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Communication

Synthesis of 1-(2-Carboxyethylbenzyl)-2-benzenesulfonamidobicyclo[2.2.1]heptane: A Novel Potent Thromboxane Antagonist

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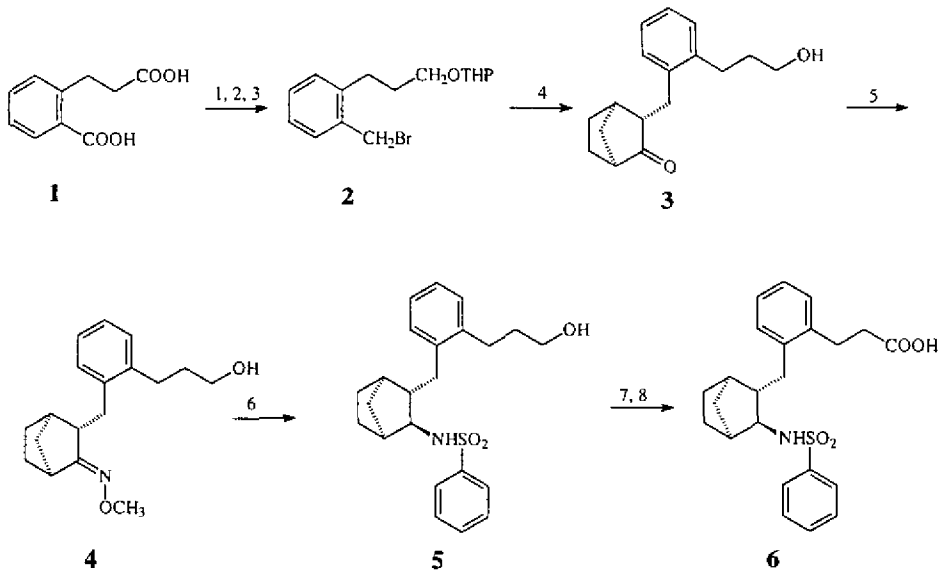
A potent thromboxane antagonist, 1-[2-(2-carboxyethyl)benzyl)]-2-benzenesulfonamidobicyclo-[2.2.1]heptane was synthesized from norcamphor in 8 steps. It was shown to be a very potent thromboxane antagonist by inhibition of platelet aggregation induced by U46,619 at nanomolar concentration. The key intermediate 3-[2-bromomethylphenyl]propyl tetrahydropyran ether may be useful for the synthesis of other interphenylene containing prostaglandin analogs.

Thromboxane A_2 (TXA_2) is produced *in vivo* from arachidonic acid through cyclooxygenase.[1] It is not only a very potent stimulator of platelet aggregation, but also an inducer of vascular and airway smooth muscle.[2] Moreover, it is also involved in many physiological and pathphysiological conditions including asthma, myocardiac infarction, coronary vasopasm and thrombosis.[3] Consequently, it attracts intensive efforts to synthesize clinically useful antagonists.[1,2] Most prostanoid TXA_2 antagonists contain a 6-carboxyhex-2-enyl upper side chain, which resembles natural prostaglandins.[1,2] However, the upper side chain undergoes β-oxidation readily *in vivo*.[4] As a result, the biological half-lives are relatively short, making them less suitable for medical use. For instance, the half-life of one of the most potent TXA_2 antagonists, S-145 is only 30 minutes in rat. In order to render the antagonist metabolically more stable while retaining its potency, the antagonist should incorporate functional groups that prevent β-oxidation. Our approach was to substitute an interphenylene in place of the ethylene group which should prevent β-oxidation of the compound. Compound **6** was synthesized to test the validity of our hypothesis.

