Synthesis of Potential Thromboxane A_2 Antagonists based on the Azabicyclo[2.2.1]heptane Skeleton

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Véronique Perrin, Véronique Riveron, Christel Traversa, Geneviève Balme and Jacques Goré*

Laboratoire de Chimie Organique I, associé au CNRS, Université Claude Bernard, CPE-Lyon, 43 Bd. du 11 Novembre 1918, 69622 Villeurbanne, France

Thirteen compounds having a 2-aza- or a 7-azabicyclo[2.2.1]heptane framework substituted at the 3-position by a prostanoic chain have been synthesized from easily obtained hetero-Diels–Alder adducts; owing to their structure, a TxA_2 antagonist activity was expected for these compounds with consequences for platelets aggregation and/or blood pressure, and these effects were effectively observed for some of them but with lower activity than previously described molecules.

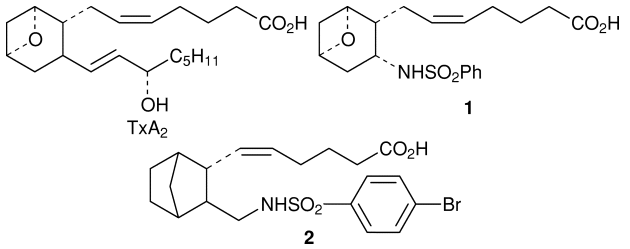
During the last two decades a considerable amount of research has been directed towards the design and the synthesis of antagonists of thromboxane A_2 (TxA_2).

The congener prostaglandin I_2 (PGI_2 or prostacyclin) is biosynthesized from prostaglandin H_2 by the action of TxA_2 synthase (the formation of PGI_2 involves PGI_2 synthase). PGI_2 and TxA_2 display opposite biological activities: PGI_2 is a blood-pressure depressor by its antiaggregative action on platelets and by its vasodilatatory effect, TxA_2 promotes the increase of this pressure being an inducer of human platelet aggregation and a vasoconstrictor agent. A pathological disequilibrium of the effects of the two enzymes in favour of TxA_2 synthase is responsible for cardiovascular, respiratory and renal diseases.

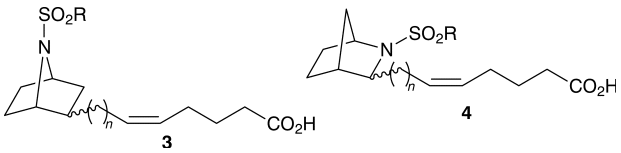
Consequently, initial efforts were devoted to the synthesis of inhibitors of TxA_2 synthase, but they failed owing to the increase of PGH_2 level and to the weak affinity of this last compound for TxA_2 receptors. Then, the only solution lay in the discovery and development of specific TxA_2 receptor antagonists: many compounds were described (for an extensive review, see ref. 3); several of these antagonists have a prostanoid-based structure while others are completely different.

Comparison of the prostanoid-based antagonists reveals some common points: (i) the majority of them have a bridged bicyclic framework: pinane, bornane, 7-oxanorbornane. (ii) The α-chain of prostaglandins is retained, but it can be slightly modified by the number of carbon atoms or by the location of the *Z* double bond. (iii) The presence of the β-chain of prostaglandins induces agonist properties. Consequently it is generally replaced by substituents having an hetero atom (O, S but more often N) directly attached to the bicyclic framework or to a vicinal carbon.

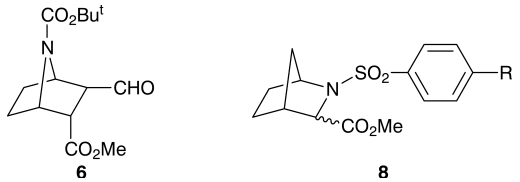
For example, compounds such as **1** and **2** (NT-126) are representative of this family of TxA_2 antagonists.



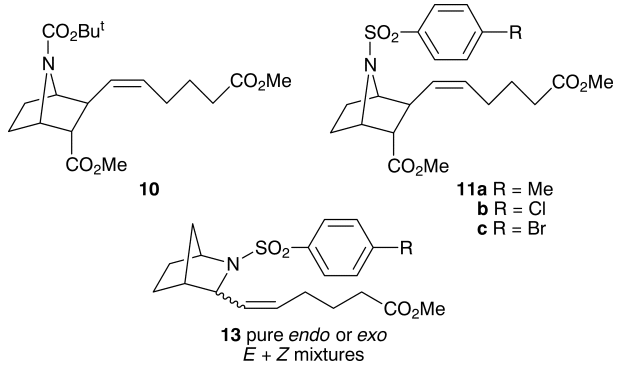
As a consequence of our interest in the chemistry of 2-aza- and 7-azabicyclo[2.2.1]heptane derivatives,[4] we became interested in the preparation of **3** and **4**, potential TxA_2 antagonists, having the nitrogen in the bicyclic system. We describe in this paper compounds where the α-chain of prostaglandins is, as in **2**, elided by one carbon atom ($n = 0$).



The starting materials for these syntheses are either **6**, previously prepared[6] from the Diels–Alder adduct of *N*-carboxy-*tert*-butylpyrrole with dimethyl acetylene dicarboxylate or **8** (**a**, R = H; **b**, R = Me; **c**, R = Cl; **d**, R = Br; **e**, R = I?) produced by a two-step sequence from the cyclopentadiene adduct of the methylglyoxylate benzylimine.

