Synthesis of the Chiral Pair of a Novel Thromboxane Antagonist, 3-[2-(3-Benzenesulfonylamino-7-oxabicyclo[2.2.1]hept-2-yl-methyl)phenyl] Propionic Acid

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Preparation of the enantiomeric pair of 3-[2-(3-benzenesulfonylamino-7-oxabicyclo[2.2.1]hept-2-yl-methyl)phenyl] propionic acid, a novel thromboxane antagonist is reported. They are synthesized from either enantiomers of known (1R,2R,3R,4S)-3-[2-(3-carboxy-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl]-propionic acid methyl ester *via* epimerization, modified Curtius' rearrangement and sulfonylamino formation. Other derivatives may be prepared similarly.

INTRODUCTION

Platelet abnormality may result in various blood clotting disorders[1] which may be fatal. The regulation of platelet functions, especially aggregation, is related to second messengers such adenosine diphosphate and thromboxane A_2 (TXA_2).[2] These molecules generate a positive feedback mechanism leading to an irreversible platelet aggregation and thrombiformation. Of the two amplifiers, thromboxane A_2 is more potent and its effects are irreversible. Moreover, thromboxane A_2 is also related to pathophysiological conditions such as asthma, myocardial infraction, coronary spasm and many other diseases. Thromboxane antagonists may then be useful for the treatment of these diseases.

There has been continuing interest in the design and synthesis of thromboxane antagonists.[3] Most prostanoid TXA_2 antagonists contain a 6-carboxyhex-2-enyl upper side chain, which resembles natural prostaglandins. However, these prostanoids undergo β-oxidation readily in vivo.[4] Consequently, their biological half-lives are relatively short, making them less useful for clinical use. For example, S-145, one of the most potent TXA_2 antagonists has a half-life of 30 minutes only in rats. In corporation of an interphenylene group may prevent β-oxidation, resulting in compounds with better pharmacokinetic profiles.

Previously we reported the synthesis of interphenylene bicyclo[2.2.1]heptane derivatives which are potent thromboxane antagonists.[5,6] In the literature, 7-oxabicyclo[2.2.1]-heptane derivatives are generally more water soluble with greater potency than their bicyclo[2.2.1]heptane counterparts. Therefore, we proposed that the same rationale may be applicable to the interphenylene analogs.[7,8] Moreover, enantiomers may have different pharmacologies.[9] As a result, we planned to synthesize both enantiomers of 3-[2-(3-benzenesulfonylamino-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl]-propionic acid **9** and **9'**. The availability of this enantiomeric pair should allow us to study their pharmacological properties.

Previously, bicyclo[2.2.1]heptane derivatives were synthesized by alkylation of norcamphor and subsequent functional group transformation of the ketone to benzensulfonamide as reported (Fig. 1).[6] Enantiomerically selective synthesis of these compounds may use either (+)-norcamphor or (-)-norcamphor as starting materials. However, the same rationale is not applicable to the 7-oxabicyclo[2.2.1]heptane derivatives. Alkylation of 7-oxabicyclo[2.2.1]heptanone is not stereospecific; both α- and β-alkylation products were obtained (data not shown). Moreover, these regio stereoisomers were also difficult to separate.

Thus, an alternative synthetic approach was sought. In this article we report the synthesis of **1** using the known (1R,2S,3R,4S)-3-[2-(3-carboxy-7-oxabicyclo[2.2.1]hept-2-yl-methyl)phenyl]propionic acid methyl ester as the starting material.[10] By epimerization of the 3-carboxylic acid, Curtius' rearrangement and subsequent sulfonylamino formation should afford the desirable target compound **9**. Although the synthesis of **1'** has not been reported, it can be prepared similarly. Thus **9'** can also be synthesized using a similar syn-