Retrosynthetic analysis of compound **6** showed that it could be dissected into three parts: a bicyclo[2.2.1]heptane ring, an interphenylene containing the upper chain and a benzenesulfonamide. Alkylation of norcamphor with compound **2** and subsequent transformation of the ketone moiety to amine should allow the synthesis of **6** after benzenesulfonamide formation. Thus, compound **6** was prepared according to Scheme I. Synthesis of compound **2** started from the reduction of 2-carboxyphenylpropanoic acid.[5] Selective formation of the benzyl bromide in the presence of an alkyl alcohol was smoothly achieved with boron trifluoride etherate and tetraethylammonium bromide in excellent yield.[6] Direct protection of the crude benzyl bromide with dihydropyran yielded synthon **2** in 86% yield (two steps). After deprotonation of norcamphor by sodium bis(trimethylsilyl)amide in THF at -78 °C, compound **2** was added and the alkylated product **3** could be isolated in 78% yield with an acidic workup. The use of lithium diisopropylamide or potassium *tert*-butoxide resulted in a significantly lower yield. The alkylation was clearly from the less hindered side of norcamphor resulting in the 2α-isomer as the sole product. Conversion of the ketone into the corresponding amine was best achieved by a two step procedure. Methoxyoxime **4** was isolated quantitatively after refluxing with methoxyamine in *n*-BuOH overnight.[7] Although the *trans*- and *cis*-isomers of methoxyoxime could be purified by liquid chromatography they were used as a mixture in the following step without separation since both isomers yielded the same amine. Reduction of **4** with metallic sodium in refluxing *n*-PrOH resulted in the corresponding amine which was used without purification in the next step. Reaction of the amine with benzenesulfonyl chloride resulted in compound **5** in 42% yield (two steps). Direct reductive amination of ketone **4** with $NaBH_3CN$ in ammonium acetate[8] yielded no product. Other reaction sequences such as formation of oxime and reduction with $NaBH_4$-$TiCl_3$[9] resulted in little or no desired products. Other methods of oxime reduction gave inferior yields. Oxidation of **6** yielded the title product in 84% yield.[10]

Preliminary results showed that compound **6** was a very potent thromboxane antagonist. Its potency in the prevention of U46,619 (a thromboxane agonist) induced human platelet aggregation at least 10 times that of S-145 (IC_{50} = 80 nM), and the half-life of which in Wistar rat was several times longer that of S-145. The biological results will be published at a later date.

Scheme I



1. LAH in THF, reflux; 2. Et_4NBr, BF_3-Et_2O, CH_2Cl_2; 3. DHP, H^+; 4. Norcamphor pretreated with TMS_2NNa in THF; H^+; 5. CH_3ONH_2 in *n*-BuOH reflux; 6. Na, *n*-PrOH; 7. $PhSO_2Cl$, Et_3N in CH_2Cl_2; 8. Jones' oxidation

In summary, a potent and metabolically stable thromboxane antagonist was synthesized. Preliminary biological data showed that incorporation of a interphenylene group in place of ethylene in the prostanoid upper chain not only increased its metabolical stability but also increased its biological activity. The availability of compound **3** should also allow simple preparation of other interphenylene containing prostaglandin analogues by a three component coupling method.[11]

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Key Words

Thromboxane antagonists; Platelet aggregation.

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10. **7**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.87-7.91 (m, 2H), 7.44-7.56 (m, 4H), 6.94-7.15 (m, 5H), 4.75 (d, 1H, J = 6 Hz), 3.05 (d, 1H, J = 2.4 Hz), 2.75-2.80 (m, 2H), 2.50-2.59 (m, 2H), 1.91-2.39 (m, 4H), 1.31-1.50 (m, 3H), 1.22-1.28 (m, 2H), 1.05-1.14 (m, 1H). ^{13}C NMR: 20.73, 26.99, 29.86, 34.78, 37.27, 39.29, 41.44, 50.77, 61.95, 126.25, 126.39, 127.04, 128.52, 130.06, 132.42, 137.91, 138.04, 140.24, 177.31. HRMS (EI⁺MS): Found: *m/z* 413.1664, Cal. for $C_{23}H_{27}O_4NS$: M, 413.1661.
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