

**MOLECULAR DESIGN OF BIOLOGICALLY ACTIVE COMPOUNDS  
BASED ON PLATELET ACTIVATING FACTOR (PAF):  
7-OXABICYCLO[2.2.1]HEPTANE SYSTEM AS A STRONG ANTAGONIST OF PAF**

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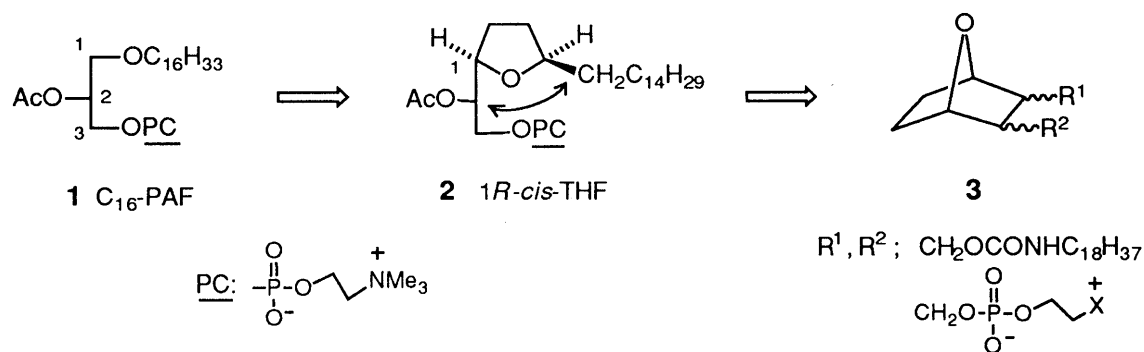
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7-Oxabicyclo[2.2.1]heptane system was designed based on the PAF structure. Among four stereoisomers synthesized, the diexo derivative turned out to be a new and strong antagonist of PAF.

**KEYWORDS** platelet activating factor; PAF; antagonist; molecular design;  
7-oxabicyclo[2.2.1]heptane

Our molecular design based on the restricted conformational isomers of platelet activating factor (PAF, **1**) allowed us to develop an interesting agonist **2**<sup>2)</sup> (*1R-cis*-THF), a partially locked analog of PAF. Then we became interested in designing more firmly locked analogs from **2**. This paper describes the preliminary results for the 7-oxabicyclo[2.2.1]heptane series of compounds **3**, which turned out to be strong antagonists of PAF.

The bicycloheptane skeleton was designed by bond formation between the C-2 of the glycerol backbone and the  $\alpha$ -carbon of the alkyl side chain of **2**. Another reason for the bicyclo ring system was that we were quite familiar with such ring systems through the chemicoenzymatic approach to various nucleosides.<sup>3)</sup> The acetoxy group was replaced with hydrogen in designing bicyclic derivatives because the first antagonist CV-3988<sup>4)</sup> has the methoxy group instead of the acetoxy group. Based on the above consideration, we were interested in the biological activity of 7-oxabicyclo[2.2.1]heptane derivatives **3**. Further, the structure-activity relationships among four stereoisomers (ignoring the absolute structure) provide valuable information about the spatial structure of PAF receptor.



**Chart 1**

The synthesis of diendo derivative **8** from **4**<sup>5)</sup> is shown in Chart 2. Thus, the treatment of the diol **5** with octadecyl isocyanate afforded the mono adduct **6** (racemic) in 57% yield. The bromoethylphosphoryl group was then introduced to the remaining hydroxy group,<sup>6)</sup> and final quaternarization with trimethylamine or thiazole<sup>4)</sup> gave diendo derivative **8** as a racemate.

