in combination with different ω-chains led to very active TXA_2-antagonists[1]. Because the half-life of all prostanoids with a natural α-chain is limited due to β-oxidation[2] of the α-chain, we tried to block this metabolic pathway exchanging the methylene group at position 3 in **I** (prostaglandin numbering) by an oxygen atom (**II**)[3].



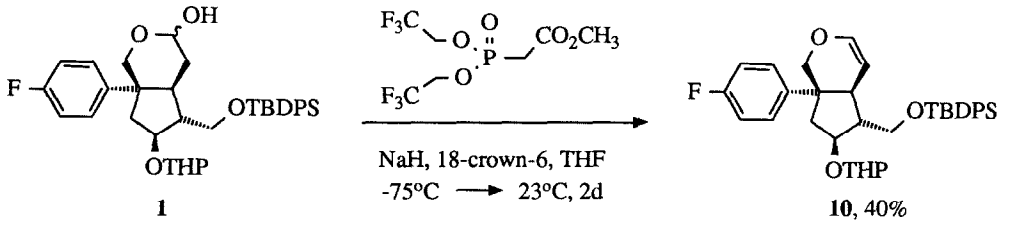
SYNTHESIS: Since the 5.6-double bond is not necessarily required for receptor binding in this structural class[1], we designed two synthetic pathways which will give access to 3-oxa-heptanoic acid as well as to 3-oxa-(5Z)-heptenoic acid derivatives. *Scheme 1* shows the route we have chosen for the first type of compounds with Z= 4-fluorophenyl, although other groups for Z were used too.

Lactol **1**, which was synthesized from (+)-Corey-lactone as described in the previous paper, was used to introduce two further carbon atoms by Wittig reaction, which proceeded with high E-selectivity as expected. After removal of the THP-protecting group, the 1,4-diol **3** was cyclized under Mitsunobu conditions to give **4** in good yield. After the mixture of esters was reduced, the double bond isomers **5** and **6** were readily separated by chromatography on silica gel. Finally the C-2 unit was introduced under phase transfer catalysis[3] to give -after removal of the silyl ether and hydrogenation of the double bond- the key intermediate **9**.