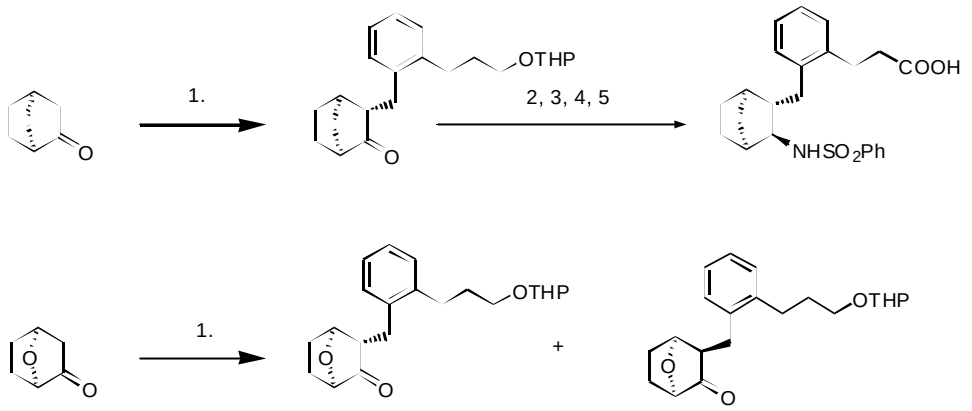

Fig. 1. Com par i son of alkylation of norcamphor and 7-oxabicylo[2.2.1]heptan-2-one. 1. LDA, -78°C; o-THPO$(CH_2)_3$-$PhCH_2Br$; 2. H_2NOCH_3; 3. LAH; H^+; 4. $PHSO_2Cl$, pyridine; 5. Jones ox i da tion.

thetic scheme.

RE SULTS AND DIS CUS SION

The syn the sis of **9** started with the known, (1R,2S,3R, 4S)-3-[2-(3-carboxy-7-oxabicyclo[2.2.1]hept-2-yl-methyl)-phenyl]propionic acid methyl es ter **1**. The ori en ta tion of the 3-carboxylic acid is on the 'wrong' side of the mol e cule (*cis*-ori en ta tion). There fore, it was nec es sary to be epimerized to the *trans*-form. Since epimerization is eas ier with an al de-hyde than an acid, **1** is con verted into its cor re spond ing al de-hyde **2** by Her bert's re duc tion[11] us ing se quen tial re ac tion with bor ane-methyl sul fide com plex and PCC ox i da tion. The rea son we used bor ane-methyl sul fide com plex in stead of diborane in THF is be cause the for mer re agent is rel a tively sta ble at room tem per a ture, which is re quired in our sit u a tion. An iso lated yield of 68.1% of al de hyde **2** can be ob tained. Epimerization with di lute NaOMe in MeOH[8] at room tem per-a ture re sulted in the trans-aldehyde in quan ti ta tive yield. The re ac tion was mon i tored with ^{1}H-NMR spec trog ra phy. The *cis*-al de hyde has a dou blet at 9.70 ppm (J = 4.2 Hz), which slowly dis ap peared with the ap pear ance of a new dou blet at 9.60 ppm (J = 1.4 Hz).

Ox i da tion of al de hyde into carboxylic acid is sel dom mentioned in the literature. Carboxylic acids are usually formed as over-oxidative prod ucts from al co hol ox i da tion in poor to low yield. Instead we employed $KMnO_4$-crown ether[12,13,14] as the ox i diz ing agent and ob tained epimerized carboxylic acid **3** in 64%, in which the crown ether serves as a host-guest com plex with K^+ to in crease the sol u bil ity of $KMnO_4$ in or ganic sol vents.

Trans for ma tion of carboxylic ac ids into amines can be done by Curtius' rearrangement. Carboxylic acid **3** was added with ethyl chloroformate, triethylamine and ac e-tone.[15,16] Af ter an hour, all start ing ma te ri als were con sumed as de tected by TLC, with the for ma tion of less po lar es ter. Aque ous NaN_3 was then added. A new product carbonyl azide **5** was formed. The to lu ene ex tract was con cen trated and refluxed for 3 hours in ac e tone. IR mon i tor ing showed a peak with strong ab sorp tion at 2268 cm^{-1}, a typ i cal ab sorp tion peak for isocyanate **6**.

