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2-AMINOALCOHOL IMMUNOSUPPRESSANTS: STRUCTURE-ACTIVITY RELATIONSHIPS

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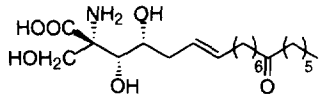
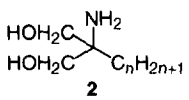
Abstract: The 2-aminoalcohol series of immunosuppressants showed a bell-shaped relationship between the activity and the carbon number. The (*R*)-isomers were more potent than the (*S*)-isomers, and (*R*)-2-aminohexadecanol displayed comparably activity to a potent immunosuppressant, FTY720.

After the isolation of the immunosuppressant ISP-I[1] (**1**: myriocin[2], thermozymocidin[3]) from the culture broth of *Isaria sinclairii*, its structural simplification and modification led to the identification of 2-alkyl-2-aminopropane-1,3-diol (**2**)[4] as the key basic structure for the immunosuppressive activity. Furthermore, introduction of a phenyl ring into the hydrophobic part afforded a potent immunosuppressant, FTY720 (**3**)[5]. Recently, modification of the hydrophilic part of **2** has indicated that 2-aminoalcohol (**4**)[6] is the minimum basic structure for the biological activity.

In this paper, we describe the structure-activity relationships of 2-aminoalcohols of defined absolute configuration at C-2.



ISP-I (**1**: myriocin, thermozymocidin)



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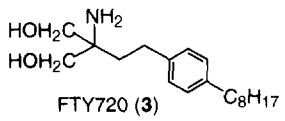
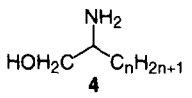


FTY720 (**3**)



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a: n= 10, **b**: n= 12, **c**: n= 14, **d**: n= 15,
e: n= 16, **f**: n= 18, **g**: n= 20, **h**: n= 22

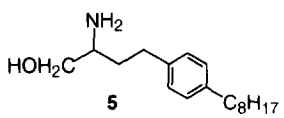

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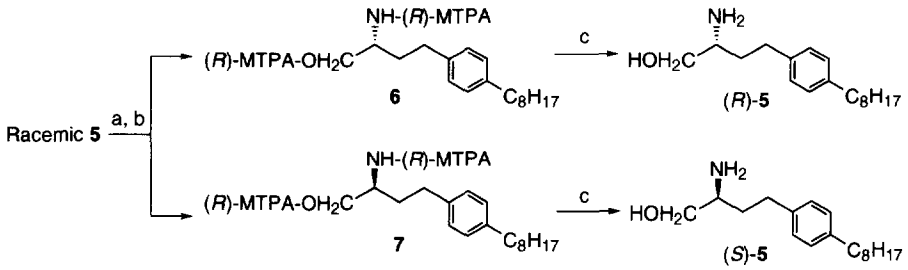
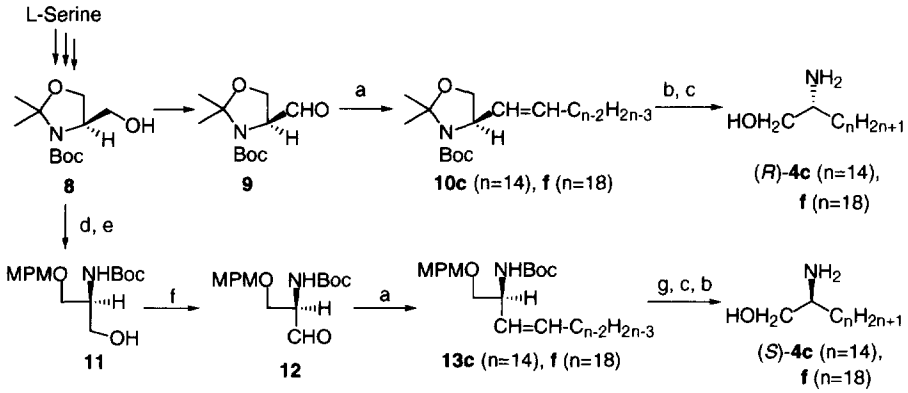
Figure 1. Structures of Immunosuppressants

Chemistry: Racemic compounds **4a-h**[7] were synthesized in the same manner as described in the previous paper[6].

Compounds (*R*)- and (*S*)-**5** were prepared by resolution of the racemate (Scheme 1). Treatment of racemic **5**[6] with (*S*)-(+)-MTPA chloride in the presence of Et_3N and *N*,*N*-dimethylaminopyridine afforded a diastereomeric mixture of the *N*,*O*-di-(*R*)-MTPA derivative. The mixture was purified by preparative HPLC to give **6** and **7**. Methanolysis of **6** and **7** with NaOMe afforded (*R*)-**5** {$[\alpha]_D$ - 0.81 (*c* = 1.73 in $CHCl_3$)} and (*S*)-**5** {$[\alpha]_D$ + 0.52 (*c* = 1.88 in $CHCl_3$)}, respectively. The absolute configurations of these compounds were confirmed by means of the modified Mosher's method[8].