Scheme 1



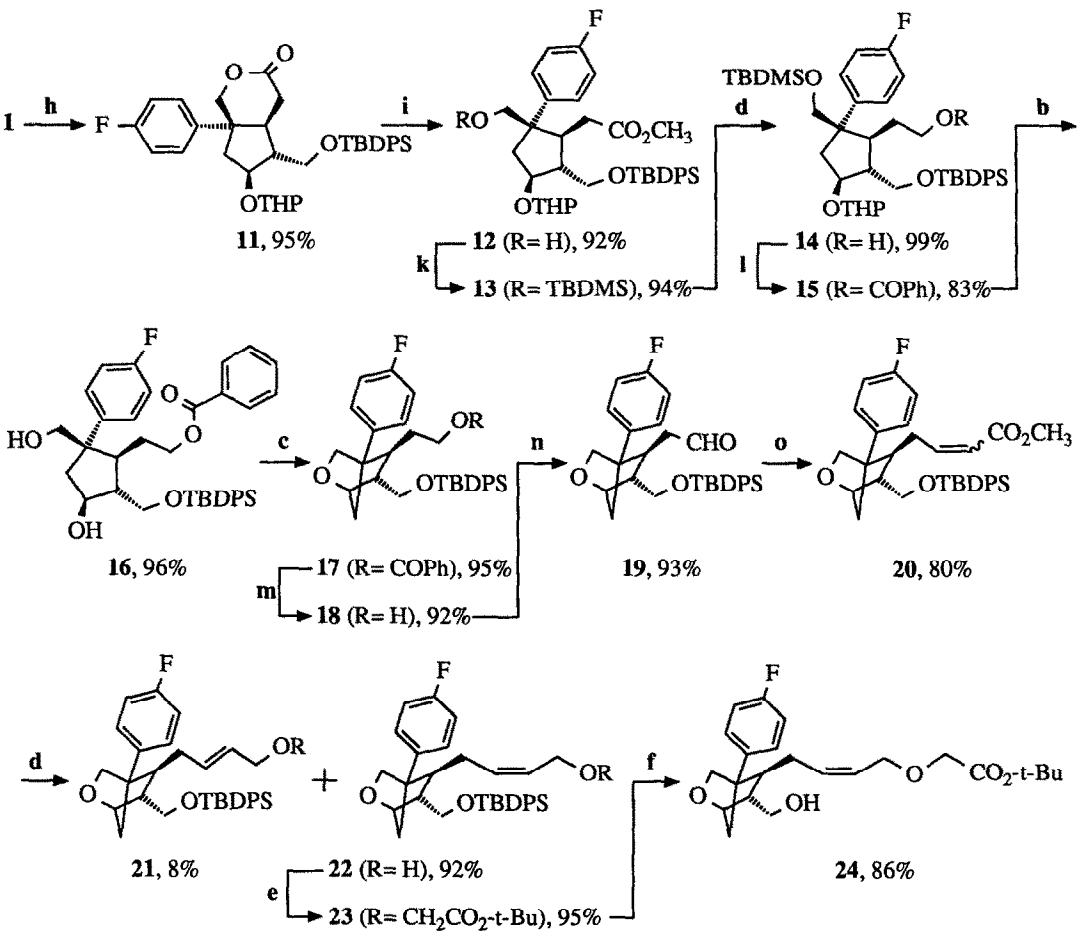
To establish the 5Z-double bond, we applied the method described by W.C. Still[4]. The lactol **1** reacted above -20°C but the only product isolated was the relatively stable enol ether **10** which had probably formed by an exchange of one of the acidic trifluoroethanol groups in the Still-phosphonate with the lactol-hydroxy group, followed by base-catalyzed elimination to the cyclic enolether **10**. Since **1** did not seem to react as ω-hydroxy aldehyde under these particular conditions, we changed our strategy to the one shown in *Scheme 2*.



Oxidation of **1**, opening of the resulting lactone **11** and immediate esterification gave the hydroxy ester **12** which cyclized to **11** by the attempt to remove the THP ether. Thus alcohol **12** was protected as t-butyldimethylsilyl (TBDMS) ether, the ester reduced and the resulting alcohol transformed into the benzoate **15**. Cleavage of the TBDMS- and THP- ether and cyclisation of diol **16** provided ether **17**. Removal of the benzoate, followed by Swern oxidation gave aldehyde **19** which cleanly reacted with the Still-phosphonate to give esters **20** as a 92:8 mixture of Z/E-isomers. Reduction and separation of the olefins

by chromatography on silica gel yielded the allylic alcohol **22** which was transformed into the key intermediate **24** as described above. Compounds **9** and **24** were used to introduce several types of ω-chains as already described in the previous paper for the synthesis of derivatives possessing natural α-chains.