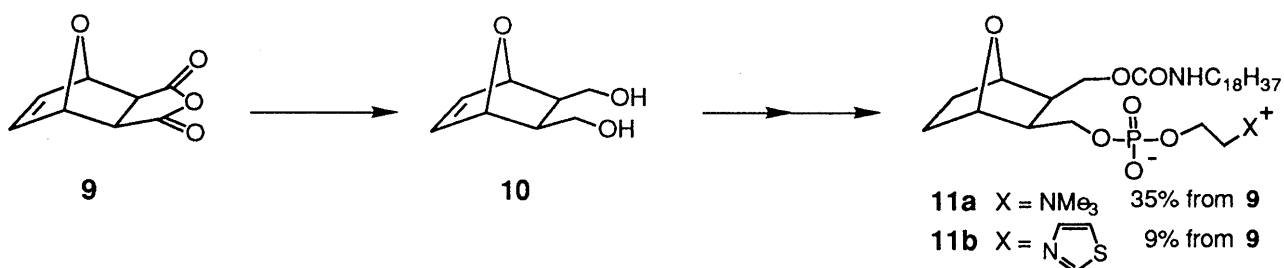
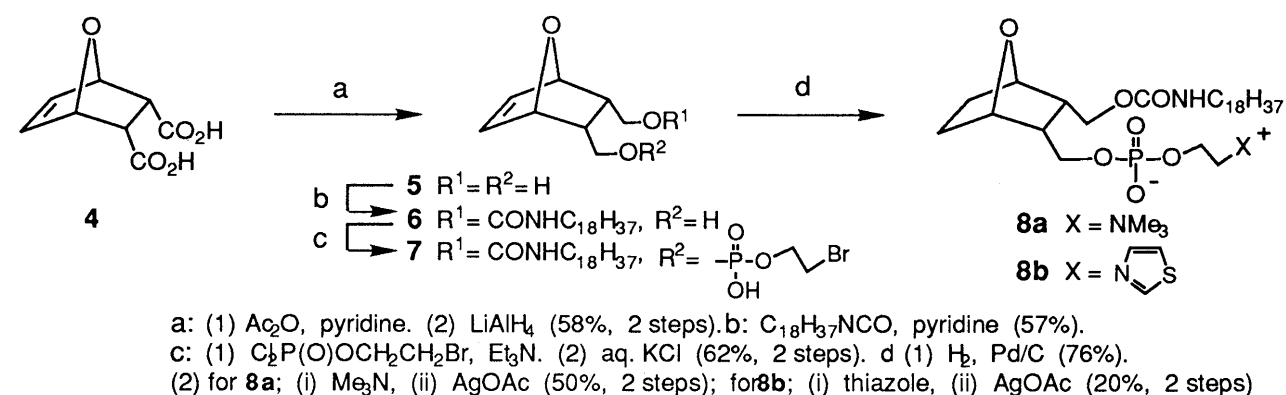