Scheme 1: (a) (*S*)-MTPA-Cl, Et_3N, DMAP. (b) preparative HPLC. (c) NaOMe, MeOH



Scheme 2: (a) $Ph_3P^+C_{n-1}H_{2n-1}Br^-$, KHMDS. (b) 4 N HCl. (c) 10% Pd-C, H_2. (d) MPM-Cl, NaH. (e) 90% AcOH aq, LiCl. (f) SO_3-pyr, Et_3N. (g) DDQ.

Compounds (*R*)- and (*S*)-**4** were synthesized by starting from L-serine as shown in Scheme 2. The known compounds **8**[9a] and **9**[9a,b] were prepared. Wittig reaction of **9** with alkyltriphenylphosphonium bromide in the presence of KHMDS afforded the condensation product **10**. Treatment of **10** with 4 N HCl followed by reduction with H_2/10 % Pd-C afforded (*R*)-**4** {**4c**: $[\alpha]_D$ - 3.7 (*c* = 0.4 in MeOH), **4f**: $[\alpha]_D$ - 3.5 (*c* = 0.4 in MeOH)}. Treatment of **8** with *p*-

methoxybenzyl chloride (MPM-Cl) in the presence of NaH followed by deprotection of the acetonide with acetic acid afforded the reverse-configuration alcohol **11**. Compound **11** was oxidized with SO_3-pyridine to give the aldehyde **12**, which was converted into the olefin **13** by Wittig reaction. Deprotection of the *p*-methoxybenzyl group in **13** with DDQ followed by hydrogenation gave the saturated alcohol, which was treated with 4 N HCl to furnish (*S*)-**4** {**4c**: $[\alpha]_D$ + 1.6 (*c* = 0.46 in MeOH), **4f**: $[\alpha]_D$ + 4.7 (*c* = 0.42 in MeOH)}.

Results and Discussion: The effect of the racemic 2-aminoalcohols (**4a-h**) on the mouse allogeneic mixed lymphocyte reaction (MLR)[1b] was examined. Figure 2 shows the IC_{50} values of **4a-h** versus their side-chain length. The 2-aminoalcohols (**4a-h**) showed a bell-shaped relationship on the graph between the activity and side-chain length. In this series, 2-aminohexadecanol (**4c**) was the most potent compound.

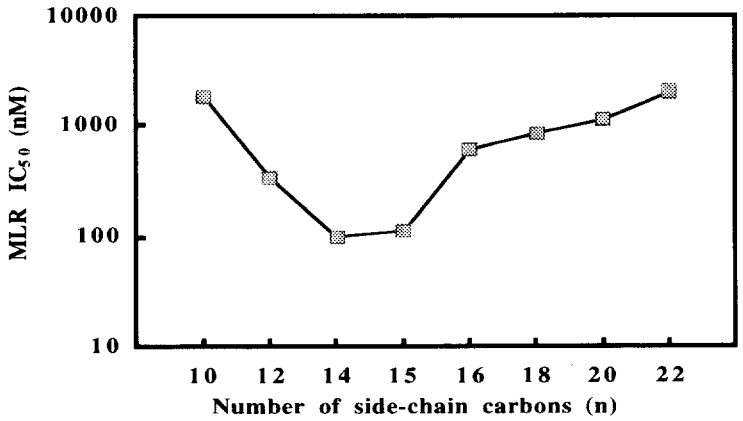


Figure 2. Effect of 2-Aminoalcohols on Mouse Allogeneic MLR

Next, the IC_{50} values of the (*R*)- and (*S*)- isomers of **4c**, **4f** and **5** on mouse allogeneic MLR were measured to investigate the relationship between the activity and the configuration at C-2 in the 2-aminoalcohol (Table). The (*R*)-isomers were more potent than the (*S*)-isomers. In particular, (*R*)-**4c** possessed the most potent activity among the isomers and showed similar activity to **3** (IC_{50} = 67.4 nM).

Table

	MLR IC_{50} (nM)		
	racemate	(*R*)-isomer	(*S*)-isomer
4c	98.3	68.8	137
4f	867	533	1390
5	211	108	427

(*R*)-2-Aminoalcohol has the same D-configuration as natural sphingosine, the biosynthesis of which is inhibited by **1**[10]. On the other hand, D,L-2-amino-4-octadecen-1-ol did not inhibit the incorporation of serine into sphingolipids[11]. Since immunosuppressively active 2-aminoalcohol is structurally similar to D,L-2-amino-4-octadecen-1-ol, it also should not inhibit the incorporation of serine into sphingolipids. We anticipate that the immunosuppressive activity of 2-aminoalcohol can be caused by inhibition of same biological action of sphingosine or a derivative, such as sphingosine-1-phosphate.

References and Notes

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8. $\Delta\delta = \delta_S - \delta_R$ for the (*R*)- and (*S*)-MTPA amides derived from (*R*)- and (*S*)-**5**: (*R*)-**5**; 1-H_2 (-0.0299), 3-H_2 (+0.0318), 4-H_2 (+0.103). (*S*)-**5**; 1-H_2 (+0.0231), 3-H_2 (-0.0342), 4-H_2 (-0.104).
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