Di rect hy dro ly sis of the isocyanate **6** by sul fu ric acid, fol lowed by trap ping of the amine formed with benzene sul-fonyl chlo ride in ba sic con di tion af fords less than 10% yield of the de sir able prod uct. There fore, a dif fer ent ap proach was sought. The in ter me di ate was trapped as tert-butoxy car-bamate 7 in stead. Thus the unpurified isocyanate **6** was dis-solved in tert-butanol and refluxed un til the 2268 cm^{-1} IR ab-sorp tion dis ap peared and a 3450 cm^{-1} peak emerged, show ing carbamate **7** for ma tion. Di lute HCl was added to the mix ture and stirred over night with the for ma tion of the am mo nium chlo ride salt **8** at 54% yield. In the pro cess, the methyl es ter was also being hydrolyzed. Benzenesulfonamide **9** was formed after reaction with benzenesulfonyl chloride in pyridine. The chiral part ner (1S,2S,3S,4R)-3-[2-(3-benzene-sulfonylamino-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl] propionic acid **9'** was syn the sized sim i larly.

The syn thetic scheme al lows the prep a ra tion of var i ous 7-oxabicyclo[2.2.1]heptane de riv a tives for the study of their structure and activity relationships. Preliminary studies showed that both (1R,2R,3R,4S)-3-[2-(3-benzene sul fonyl-amino-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl]propionic acid **9** and (1S,2S,3S,4R)-3-[2-(3-benzenesulfonyl-amino-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl]propionic acid **9'** pro cess in ter est ing but dif fer ent phar ma co log i cal prop er-

