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THE SYNTHESIS OF POTENT THROMBOXANE A_2/ PROSTAGLANDIN ENDOPEROXIDE RECEPTOR ANTAGONIST

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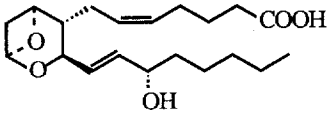
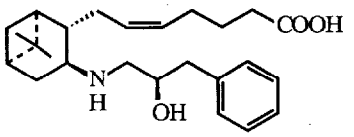
SUMMARY: *A design of new and most potent thromboxane A_2/prostaglandin endoperoxide antagonist is reported.*

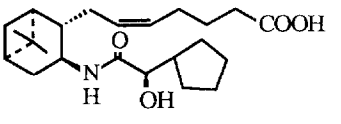
In diseases such as angina pectoris and thrombosis, thromboxane A_2(TXA_2) **1** plays a very important role.[1] We have been working on the development of drugs to treat such diseases by synthesizing compounds which antagonize the actions of both TXA_2 and PG endoperoxide. During the course of such investigations, ONO-11120 **2**[2], ONO-3708 **3**[3], and the compound **4**[4,5,6] have proved to be particularly effective based on experimental pharmacological properties, *e. g.*, inhibition of platelet aggregation induced by STA_2[7] (TXA_2 agonist), and inhibition of smooth muscle construction



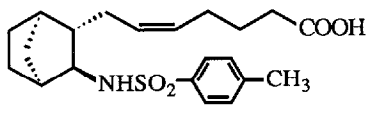
1 Thromboxane A_2



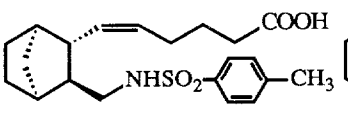
2 ONO-11120



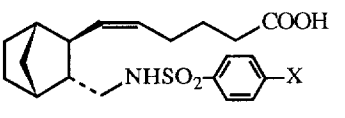
3 ONO-3708



4



5 dl form
6



7 X=CH3
8 X=Br

induced by U-46619[8] (PGH_2 agonist). In this series of compounds, the biological activity was strengthened as follows: the lower solubility of compound **2** in water was improved significantly in **3** and short duration of **3** was improved in **4**. Although now orally active compound **4** was more potent in inhibitory activity than **2** or **3**, it was unfortunately accompanied with an unfavorable property of transient and weak agonistic activity on platelets and vascular smooth muscle. In this communication we describe our efforts in the rational design and synthesis of potent TXA_2 antagonists free from the above unfavorable agonistic properties.

The structures of **5**, **6**, **7**, and **8** were designed and synthesized according to the strategies shown below.

1) relocation of the ring system
2) confirmation of preferred optical isomer
3) modification of the side chain

The biological activities of **5**, **6**, **7**, and **8** are listed in Table I and II. Relocation of the ring system of **4** by sliding toward the carboxylic acid terminal resulted in the structure **5**, which showed comparable potency to **4** even in its racemic form. Compound **4** should be a preferred optical isomer since its activity was twice as potent as that of the corresponding *dl*-mixture. Surprisingly, however, **6**, the absolute configuration of which is equivalent to **4**, was only one-tenth as potent as its enantiomeric mixture **5**, and consequently compound **7**, the enantiomeric isomer of **6**, was about 20 times more potent than **6**. This result should be interpretable only by the conformational similarity of **4** and **7**. *Based on the conformational analysis, we concluded that the ring skeleton and its structural bulkiness are not essential for the biological activity but only act to suppress the conformational mobility of the molecule.*

Further but simple modifications of the side chain by replacement of the tosyl group with a variety of benzenesulfonyl derivatives were made. Among them,

TABLE I Inhibition of Human Platelet Aggregation*

Compound	IC_{50} (M)
3	4×10^{-7}
4	7×10^{-8}
5	9×10^{-8}
6	9×10^{-7}
7	5×10^{-8}
8	9×10^{-9}

* Induced by STA_2 (10^{-6}M)

