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Stereocontrolled Synthesis of All Stereoisomers of the Proposed Flavolipin

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Abstract: *All four stereoisomers of flavolipin were synthesized from D-glucose in a stereocontrolled manner. None of them was identical with the reported natural product.*
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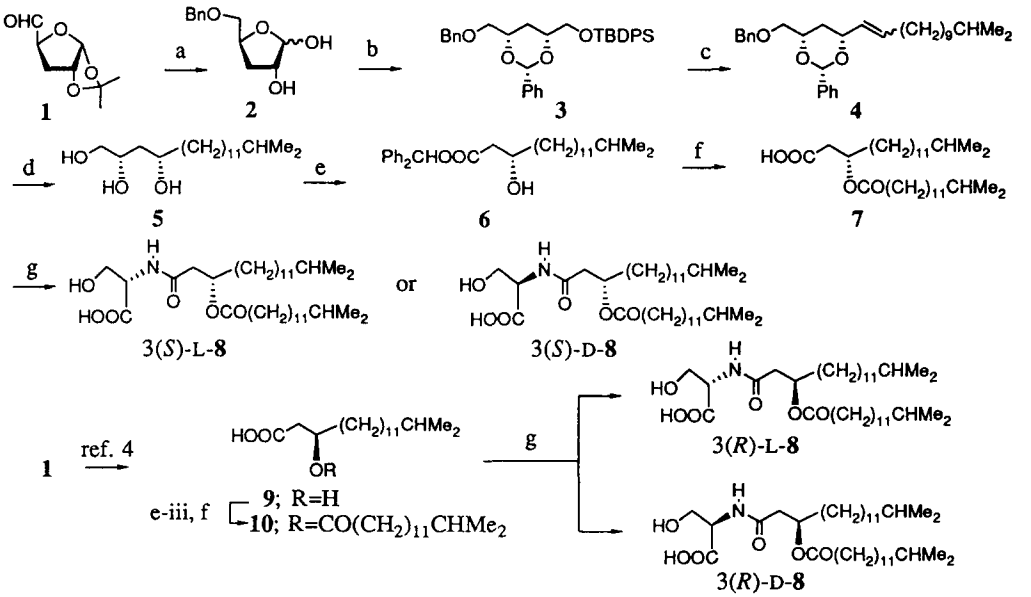
A serine-containing lipid, flavolipin,[1] which was isolated by Kawai et al. from an opportunistic pathogen, *Flavobacterium meningosepticum*, exhibits definite hemagglutinating activity[1] and strongly activates the macrophages to generate immunoregulatory substances. However, it exhibits none of the lethal toxicity in mice which is exhibited by lipopolysaccharide.[2] This fact obviously suggests that it is a nontoxic immunoactivater. The proposed structure of flavolipin is a lipoamino acid, *N*-(3-acyloxyacyl)serine, an isomer of the four compounds (**8**s). In this paper we describe the syntheses of four stereoisomers of flavolipin used to confirm the structure.

15-Methyl-3-[(*S*)-(13-methyl)tetradecanoyloxy]hexadecanoic acid (**7**) was obtained from aldehyde **1**.[3] Reduction of **1** with $NaBH_4$ followed by benzylation of the alcohol with benzyl bromide and NaH and treatment with 1M HCl in aqueous dioxane, gave hemiacetal **2**. The compound **2** was treated with $NaBH_4$ to give a triol. The primary alcohol of the triol was protected as *t*-butyldiphenylsilyl ether, and then the remaining diol was protected as a benzylidene group by treatment with $PhCH(OMe)_2$ and PPTS to give **3**. Sequential deprotection of the silyl ether of **3** with tetrabutylammonium fluoride, Swern oxidation of the alcohol, and Wittig reaction of the aldehyde with 11-methyldodecyltriphenylphosphorane gave **4**. This was hydrogenated over $Pd(OH)_2$ on carbon to give triol **5**. The vicinal diol part of **5** was oxidatively cleaved by $NaIO_4$ to an aldehyde, which was further oxidized with *m*-CPBA to a carboxylic acid. Esterification of the carboxylic acid with diphenyl diazomethane afforded **6**. Reaction of **6** with 13-methyltetradecanoic acid[4] using DCC as dehydrating agent gave the benzhydryl ester of **7**. Subsequent hydrogenolysis over $Pd(OH)_2$ on carbon furnished acid **7**. Reaction of **7** with L- and D-serine benzyl ester using DCC as a dehydrating agent followed by hydrogenolysis of the resulting benzyl ester produced 3(*S*)-L-**8** ($[\alpha]_D^{24}$= +12.8° (c 0.13, $CHCl_3$)) and 3(*S*)-D-**8** ($[\alpha]_D^{24}$= -13.7° (c 0.18, $CHCl_3$)), respectively. On the other hand, 15-methyl-3-[(*R*)-hydroxy]hexadecanoic acid (**9**) obtained from **1**[3] by the reported method[4] was converted to 3(*R*)-L-**8**

($[\alpha]_D^{24}$= +13.3° (c 0.14, $CHCl_3$)) and 3(*R*)-D-**8** ($[\alpha]_D^{24}$= -14.4° (c 0.18, $CHCl_3$)) via 15-methyl-3(*R*)-(13-methyltetradecanoyloxy)hexadecanoic acid (**10**) in the same manner as mentioned in the 3(*S*) series.

Strangely enough, none of the four compounds, 3(*S*)-L-**8**, 3(*S*)-D-**8**, 3(*R*)-L-**8**, and 3(*R*)-D-**8** thus synthesized in a stereocontrolled manner, was identical with the natural flavolipin.[5] We are now investigating the correct structure of natural flavolipin.

Scheme 1



Reagents and conditions: a) (i) $NaBH_4$, EtOH, 92%; (ii) BnBr, NaH, DMF, 80%; (iii) 1M HCl, dioxane-H_2O (10:1), 60%; b) (i) $NaBH_4$, EtOH, 94%; (ii) TBDPSCl, Et_3N, 79%; (iii) $PhCH(OMe)_2$, PPTS, DMF, 78%; c) (i) Bu_4NF, THF, 98%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 93%; (iii) $Me_2CH(CH_2)_9CH{=}PPh_3$, THF,63%; d) H_2, Pd/C, THF, 85%; e) (i) $NaIO_4$, dioxane-H_2O (4:1); (ii) *m*-CPBA, $CHCl_3$; (iii) Ph_2CN_2, EtOAc, 3 steps 83% (**6**); f) (i) $Me_2CH(CH_2)_{11}COOH$, DCC, DMAP, CH_2Cl_2; (ii) $Pd(OH)_2$/C, EtOH, 52% (**7**, 2 steps), 80% (**10**, 3 steps from **9**; g) (i) L- or D-serine benzyl ester, DCC, DMAP; (ii) H_2, Pd/C, 57-77% (2 steps).

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5. FABMS of natural flavolipin: *m/z* 655 $(M+H)^+$. FABMS of synthetic **8**s: *m/z* 598 $(M+H)^+$.

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