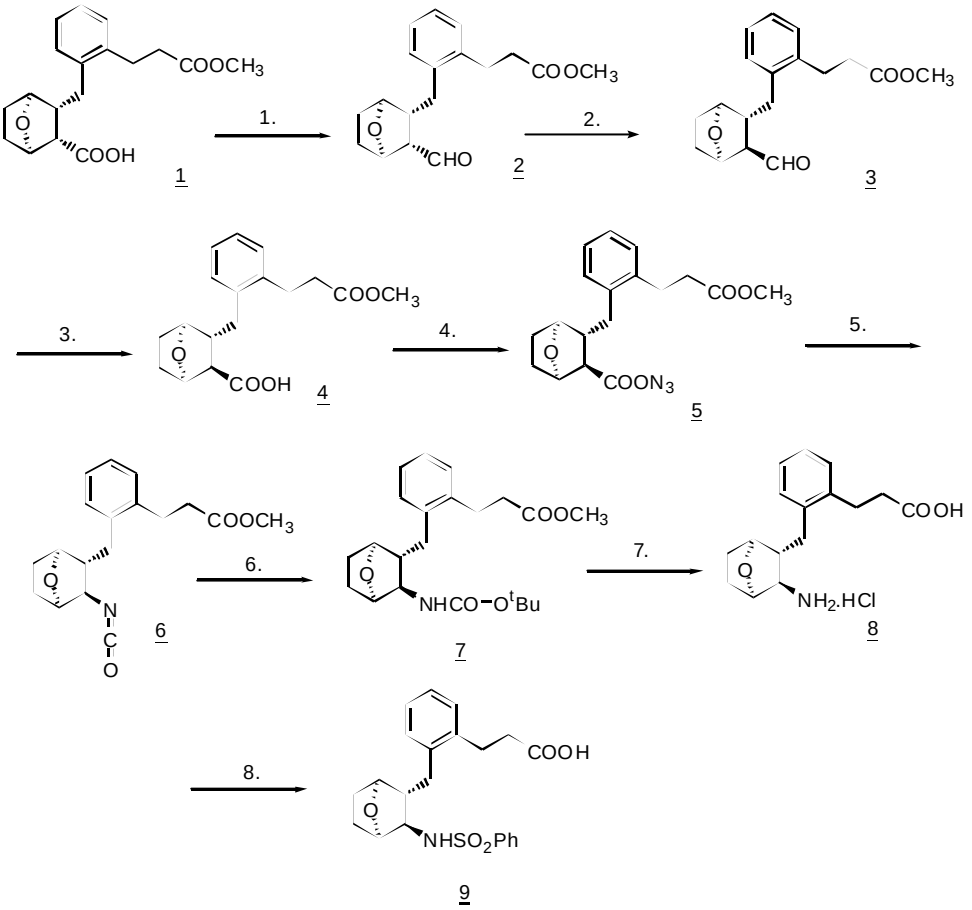

Fig. 2. Synthesis of (1R,2R,3R,4S)-3-[2-(3-benzenesulfonylamino-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl]propionic acid. 1. $BH_3 \cdot Me_2S$; 2. NaOMe; 3. $KMnO_4$, 18-crown-6; 4. ClCOOEt, Et_3N; NaN_3; 5. Toluene, Δ; 6. tBuOH, Δ; 7. 5% HCl; 8. $PhSO_2Cl$, Et_3N.

ties. Compound **9** prevents U46, 619, a potent thromboxane agonist induced rat aorta ring contraction at nanomolar concentration while it also inhibits human platelet aggregation induced by the same agonist. On the other hand, compound **9'** was far less potent than its enantiomer. Their pharmacological studies will be reported in due course. Efforts will also be made in synthesizing more potent antagonists based on the same chemistry. Epimerization of the 3-carboxylic acid exemplifies a mild and practical method for such a conversion. It may also be applicable in other similar transformations.

EXPERIMENTAL

Melting points were determined on a Fargo MP-ID hot-stage apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-1010 digital polarimeter. Proton NMR spectra were recorded at 200 MHz on a Varian Mercury-200 NMR spectrometer. Carbon NMR spectra were recorded at 50 MHz on a Varian Mercury-200 NMR spectrometer. Proton and carbon chemical shifts are reported on the delta scale as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal reference. Mass spectra were measured with a VG Analytical Model 70-250s Mass Spectrometer. Infrared (IR) Spectra were recorded on a Perkin Elmer Paragon 500 IR Spectrometer. All reagents were used as obtained commercially.

Synthesis of (1R,2S,3R,4S)-3-[2-(3-formyl-7-oxabicyclo-[2,2,1]hept-2-yl-methyl)phenyl]propionic acid methyl ester 2

Carboxylic acid **1** (5.75 g, 18.10 mmol) was dissolved in 50 mL of anhydrous THF. At room temperature and under an argon atmosphere, borane-methyl sulfide complex (1.75 mL, 18.10 mmol) was added dropwise. After stirring for 2 hours, 50 mL of ice-water was added into the reaction mix-

ture cau tiously. The so lu tion was ex tracted with ethyl ac e tate (50 mL × 4). The com bined or ganic layer was washed with sat u rated brine and dried with an hy drous Na_2SO_4. Af ter fil tra tion and evap o ra tion, an oily res i due was ob tained.