Chart 2. Synthesis of 2,3-*syn* Isomers, **8** and **11**

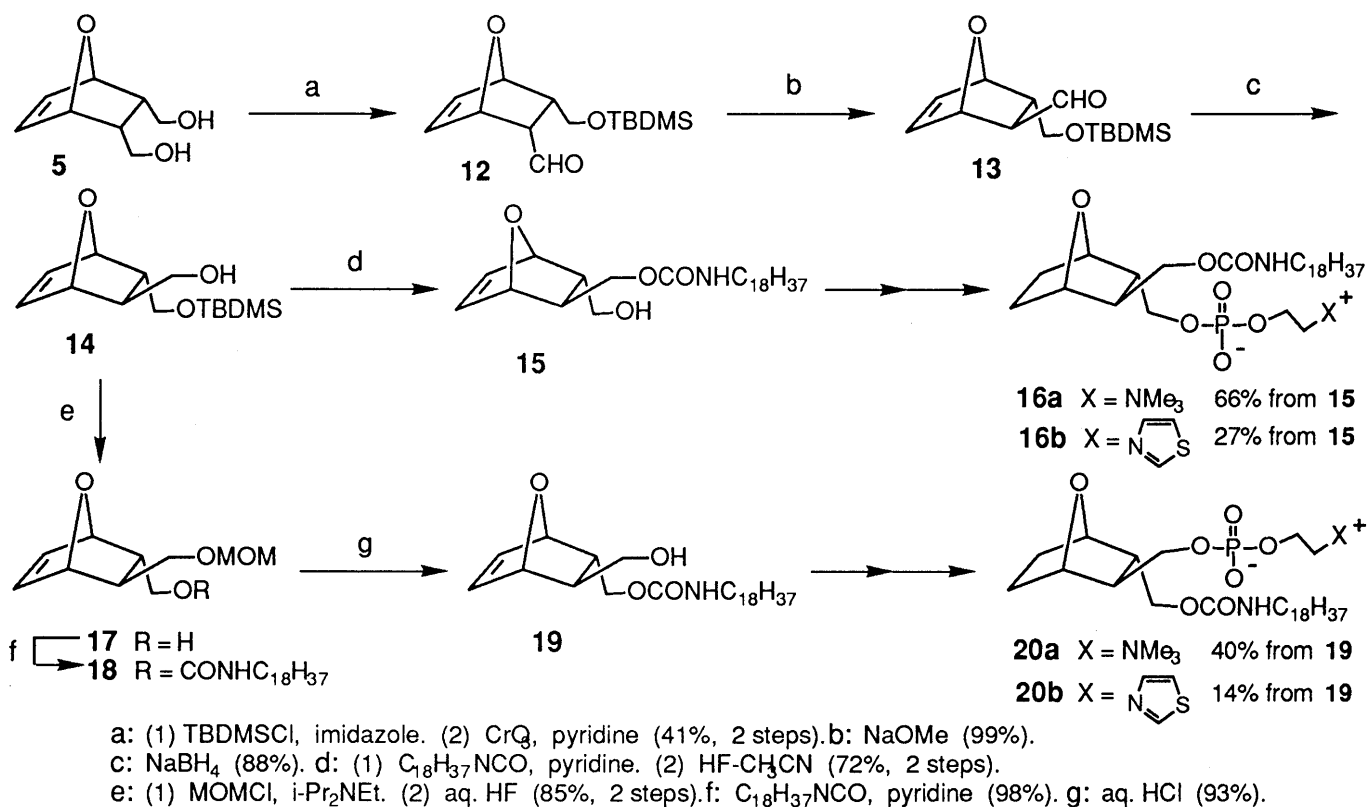


Chart 3. Synthesis of 2,3-*anti* Isomers, **16** and **20**

In a similar manner, diexo derivatives **11a** and **11b** were synthesized from the anhydride **9** via diexo diol **10** in 35% and 9% overall yields, respectively (Chart 2). The synthesis of *anti* isomers **16** and **20** is also summarized in Chart 3. The *anti* stereochemistry was established by isomerization of the *endo* isomer **12** to the *exo* isomer **13**.

Biological activities of bicyclic derivative **8**, **11**, **16**, and **20** were then investigated. These compounds, although they have no agonistic activity, were found to exhibit antagonistic activity of PAF.<sup>7)</sup> The relationships of the stereochemistry and activity are summarized in Table I, in which relative antagonistic activities compared to CV-3988 are shown. The diexo derivative **11b** is strongest, and this point is quite different from furanoid derivatives in which *trans* isomers are much potent inhibitors of PAF.<sup>8)</sup>

Table I. Relative Antagonistic Activity of **8**, **11**, **16**, and **20** vs CV-33988

	<b>8</b>	<b>11</b>	<b>16</b>	<b>20</b>	CV-3988
<b>a</b>	0.09	0.09	0.04	<0.04	-
<b>b</b>	1.3	4.7	0.35	0.12	1.0

In conclusion, we have demonstrated that 7-oxabicyclo[2.2.1]heptane derivative can serve as a potential lead compound; and, further, we believe that the conformationally restricted model approach is quite useful in the development of more effective antagonists of PAF.

**ACKNOWLEDGEMENT** This work was financially supported in part by a Grant-in-Aid for Developmental Scientific Research from the Ministry of Education, Science and Culture of Japan.

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(Received August 25, 1992)