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ENANTIOSPECIFIC SYNTHESIS OF THE IMMUNOPOTENTIATORS erythro-9 (2-HYDROXY-3-NONYL) HYPOXANTHINES AND THE threo-DIASTEREOMERS.

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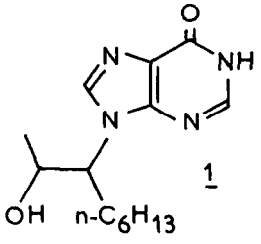
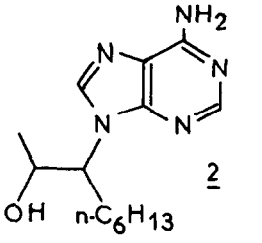
Summary : The title compounds were prepared enantiospecifically by kinetic resolution of (+/-) 1-nonene-3ol via Sharpless oxidation. The products 1,2R-epoxy-nonane-3S-ol and 1-nonene-3R-ol were efficiently converted to all four stereoisomers of 2-hydroxy-3-nonylamine, which were subsequently incorporated into the target hypoxanthines to evaluate their immunopotentiating activity.

(+/-) Erythro-9(2-hydroxy-3-nonyl) hypoxanthine (1, NPT 15392) has been reported to have immunopotentiating activity[1]. This compound is structurally related to the adenine analog 2 (EHNA), which is a potent inhibitor of adenosine deaminase[2], and has antiviral activity in vitro[3]. It was recently shown[4,5] that chirality in the nonyl chain of EHNA played a role in determining binding to the enzyme, a property not observed in the antiviral evaluation of these compounds[6]. The structural similarities of 1 and 2, prompted us to synthesize the enantiomers and diastereomers of 1 to study the effect of chirality on the immunopotentiating activity.



1



2

We recently described the synthesis of 2S-hydroxy-3R-nonylamine starting from natural chiral synthons[7]. We report here the enantiospecific synthesis of the four stereoisomers of 2-hydroxy-3-nonylamine starting from non chiral substrates, and their conversion to the title compounds.

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Retrosynthetic analysis led us to (+/-) 1-nonene-3-ol 3 as the starting material which is easily obtained from heptaldehyde and vinyl magnesium bromide. Oxidation of 3 using the Sharpless method[8], ((+) DIPT, $Ti(OiPr)_4$, anhydrous TBHP, -20°, 18 h) furnished a mixture of 3a and 4, separation of these compounds was accomplished by fractional vacuum distillation[9] to give pure 3a (bp 48°, 0.03 mm, $[\alpha]_D$ = - 13.4°, c = 1.12 EtOH) and 4 (bp. 54°, 0.03 mm, $[\alpha]_D$ = - 4°, c = 1.24 EtOH, 84 %[10]).

Protection of the hydroxyl group in 4 as the tetrahydropyranyl ether (DHP, TsOH 1 %, CH_2Cl_2, 30 mn) gave 5 which was regioselectively reduced (LAH, ether, 0°, 30 mn) to give alcohol 6 in 90 % overall yield from 4.

Benzoylation of 6 followed by acid hydrolysis led to the semi protected diol 8 (80 % overall). The azido derivative 9 was obtained by the modified Mitsunobu reaction[11] (Ph_3P, DEAD, HN_3, benzene, 2h, 20°) and was purified by flash chromatography (hexane, EtOAc 5 %, quantitative). Base hydrolysis of 9 followed by catalytic reduction over palladium (10 % on carbon, EtOH), afforded the threo 2R, 3R-hydroxyamine 11a ($[\alpha]_D$ = + 17°, c = 1.2 EtOH).

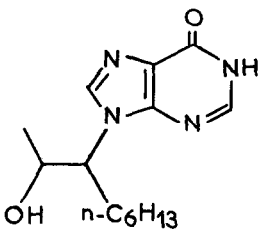
The erythro 2S, 3R diastereomer 11b was obtained by a modification in the sequence of reaction just described. Thus catalytic reduction of the azido benzoate 9 gave after in situ transbenzoylation, benzamide 12 (mp. 106°).