Un der ar gon at mo sphere at room tem per a ture, the oily res i due was dis solved in 35 mL of di chloro methane. The re ac tion flask was placed into an ice bath. Af ter 10 min utes, PCC (7.37 g, 34.02 mmol) was added. It was al lowed to stir for an other 10 min utes be fore the ice bath was re moved. Af ter the re ac tion mix ture was stirred at room tem per a ture for one and a half hours, it was fil tered through a pad of Celite. The fil trate was con cen trated and the prod uct was pu ri fied with sil ica gel chro ma tog ra phy (EtOAc:n-Hexane = 1:2). The al de hyde **2** 3.72 g (72.1% yield) of was ob tained as an oil, $[\alpha]_D^{25}$ +24.1° (c 1.0, CH_2Cl_2); IR ν (CH_2Cl_2) cm^{-1}: 2998, 2955, 1734, 1718, 1438, 1268, 1246, 1201, 1175; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 9.70 (1H, d, *J* = 4.2 Hz), 7.18 (4H, s), 4.86 (1H, d, *J* = 4.4 Hz), 4.36 (1H, d, *J* = 4.4 Hz), 3.68 (3H, s), 2.96 (2H, dd, *J* = 8.0 Hz, 7.4 Hz), 2.71~2.55 (6H, m), 1.82~1.40 (4H, m); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 203.0, 173.1, 138.5, 137.9, 129.5, 129.0, 126.8, 78.3, 77.5, 58.8, 51.7, 49.1, 34.8, 32.2, 29.5, 28.9, 27.4; MS, *m/e* (rel a tive in ten sity %): 302 (M^+, 4), 284 (26), 266 (14), 240 (17), 177 (24), 159 (30), 141 (31), 129 (51), 117 (100), 115 (55), 105 (41), 91 (52), 81 (49), 77 (21), 55 (14); HRMS Calcd for $C_{18}H_{22}O_4$: 302.15181. Found: 302.15190.

Synthesis of (1S,2R,3S,4R)-3-[2-(3-formyl-7-oxabicyclo-[2,2,1]hept-2-yl-methyl)phenyl]propionic acid methyl ester 2′

Sim i larly, al de hyde **2′** was ob tained from **1′** in 60% yield as a light yel low ish oil. $[\alpha]_D^{25}$ -23.8° (c 1.0, CH_2Cl_2).[17]

Synthesis of (1R,2R,3R,4S)-3-[2-(3-formyl-7-oxabicyclo-[2,2,1]hept-2-yl-methyl)phenyl]propionic acid methyl ester 3

Al de hyde **2** (0.05 g, 0.166 mmol) was dis solved in 1 mL of an hy drous MeOH. The mix ture was placed un der an ar gon at mo sphere and the re ac tion flask was placed into an ice bath. It was stirred for 10 minutes before $NaOCH_3$ (0.0037 g; 0.0068 M in MeOH) was added. The ice bath was re moved af ter 10 min utes of stir ring. The mix ture was al lowed to warm to am bi ent tem per a ture and re acted for 3 hours. One mL of sat u rated am mo nium chlo ride so lu tion was added, and the mix ture was ex tracted with EtOAc (2.0 mL × 3). The com bined or ganic lay ers were washed with sat u rated brine and dried with an hy drous Na_2SO_4. Af ter fil tra tion and evap o ra tion, 0.05 g of the al de hyde was ob tained. (Quan.), $[\alpha]_D^{26}$ +8.0° (c 1.0, CH_2Cl_2); IR ν (CH_2Cl_2) cm^{-1}: 2996, 2955, 1733, 1720, 1438, 1293, 1201, 1176; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 9.60 (1H, d, *J* = 1.4 Hz), 7.16 (4H, s), 4.88 (1H, t, *J* = 4.4 Hz), 3.68 (3H, s), 3.00 (2H, dd, *J* = 8.4 Hz, 7.0 Hz), 2.86~2.47 (6H, m), 1.79~1.40 (4H, m); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 200.5, 173.2, 138.6, 137.2, 129.7, 128.9, 126.7, 126.5, 80.9, 77.1, 62.8, 51.6, 45.0, 37.0, 35.0, 29.2, 27.5, 26.1; MS, *m/e* (rel a tive in ten sity %): 302 (M^+, 4), 284 (24), 277 (24), 275 (24), 187 (29), 177 (29), 157 (44), 143 (34), 129 (49), 117 (100), 115 (51), 105 (49), 91 (60), 81 (55), 77 (47), 65 (20), 55 (19); HRMS Calcd for $C_{18}H_{22}O_4$: 302.15181. Found: 302.15181.

