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Stereoselective Synthesis of Novel Thromboxane A_2 Receptor Antagonists via Stereoselective 1-Azadiene Isomerization

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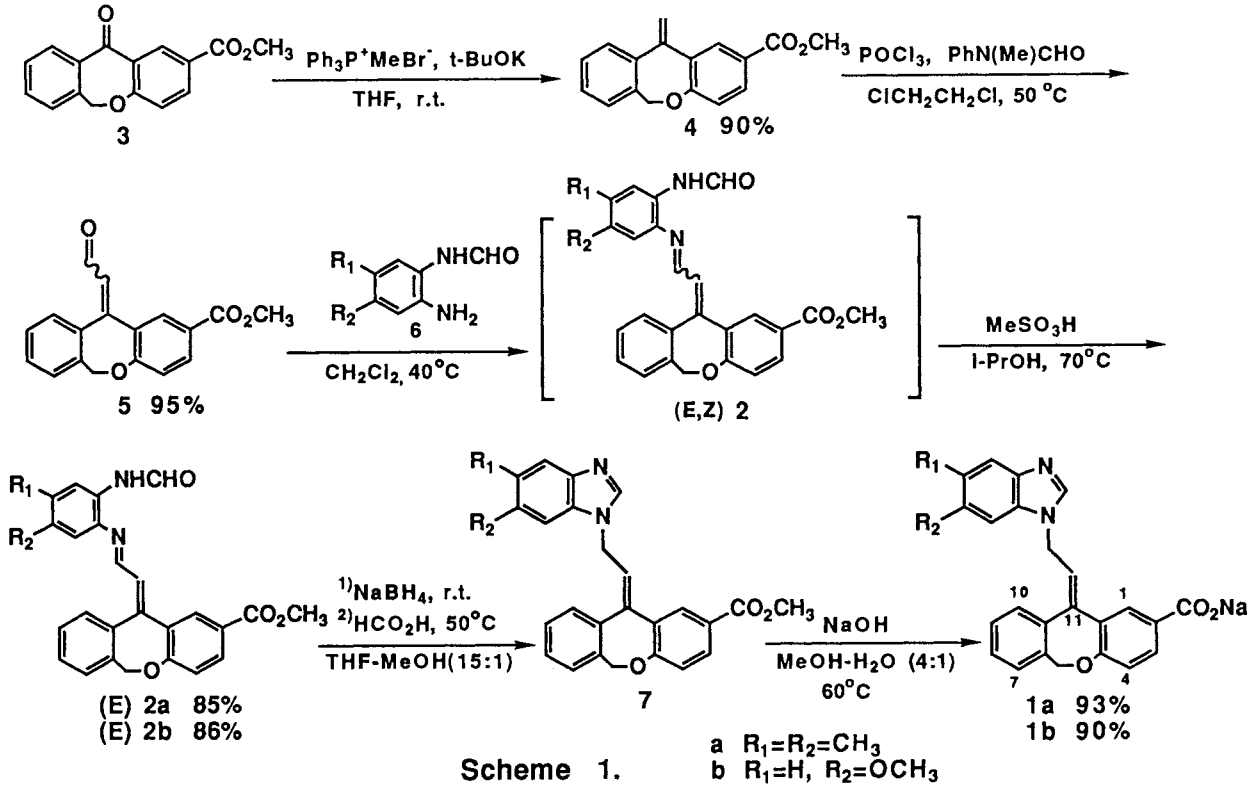
Novel non-prostanoid thromboxane A_2 receptor antagonists were synthesized stereoselectively using the transformation of (E,Z)-1-azadiene intermediates to the only (E) isomers under acidic conditions.

Thromboxane A_2 (TXA_2) has been considered to be an important mediator in a variety of circulatory diseases. Several drugs with prostanoid structures have been reported to possess the TXA_2 receptor antagonistic activities.[1] Recently dibenzoxepine derivatives **1a** and **1b** have been found to show potent activities and their non-prostanoid structures are worthy of attention.[2] About the stereochemistry of C(11) *exo* methylene groups, the (E) forms have more potent activities. So we are very interested in finding the (E) selective synthesis of **1**. In the course of synthetic studies of **1**, we found that (E,Z) mixtures of 1-azadiene intermediates **2** were transformed to (E) isomers exclusively under acidic conditions. (Scheme 1)



Scheme 1.