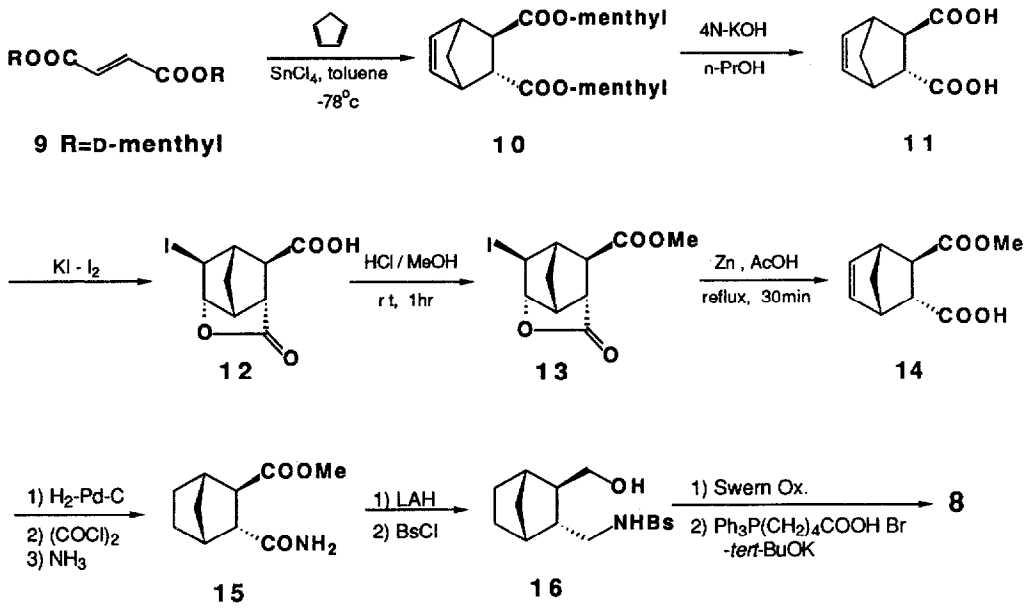
TABLE II Inhibition of Rabbit Aorta Constriction**

Compound	IC_{50} (M)
4	3×10^{-9}
7	3×10^{-9}
8	1×10^{-9}

** Induced by U-46619 (10^{-6}M)

compound **8** was proved to be effective even at the amount of 100 μg/kg by oral administration not only in inhibiting platelet aggregation (*ex vivo*), but also in inhibiting an increase in the pressor response (*in vivo*) caused by various stimulants related to TXA_2. Unfortunately, however, weak and transient agonistic activities still remain. Further work to eliminate these undesirable action is continuing and the results will be reported elsewhere.

Compound **8** was synthesized by the following reaction sequences.[9] Diels-Alder reaction of the di-D-menthyl fumarate **9** with cyclopentadiene(1 eq) in toluene in the presence of 1.2 eq stannic chloride(-78°, 1 h) followed by hydrolysis with 4N KOH (40 h, reflux) gave the di-acid **11**. Iodolactonization with KI_3 and then single recrystallization gave an optically pure iodo-lactone **12** (69% from **9**, $[\alpha]_D$ +53.3°, >99% ee). Esterification of **12** with methanol and hydrogen chloride followed by zinc-acetic acid reduction produced the half ester **14** quantitatively. After hydrogenation (Pd-C, 1 atm H_2, MeOH) of the double bond of **14**, the resulting carboxylic acid was converted to the amide **15** in 84% yield by a two step reaction sequence, *i. e.*, acid chloride formation with oxalyl chloride in methylene chloride and subsequent treatment with



gaseous ammonia. Simultaneous reduction of both amide and ester moieties in **15** with lithium aluminum hydride in THF at reflux for 3 h, followed by selective sulfonylation of amino function with *p*-bromobenzenesulfonyl chloride gave **16** (60% from **15**). The α-side chain was introduced by the following sequence. After Swern

oxidation of **16**, the resulting crude aldehyde was treated with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide in THF to afford the crude **8** (63% from **16**), which contained 9% of the (*E*)-double bond isomer. Recrystallization *via* the cyclohexylamine salt afforded, after removal of the amine, the optically pure **8**: oil, $[\alpha]_D$ +20.4° (EtOH).

Compounds **5**, **6**, and **7** were also synthesized in a similar manner from the corresponding starting materials.

References and Notes

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