Synthesis of (1S,2S,3S,4R)-3-[2-(3-formyl-7-oxabicyclo-[2,2,1]hept-2-yl-methyl)phenyl]propionic acid methyl ester 3′

Similarly, carbaldehyde **3′** was obtained from **2′** in 91.2% yield. $[\alpha]_D^{25}$ -7.7° (c 1.0, CH_2Cl_2).[17]

Synthesis of (1R,2R,3R,4S)-3-[2-(3-carboxy-7-oxabicyclo-[2,2,1]hept-2-yl-methyl)phenyl]propionic acid methyl ester 4

Al de hyde**3** (1.16 g, 3.84 mmol) was dis solved in 30 mL of an hy drous ac e tone. Un der room tem per a ture and ar gon at mo sphere, a cat a lytic amount of 18-crown-6 was added and stirred for 10 min utes. Po tas sium per manga nate (0.67 g, 4.23 mmol) was added por tion wise over an hour. Af ter the re sulting mix ture was then stirred for an other 2 hours, it was evap o rated un der re duced pres sure. The solid was washed with hot wa ter (20 mL × 2) and was fil tered through a pad of Celite. The fil trate was washed with di chloro methane (60 mL × 1) and the aque ous layer was acid i fied with 2N HCl. Af ter extrac tion with di chloro methane (30 mL×5), the com bined organic layer was washed with sat u rated brine. The or ganic layer was then dried with an hy drous Na_2SO_4. Af ter fil tra tion and evap o ra tion, the oil res i due was pu ri fied by sil ica gel chro ma tog ra phy (EtOAc: nHexane = 1:1). A slightly yel low ish oil was ob tained in 0.78 g (63.9% yield), $[\alpha]_D^{26}$ +35.5° (c 1.0, $CHCl_3$); IR ν (CH_2Cl_2) cm^{-1}: 3490, 2998, 2955, 1735, 1710, 1422, 1274, 1176; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.65 (1H, bs), 7.17 (4H, s), 4.80 (1H, d, *J* = 5.2 Hz), 4.32 (1H, d, *J* = 3.2 Hz), 3.67 (3H, s), 3.02 (2H, dd, *J* = 8.4 Hz, 7.6 Hz), 2.80~2.40 (6H, m), 1.71~1.25 (4H, m); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 177.1, 173.4, 138.7, 137.5, 129.8, 129.0, 126.6, 126.4, 80.7, 78.0, 55.0, 51.7, 46.7, 37.3, 35.0, 29.2, 27.5, 25.9; MS, *m/e* (rel a tive in ten sity %): 318 (M^+, 16), 300 (38), 272 (26), 178 (14), 155 (25), 141 (58), 129 (51), 117 (100), 115 (65), 105 (48), 91 (60), 77 (35), 67 (21), 55 (14); HRMS

Calcd for $C_{18}H_{22}O_5$: 318.14673. Found: 318.14672.

Synthesis of (1S,2S,3S,4R)-3-[2-(3-carboxy-7-oxabicyclo-[2,2,1]hept-2-yl-methyl)phenyl]propionic acid methyl ester 4'

Carboxylic acid **4'** was obtained similarly from **3'** in 65.9% yield. $[\alpha]_D^{25}$ -35.1° (c 1.0, CH_2Cl_2).[17]

Synthesis of (1R,2R,3R,4S)-3-[2-(3-amino-7-oxabicyclo-[2,2,1]hept-2-yl-methyl)phenyl]propionic acid 8

The above carboxylic acid **4** (0.792 g, 2.49 mmol) was dissolved in 6 mL of anhydrous acetone. Under room temperature and argon atmosphere, triethylamine (0.29 mL, 2.08 mmol) was added. The reaction vessel was then placed into an ice bath. Ethyl chloroformate (0.20 mL, 2.05 mmol) was added dropwise. After stirring for 5 minutes, 0.6 mL of ice water was added cautiously. Sodium azide (0.194 g, 2.98 mmol in 1 mL of water) was added dropwise and the reaction temperature was maintained at 0°C.

