SHORT PAPER

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2-Aza [2,2,1] bicyclo heptane derivatives: ring expansion, fragmentation and synthesis of a potential TxA_2 antagonist†

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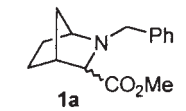
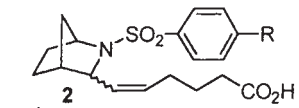
The synthesis of N-tosyl 2-aza [2,2,1] bicycloheptane substituted in 3-position by the α-chain of prostaglandins is described. This synthesis allowed the observation of two valuable transformations of the bicyclic framework : a ring expansion to a 2-aza [3,2,1] bicyclooctane derivative and a fragmentation to *cis*-1,3 disubstituted cyclopentyl amines.

We have previously reported our results concerning the search for new TxA_2 antagonists which can be useful for the treatment of cardiovascular diseases.[1]

Based on some structural common points of known TxA_2 antagonist[2], we have prepared from **1a** resulting from the hydrogenation of the cyclopentadiene adduct of the methylglyoxylate benzylimine[3], prostanoids of type **2** in both diastereomeric *exo* and *endo* series, as E + Z mixtures or as pure compounds[1].



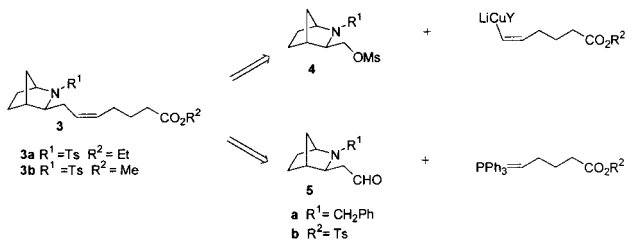
1a
endo or *exo*



2
endo or *exo*

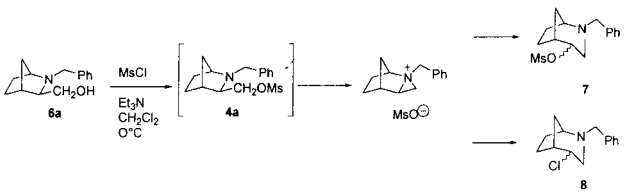
Some of these compounds have displayed the expected biological activity, being inhibitors of the aggregation of platelets (*in vitro*) and/or being able to decrease the blood pressure of conscious rats (*in vitro* tests) but their effects were notably smaller than those of previously described TxA_2 antagonists. Also, it was difficult to rely the bio-activity with the structural characteristics of **2** and generally *endo* and *exo* isomers as well as Z and E configuration gave similar responses. The only effect was that of the nature of R with a moderate increase of the activity of the halogenated compounds referred to the tosyl group. Our last attempt in order to try to reach the expected bio-activity was to obtain the homolog of **2** having the normal α-chain of prostaglandins. Two ways were explored in order to prepare **3**: the coupling of a mesylate **4** with a vinylic cuprate and the Wittig reaction of the aldehyde **5** (Scheme 1).

The first one required the preparation of the mesylate **4a** from the corresponding alcohol **6a** easily obtained from **1a** *exo*[1]. The mesylation of **6a** gave quantitatively a mixture of



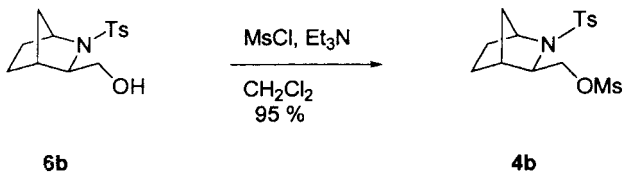
Scheme 1

rearranged products : the mesylate **7** (85%) and the chloride **8** (15%). Both products are stereochemically pure as judged by ^1H and ^{13}C NMR spectra but their exact structures were difficult to determinate unambiguously. This ring expansion is probably the consequence of a participation of the nitrogen atom giving an aziridinium intermediate, preferentially attacked at the more substituted carbon (Scheme 2).[4]



Scheme 2

On the contrary, the alcohol **6b**[1] gives the expected mesylate **4b** showing that the presence of an electron withdrawing group on the nitrogen disfavoured the rearrangement.



6b **4b**

Scheme 3

Unfortunately, the coupling of **4b** with the appropriate cuprates (lithium homocuprate, cyanocuprate and high-order cuprate), proved to be unrealisable in spite of numerous attempts giving degradation products or the starting material.

Consequently, we studied the Wittig reaction depicted in Scheme 1 which needs the preparation of the aldehyde **5a – b** starting from **1a** *exo* or from its homolog **1b**[1].

The conversion of the aldehyde **1b** to the aldehyde **9** was done by (i) reduction with LAH (93%) and (ii) Swern oxidation[5] (94%). The Wittig reaction of **9** with the ylid formed from methoxymethyl triphenylphosphonium chloride gave without problem the enol ester **10**. In place of the expected aldehyde **5b**, the acidic hydrolysis of **10** led exclusively to the fragmentation product **11b** (Scheme 4), the best yield (81%), being obtained by using aqueous formic acid ($ISiMe_3$ in dry-conditions gives the same result but with a 33% yield) (Scheme 4).