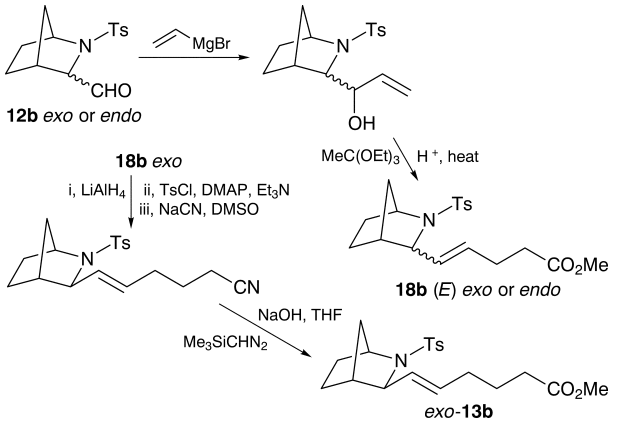


As this last adduct was a 2:1 mixture of *endo* and *exo* isomers that were easily separated by flash-chromatography, it was possible to obtain **8a**–**d** in both diastereomeric series. All these compounds were transformed into the aldehydes **12a**–**e**, *endo* or *exo* (only *exo* for **12e**). A Wittig reaction carried out on **6** and **12** using the ylid formed from (4-carboxybutyl)phosphonium bromide (NaH–DMSO) followed by esterification ($N_2CHSiMe_3$) led, respectively, to **10** (52%; $Z > 98\%$) and **13** (32–79%; Z/E 65/35 to 80/20). In this last series (8 compounds), the stereoselectivity of the Wittig reaction is modest, the two stereoisomers being difficult to separate by HPLC (done only in one case). However, the same reaction is completely stereoselective in the case of **6**; it was followed by deprotection of the nitrogen and sulfonylation with the appropriate sulfonyl chloride, leading to **11a**–**c**.



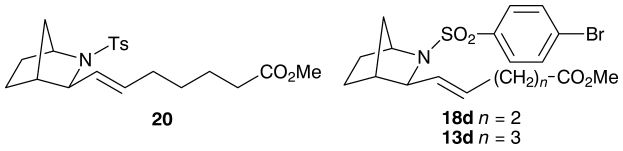
*To receive any correspondence.

Compounds **13** were submitted to biological tests as $E + Z$ mixtures; to determine the possible influence of the double bond configuration on the bio-activity, *exo*-**13b** was prepared in pure E form by using a sequence in which the key step is a Claisen–Johnson transposition.[12]



The Claisen–Johnson transposition was also performed in the *endo* series, giving *endo*-**18b**. Compared with **13b**, **18b** can give information in biological tests of the influence of the chain length between the unsaturation and the carboxymethyl. For the same reason **20** was prepared from *exo*-**18b** by LAH reduction, mesylation, reaction of methyl sodiomalonate with the mesylate and lastly decarboxymethylation (65% overall).

The last compounds of the series, namely **18d** and **13d**, were prepared by the same sequences, starting from **12d**, and were to test the influence of the sulfonamide group.



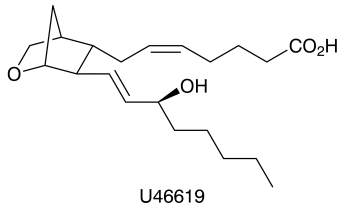
Having produced 13 azaprostanoids that were potential antagonists of TxA_2, differing in the azabicyclic framework, the carbon number of the lateral chain or by the configuration of the double bond, it was possible to submit them to biological tests after saponification of the ester by aqueous NaOH.

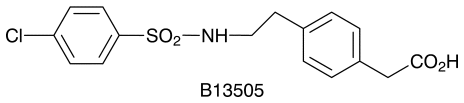
In vitro Activity. The effect of the synthesized products on the aggregating response of Guinea pig platelets induced by U46619 and arachidinic acid was determinated by the usual techniques.[13] Generally, the majority of the products proved to be inactive as antiaggregant, with some exceptions: **13c** and **13d** (*endo*) have a significant effect on the aggregation induced by arachidionic acid with a CI_{50} of the order of 12 μM. However, this effect is considerably smaller than that of BM13505, one of the most powerful TxA_2 antagonists previously described[3] and used as reference in the present study ($CI_{50} = 50$ nM). In addition, **13c,d**, as well as *exo*-**12b**, have a weak effect when U46619 was used as aggregative agent.

With both U46619 and arachidonic acid, *exo*-**13c** appeared to be the most interesting with respective an antiaggregative effect, 69 and 65% respectively at 10 μM. However, this activity was no longer observed in an *ex vivo* test, *i.e.* the administration of an oral dose of *exo*-**13c** to a living Guinea pig followed, 1 h later, by measurement of the cut-off blood of the aggregative effect of U46619. This proved that **13c** is probably transformed in the digestive system of the animal.

In vivo Activity. The tests were made by measurement of the blood pressure of conscious rats treated at regular time intervals with 10 μg kg^{-1} of the agonist U46619 (this dose increased the systolic pressure by about 30 mmHg).[14]

As in the *in vitro* tests, the majority of the products proved to be inactive or slightly active, with the only exception of **13d** (*exo* and *endo*; $Z + E$ mixtures) which exert a complete inhibition of U46619 during more than 4 h at 50 mg kg^{-1}. This activity shows that both diastereomers are probably TxA_2 antagonists but again their effect is far smaller than that of known and powerful antagonists such as BM13505.





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Techniques used: IR, ^{1}H and ^{13}C NMR, GC-MS

References: 14

Table 1: Yield and stereoselectivity of **13** from **12**

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