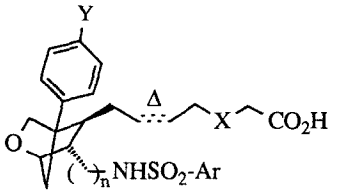
Scheme 2



CONDITIONS: a: Ph_3P=CH-CO_2Et, toluene, 80°C, 35h, argon, SiO_2; **b:** PPTs, EtOH, 55°C, 2.5h, argon, SiO_2; **c:** DEAD, Ph_3P, toluene, 50°C, 2.5h, argon, SiO_2; **d:** DIBAL, toluene, 0°C, 0.5h, argon, SiO_2; **e:** Br-CH_2CO_2-t-Bu, 50% KOH, cat. Bu_4NHSO_4, 2.5h, argon, SiO_2; **f:** Bu_4NF, THF, 23°C, 1h, argon, SiO_2; **g:** H_2, cat. Pd/C (5%), ethyl acetate, 23°C, 1 atm, 5 min; **h:** Jones-oxidation, -30°C, 3h, argon, SiO_2; **i:** 1N KOH, THF, 23°C, 16h; citric acid, 5°C, pH = 4-5; CH_2N_2, ether, argon, SiO_2; **k:** TBDMS-Cl, imidazole, DMF, 23°C, 3h, argon, SiO_2; **l:** PhCOCl, pyridine, 23°C, 3h, argon, SiO_2; **m:** 5% LiOH, MeOH, 23°C, 16h, argon, SiO_2; **n:** Swern-oxidation; **o:** $(F_3CCH_2O)_2P(=O)CH_2CO_2CH_3$, 18-crown-6, NaHMDS, -60°C, 3h, argon, SiO_2.

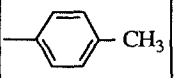
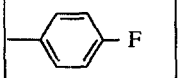
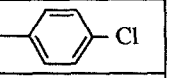
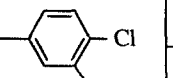
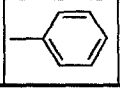
RESULTS AND DISCUSSION: The biological data of some derivatives with sulfonamides as ω-chains are given in *Table 1*. In general, the receptor affinity as well as the ability to inhibit the aggregation of human platelet rich plasma induced by the standard TXA_2/PGH_2-receptor agonist U 46619 will not be influenced significantly if the methylene group at position 3 is exchanged by an oxygen atom ($X=CH_2 \Rightarrow X=O$). Furthermore, in the presence of a 3-oxa moiety, a double bond at position 5 is not required as was already demonstrated for derivatives with a natural or shortened α-chain[1]. A pronounced increase in receptor binding and potency is observed, if a sulfonamide is separated by one methylene group from the bicyclic ring system (compare entries 01↔04, 03↔05 and 06↔08, respectively). A fluorine atom as substituent Y is more suitable than a phenyl group.

Table 1



*The TXA_2/PGH_2-receptor affinities are given as competition factor $C_F=(ID_{50}\text{-test})/(ID_{50}\text{-standard})$ with SQ 29548 used as standard TXA_2/PGH_2-receptor antagonist; np means not parallel.

**The potency refers to the inhibition of aggregation of human platelet rich plasma induced by 10^{-6}M U 46619, the standard TXA_2/PGH_2-receptor agonist. (SQ 29548: $IC_{50}=2\cdot10^{-8}$M)

Entry	X	Δ	n	-Ar	-Y	C_F* (TXA_2)	potency** relative to SQ 29548
01	CH_2	Z	0			45	0.001
02	O	Z	0			170np	0.003
03	O	sat.	0			27	0.003
04	CH_2	Z	1			0.4	0.01
05	O	sat.	1			0.4	0.03
06	CH_2	Z	0			120	0.0004
07	O	Z	0			400np	0.003
08	CH_2	Z	1			0.3	0.03
09	O	sat.	1			0.5	0.08
10	CH_2	Z	1			0.2np	0.01
11	O	sat.	1			0.1	0.08
12	CH_2	Z	1			0.5	0.01
13	O	sat.	1			0.4	0.08
14	CH_2	Z	1			4.2	0.01
15	CH_2	sat.	1			12	0.01
16	O	sat.	1			3.0	0.03

ACKNOWLEDGMENT: We thank Drs. K.-H. Thierauch and P. Verhallen for the biological data.

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1) Deicke P., Klar U. *this journal, previous paper.*

2) a) Samuelsson B. *Adv. Prostaglandin Thromboxane Res.* 1976, *1*, 1; b) Green K., Hamberg M., Samuelsson B. *Adv. Prostaglandin Thromboxane Res.* 1976, *1*, 47.

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4) Still W.C., Gennari C. *Tetrahedron Lett.* 1983, *24*, 4405.