To the reaction was added 5 mL of pure water and was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with saturated brine and dried with anhydrous Na_2SO_4. The organic layer was then filtered and evaporated under reduced pressure to remove the acetone. The residue to luene solution was allowed to reflux for 3 hours. After evaporation, yellowish oil **6** was obtained. IR spectroscopy confirmed it as an isocyanate (2268 cm^{-1} absorption peak).

The isocyanate **6** was dissolved in 5 mL of tert-butanol. After refluxing for 12 hours, the excessive alcohol was removed under reduced pressure. To the residue oil **7**, 25 mL of 5% HCl was added and the solution was stirred overnight. The aqueous solution was extracted with dichloromethane (20 mL × 3). The remaining aqueous solution was evaporated under vacuum. The ammonium salt **8** (0.264 g) was obtained at 54% yield, which was used in the next step without further purification, ^{1}H-NMR (d_6-MeOH, 200 MHz) δ: 7.22~7.17 (4H, m), 4.69 (1H, bs), 4.24 (1H, bs), 3.25 (1H, m), 3.01~2.57 (7H, m), 2.02~1.53 (4H, m); ^{13}C-NMR (d_6-MeOH, 50 MHz) δ: 176.8, 140.2, 138.1, 130.9, 130.2, 128.1, 127.7, 81.5, 78.5, 59.0, 50.4, 37.0, 35.9, 29.9, 28.5, 24.0.

(1S,2S,3S,4R)-3-[2-(3-amino-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl]propionic acid 8' was synthesized similarly from **4'** in 57% yield (crude).[17]

Synthesis of (1R,2R,3R,4S)-3-[2-(3-benzenesulfonyl-amino-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl]-propionic acid 9

The above amine **8** (0.05 g, 0.161 mmol) was dissolved in 2 mL of anhydrous pyridine under argon atmosphere. The reaction vessel was placed into an ice bath. Benzenesulfonyl chloride (0.023 mL, 0.177 mmol) was added and stirred at 0 °C for 2 hours. Afterwards 8 mL of ice water was added and the mixture was extracted with EtOAc (3 mL × 3). The combined organic layer was washed with brine and dried with Na_2SO_4. After filtration and evaporation, the residue was purified with silica gel chromatography (EtOAc: nHexane = 1:1). The target compound **9** was obtained in 50.1% yield (0.02 g), $[\alpha]_D^{25}$ -2.4° (c 1.0, CH_2Cl_2); IR ν (CH_2Cl_2) cm^{-1}: 3686, 3601, 3054, 2956, 1737, 1606, 1422, 1270, 1164, 1093; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.79 (2H, d, *J* = 7.0 Hz), 7.70~7.46 (3H, m), 7.16~7.05 (2H, m), 7.03~6.90 (2H, m), 6.04 (1H, d, *J* = 4.8 Hz), 4.51 (1H, t, *J* = 4.0 Hz), 4.16 (1H, d, *J* = 4.0 Hz), 4.11~2.37 (7H, m), 1.93~1.25 (4H, m); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 177.8, 139.2, 138.1, 136.9, 132.8, 130.3, 129.2, 128.5, 127.1, 126.8, 126.5, 79.9, 79.3, 60.7, 51.2, 36.8, 34.6, 29.7, 26.8, 23.3; MS, *m/e* (relative intensity %): 415 (M^+, 11.5), 274 (96), 252 (79), 141 (30), 117 (32), 77 (100); HRMS Calcd for $C_{22}H_{25}NO_5S$: 415.14534. Found: 415.14534.

Synthesis of (1S,2S,3S,4R)-3-[2-(3-benzenesulfonylamino-7-oxabicyclo[2,2,1]hept-2-yl-methyl)phenyl]propionic acid 9'

The enantiomer was obtained similarly from **8**, $[\alpha]_D^{25}$ +2.2° (c 1.0, CH_2Cl_2).[17]

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Key Words

Thromboxane antagonist; Platelet inhibitor.

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17. Their ^{1}H-NMR, ^{13}C-NMR, IR, MS and HRMS are sim i lar to that of their re spec tive chiral part ners.