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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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**[2)] (1*R*-*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 α–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.[3)] The acetoxy group was replaced with hydrogen in designing bicyclic derivatives because the first antagonist CV-3988[4)] 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.

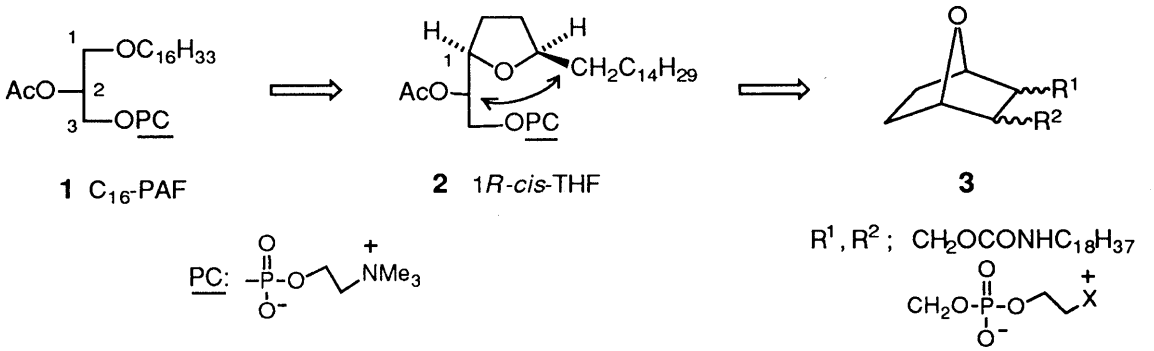
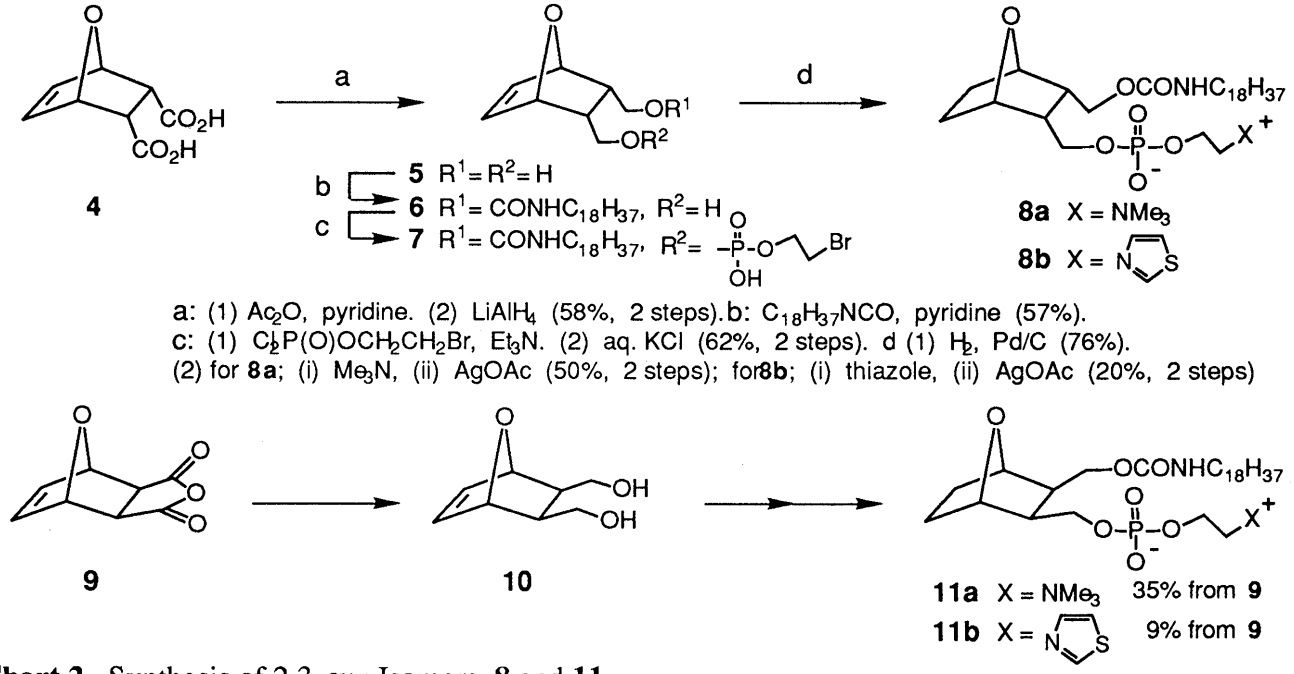