Inversion of configuration at C-2 was accomplished through oxazoline 13a which was subsequently hydrolysed to 11b ($[\alpha]_D$ = + 11.8°, c = 0.93, EtOH).

Although the described sequence gave the chiral amines in very good yields, the number of steps required prompted us to search for a more efficient synthetic route. Thus treatment of epoxide 4 in the conditions described earlier [11], gave quantitatively the azido epoxide 14 ($[\alpha]_D$ = - 19.6°, c = 1.25 EtOH). Simultaneous LAH reduction of the two functionalities gave amine 11a, from which diastereomer 11b was obtained through oxazoline 13b [12].

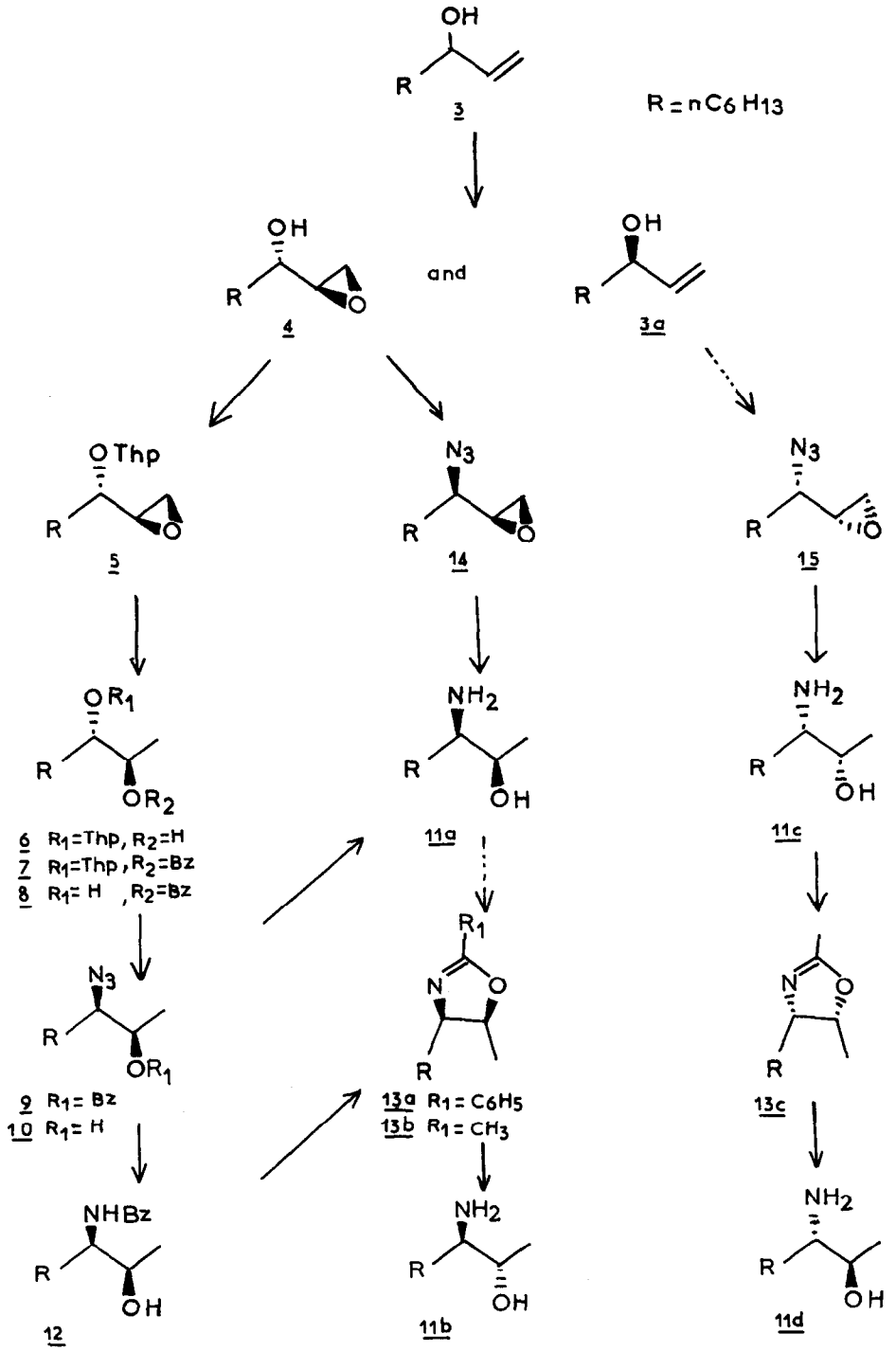
Similarly epoxidation of 3a using (-)DIPT and introduction of the azide fonction gave 15 ($[\alpha]_D$ = + 20.9°, c = 1.27 EtOH) ; subsequent reduction gave the amine 11c ($[\alpha]_D$ = -15,8°, c = 1.17 EtOH), from which diastereomer 11d was obtained ($[\alpha]_D$ = - 14.5°, c = 1.2 EtOH)[13].