1-Azadienes **2** were synthesized from the known compound,[3] methyl 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepine-2-carboxylate **3**. The ester **3** was converted to 11-methylidene com-

pound **4** by the Wittig reaction. The Vilsmeier reaction of 4 afforded the α,β-unsaturated aldehyde **5**. In this reaction, **4** disappeared on TLC within 1 h at 60 °C when using N-methyl formanilide with $POCl_3$ as Vilsmeier reagent, but the use of DMF needed the longer period (8 h). NMR peak intensity ratio of aldehyde protons in **5** was about 2:1 ($CDCl_3$ 9.66 ppm, d, J= 7.9 Hz ; 9.94 ppm, d, J=7.9 Hz). Then **5**, not separated, reacted with 1,2-phenylenediamines[4] **6a** and **6b** to give 1-azadiene intermediates **2a** and **2b** respectively. Before the acidic treatments,[5] **2a** was observed as 2:1 mixtures of stereoisomers in NMR. But after heating at 70 °C in isopropanol with 0.1 equiv. $MeSO_3H$, followed by the neutralization with Et_3N, only (E) isomer of **2a** was obtained within the limits of NMR detections.[6] The (E) isomer of **2b** was obtained in the same way. On the basis of NOE experiments, they are regarded as (E) isomers as seen in Fig.1. Then C=N bonds of (E) **2** were reduced by $NaBH_4$ at room temperature and the obtained amines were transformed to benzimidazoles **7** in the known methods.[4,7] Finally without purifications of **7**, alkaline hydrolysis gave the desired compounds **1** as white crystals.[8,9]

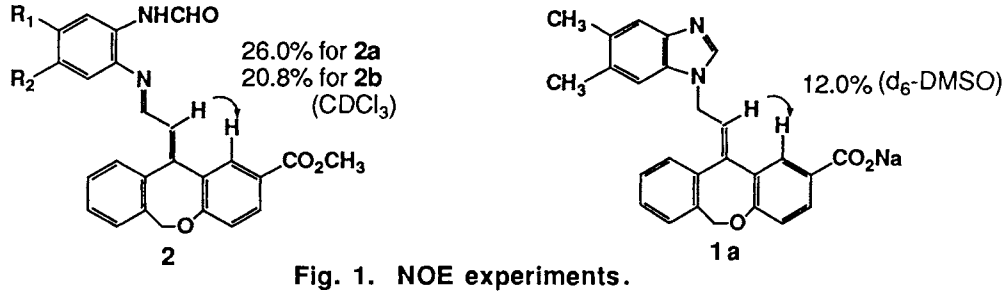


Fig. 1. NOE experiments.

The stereochemistry of **1a** was also determined from NOE experiments. In addition, by the quantitative HPLC analysis [15 cm ODS column, 40 °C, methanol-water (2:1), sodium 1-octanesulfonate 1.2 g / l, pH 2.7 by H_3PO_4, UV 254 nm] (Z) form was not detected. Here we have accomplished the stereoselective synthesis of **1**. We presume that 1-azadiene isomerization, readily undergone by only a catalytic amount of acid, is due to the stabilization of C(11) cation which is equilibrated with protonated 1-azadiene and the more stable (E) form can be produced by the loss of proton. We thank to Mr. Osamu Morita and Mr. Hideo Ueno at Kyowa Hakko Kogyo Pharmaceutical Research Laboratories for NOE experiments.

References

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2) K.Kubo and A.Karasawa, *XI International Congress of Pharmacology*, Amsterdam, The Netherlands, 1-6 July, 1990.
3) K.Ueno, S.Kubo, H.Tagawa, T.Yoshioka, W.Tsukada, M.Tsubokawa, H.Kojima, and A.Kasahara, *J. Med. Chem.*, **19**, 941 (1976).
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5) Merck Sharp and Dohme Researchers recently reported that anhydrous acidic treatment of (E,Z) mixtures of α-methyl-α,β-unsaturated imines followed by hydrolysis gave the corresponding (E) aldehydes. R.Desmond, S.G.Mills, R.P.Volante, and I.Shinkai, *Tetrahedron Lett.*, **29**, 3895 (1988).
6) NMR($CDCl_3$) CH=N proton for (E) **2a** at 8.33 ppm (d, J=9.2 Hz) ; for (E) **2b** at 8.29 ppm (d, J=9.4 Hz)
7) P.N.Preston, *Chem. Rev.*, **74**, 279 (1974).
8) **1a** NMR(d_6-DMSO) δ =2.29(3H, s), 2.34(3H, s), 4.78(1H, br), 5.07(2H, m), 5.40(1H, br), 6.31 (1H, t, J=7.2 Hz), 6.71(1H, d, J=8.5 Hz), 6.73(1H, s), 7.47-7.54(4H,m), 7.48(1H,s), 7.77(1H,dd, J=2.1, 8.5 Hz), 8.00(1H, s), 8.03(1H, d, J=2.1 Hz).
9) **1b** NMR(d_6-DMSO) δ =3.72(3H, s), 4.54(1H, br), 5.03(2H, m), 5.55(1H, br), 6.28(1H, t, J=7.0 Hz), 6.60(1H, s), 6.77(1H, m), 6.80(1H, d, J=8.6 Hz), 7.46-7.50(4H, m), 7.60(1H, d, J=7.3 Hz), 7.72(1H, d, J=8.6 Hz), 7.96(1H, s), 8.02(1H, s).

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