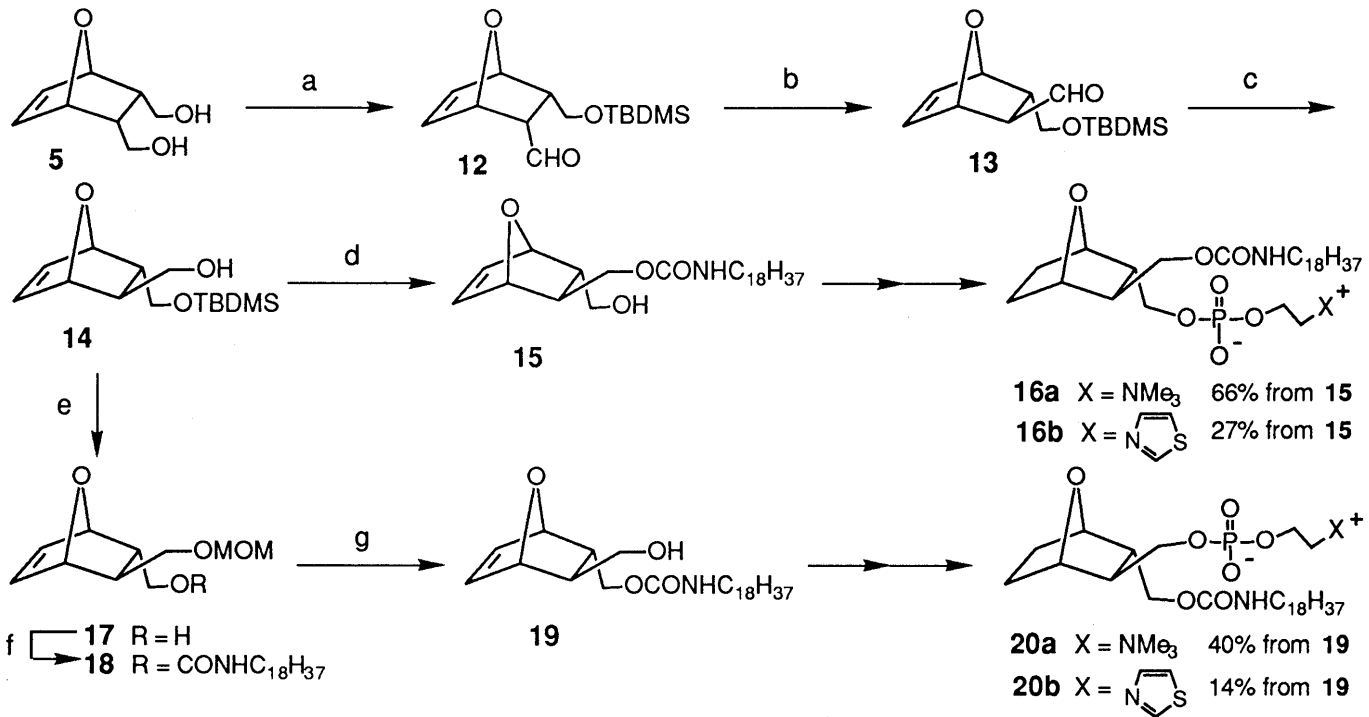
Chart 1

The synthesis of diendo derivative **8** from **4**[5] 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,[6] and final quaternarization with trimethylamine or thiazole[4] gave diendo derivative **8** as a racemate.



a: (1) Ac_2O, pyridine. (2) $LiAlH_4$ (58%, 2 steps). b: $C_{18}H_{37}NCO$, pyridine (57%).
c: (1) $Cl_2P(O)OCH_2CH_2Br$, Et_3N. (2) aq. KCl (62%, 2 steps). d (1) H_2, Pd/C (76%).
(2) for **8a**; (i) Me_3N, (ii) AgOAc (50%, 2 steps); for **8b**; (i) thiazole, (ii) AgOAc (20%, 2 steps)

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



a: (1) TBDMSCl, imidazole. (2) CrO_3, pyridine (41%, 2 steps). b: NaOMe (99%).
c: $NaBH_4$ (88%). d: (1) $C_{18}H_{37}NCO$, pyridine. (2) HF-CH_3CN (72%, 2 steps).
e: (1) MOMCl, i-Pr_2NEt. (2) aq. HF (85%, 2 steps). f: $C_{18}H_{37}NCO$, pyridine (98%). g: aq. HCl (93%).

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.[7] 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.[8]

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

	8	**11**	**16**	**20**	CV-3988
a	0.09	0.09	0.04	<0.04	-
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.

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