Having completed the synthesis of the amines, their incorporation into the hypoxanthine nucleus followed published procedures[14]. Successive condensation of each amine with 5-amino-2,6-dichloropyrimidine and triethyl orthoformate furnished the corresponding chloropurines which were hydrolyzed to the title compounds 1a-d[15]:



	$[\alpha]_D$, EtOH	mp°
1a : 2R, 3R	+ 38.5°	176°
1b : 2S, 3S	- 32°	174°
1c : 2S, 3R	+ 30.4°	204°
1d : 2R, 3S	- 29.2°	193°

The potential synthetic utility of epoxy azides 14 and 15 as well as the synthesis of analogs of NPT 15392 are currently under investigation.


OH
R
3
R = nC6 H13
and
4
3a
OThp
5
N3
14
15
OR1
OR2
6 R1=Thp, R2=H
7 R1=Thp, R2=Bz
8 R1= H , R2=Bz
NH2
11a
11c
N3
OR1
9 R1= Bz
10 R1= H
R1
N
O
13a R1 = C6H5
13b R1 = CH3
13c
NHBz
12
11b
11d

TABLE

^{1}H (CCl_4) and ^{13}C ($CDCl_3$) nmr chemical shifts (in ppm from TMS)

Compound	H1	H2	H3	C1	C2	C3
4	2.8	3	3.8	43.7	54.8	68.9
3a	5.1	5.9	4.1	114.4	141.5	73.2
7	1	5-5.4	3.6-3.8	22.6	78.7-77.9	
9	1	5.1	3.1	17.4	72.9	65.5
11a	1	3.5	2.4	20.3	70.2	57.5
12	1	3.8		20.4	68.5	54.9
13a	1.3	4.8	4.1	15.7	76	71
14		2.8-3.2		44.9	54.4	64.1

Acknowledgments

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9 - The decomposition of excess tBHP was accomplished using excess $NaBH_4$. This reagent formed a borate ester with DIPT and prevented its distillation thus allowing the separation of 3a and 4 . The use of other reducing agents was less satisfactory.
10 - This yield was calculated considering the oxidation of only one enantiomer of racemic 1.
11 - H. Loibner and E. Zbiral, Helv. Chim. acta, 59, 2100, (1976).
12 - The optical rotations were in agreement with values obtained earlier : M. Bessodes, G. Bastian, R.P. Panzica and E. Abushanab, unpublished results.
13 - Presented at the V international conference on organic synthesis (ICOS-5, Freiburg I. Br., 1984), Abstr. N° T42.
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15 - Satisfactory elemental analysis have been obtained on all key compounds.

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