Again **11b** is stereochemically pure as proved by ^1H and ^{13}C NMR spectra, the 1,3-*cis* relationship of the substituents being highly probable.

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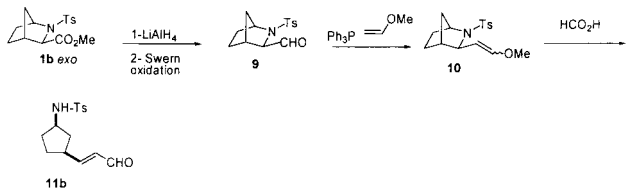
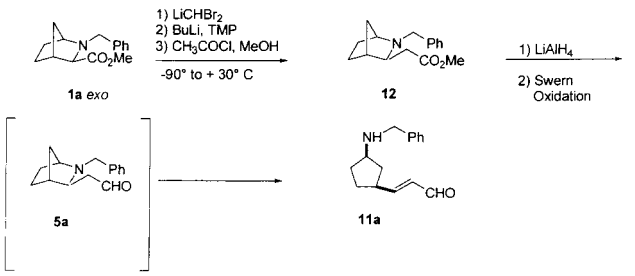
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



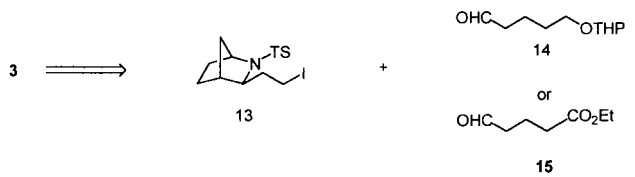
Scheme 4

Another sequence was followed in order to prepare the aldehyde **5a** (Scheme 5) with the aim that the replacement of the N-tosyl group by a N-benzyl group will disfavor this fragmentation. The ester **1a** *exo* was first homologated to **12** by the method of Kowalski *et al.*[6] with a 55% yield (the reaction does not work with **1b**), **12** being then reduced by LAH in standard conditions (yield : 70%). The Swern oxidation of the intermediate alcohol led to the expected aldehyde **5a** which rapidly isomerized to the fragmentation product **11a**.



Scheme 5

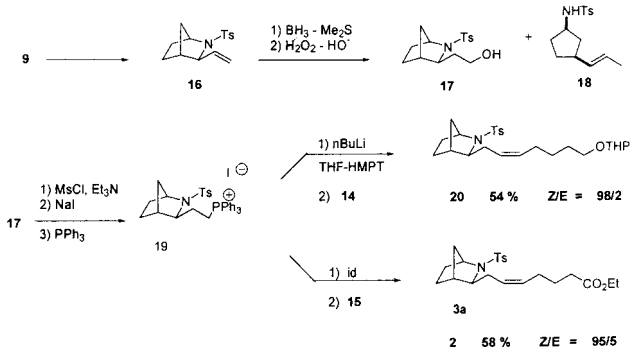
In spite of its interest for the preparation of valuable compounds, this fragmentation suppresses the possibility of obtaining **3** by the Wittig reaction of Scheme 1. However, **3** could also be prepared by a Wittig reaction between the ylid derived from iodide **13** and either the aldehyde **14**[7] or 4-formyl ethyl butonoate **15**[8].



The iodide **13** was prepared starting from **9** by the sequence depicted in Scheme 6. A Wittig reaction between **9** and the instant ylid[9] of methyltriphenyl phosphonium bromide gives **16** with a 90% yield; hydroboration-oxidation of **16** leads to the alcohol **17** (62%) accompanied by 30% of a rearranged product **18** probably formed by an intramolecular hydride transfer.[10] After flash chromatographic purification, **17** is transformed to the iodide **13** by (i) mesylation (quantitative yield) (ii) reaction of the mesylate with sodium iodide in acetone (yield : 90%). Lastly, **13** is quantitatively transformed to the phosphonium salt **19** by reacting triphenylphosphine in refluxing aceonitrile.

The two Wittig reactions gave effectively the expected products with acceptable yields and high stereoselectivity. Compound **20** can be easily converted to the methyl ester **3b** by deprotection (Amberlyst IR 120-MeOH) followed by Jones oxidation and esterification using silydiazomethane.[1]

The target molecules **3a – b** were easily purified by flash chromatography and identified by usual analytical methods.



Scheme 6

Their saponification leads to the corresponding sodium carboxylate used in the *in vivo* tests[11] while the acid was used in the *in vitro* tests[12] after acidification and dissolution in physiological serum. The synthesized product had no activity on the aggregating response of guinea pig platelets induced by either U 46619 or arachidonic acid. It had also no effect on the blood pressure of conscious rats treated by the agonist U 46619. In this aza-2 series, it seems that the presence of the normal α-chain of prostaglandins is less effective for biological activity than that of the shortest chain of compounds of type **2**. Consequently, the work presently described completes our previous one[1] and shows that the 2-aza bicyclo [2,2,1] heptane does not bring significant progress in the search for new TxA_2 antagonists. Nevertheless, the described rearrangement and fragmentation of the bicyclic framework can be the source of potentially valuable amines.

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